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(54) Titre : SEQUENCES D'ACIDES AMINES DIRIGES CONTRE DES CYTOKINES HETERODIMERES ET/OU LEURS RECEPTEURS ET POLYPEPTIDES LES COMPRENANT

(54) Title: AMINO ACID SEQUENCES DIRECTED AGAINST HETERODIMERIC CYTOKINES AND/OR THEIR RECEPTORS AND POLYPEPTIDES COMPRISING THE SAME

(57) Abrégé/Abstract:
The present invention relates to amino acid sequences that are directed against (as defined herein) heterodimeric cytokines and/or their receptors, as well as to compounds or constructs, and in particular proteins and polypeptides, that comprise or essentially consist of one or more such amino acid sequences (also referred to herein as 'amino acid sequences of the invention', 'compounds of the invention', and 'polypeptides of the invention', respectively). The invention also relates to nucleic acids encoding such amino acid sequences and polypeptides (also referred to herein as 'nucleic acids of the invention' or 'nucleotide sequences of the invention'); to methods for preparing such amino acid sequences and polypeptides; to host cells expressing or capable of expressing such amino acid sequences or polypeptides; to compositions, and in particular to pharmaceutical compositions, that comprise such amino acid sequences, polypeptides, nucleic acids and/or host cells; and to uses of such amino acid sequences or polypeptides, nucleic acids, host cells and/or compositions, in particular for prophylactic, therapeutic or diagnostic purposes, such as the prophylactic, therapeutic or diagnostic purposes mentioned herein.

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(57) Abstract: The present invention relates to amino acid sequences that are directed against (as defined herein) heterodimeric cytokines and/or their receptors, as well as to compounds or constructs, and in particular proteins and polypeptides, that comprise or essentially consist of one or more such amino acid sequences (also referred to herein as '*amino acid sequences of the invention*', '*compounds of the invention*', and '*polypeptides of the invention*', respectively). The invention also relates to nucleic acids encoding such amino acid sequences and polypeptides (also referred to herein as '*nucleic acids of the invention*' or '*nucleotide sequences of the invention*'); to methods for preparing such amino acid sequences and polypeptides; to host cells expressing or capable of expressing such amino acid sequences or polypeptides; to compositions, and in particular to pharmaceutical compositions, that comprise such amino acid sequences, polypeptides, nucleic acids and/or host cells; and to uses of such amino acid sequences or polypeptides, nucleic acids, host cells and/or compositions, in particular for prophylactic, therapeutic or diagnostic purposes, such as the prophylactic, therapeutic or diagnostic purposes mentioned herein.

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Amino acid sequences directed against heterodimeric cytokines and/or their receptors and polypeptides comprising the same.

The present invention relates to amino acid sequences that are directed against (as defined herein) heterodimeric cytokines and/or their receptors, as well as to compounds or constructs, and in particular proteins and polypeptides, that comprise or essentially consist of one or more such amino acid sequences (also referred to herein as "*amino acid sequences of the invention*", "*compounds of the invention*", and "*polypeptides of the invention*", respectively).

The invention also relates to nucleic acids encoding such amino acid sequences and polypeptides (also referred to herein as "*nucleic acids of the invention*" or "*nucleotide sequences of the invention*"); to methods for preparing such amino acid sequences and polypeptides; to host cells expressing or capable of expressing such amino acid sequences or polypeptides; to compositions, and in particular to pharmaceutical compositions, that comprise such amino acid sequences, polypeptides, nucleic acids and/or host cells; and to uses of such amino acid sequences or polypeptides, nucleic acids, host cells and/or compositions, in particular for prophylactic, therapeutic or diagnostic purposes, such as the prophylactic, therapeutic or diagnostic purposes mentioned herein.

Other aspects, embodiments, advantages and applications of the invention will become clear from the further description herein.

Heterodimeric cytokines, their receptors and the pathways, signalling, biological mechanisms and physiological effect in which they and their receptors are involved are known from the prior art.

Some of the best-known examples of heterodimeric cytokines and their receptors are IL-12, IL-23 and IL-27, and their receptors IL-12R, IL-23R, and IL-27, respectively. As their name implies, these cytokines are heterodimeric, consisting of two different subunits, i.e. IL12p40 and IL12p35 in case of IL-12, IL12p40 and IL23p19 (also called IL-30B) in case of IL-23, and EBI3 and IL27p28 in case of IL-27. Also, the receptors for these heterodimeric cytokines consist of multiple subunits, i.e. IL12Rbeta1 and IL12Rbeta2 in case of IL-12R, IL12Rbeta1 and IL23R in case of IL-23R, and WSX1 and gp130 in case of IL-27R.

IL12 remains the prototypical heterodimeric cytokine (composed of IL12p40 and IL12p35), it was not until relatively recently that other related heterodimers exist.

In 2000, IL-23 and its subunit p19 (IL23p19) were identified on the basis of a homology search for IL-6-family members. Their studies revealed that p19 dimerizes with IL12p40 and that this cytokine, known as IL23, uses IL12Rβ1, but not IL12Rβ2, as a component of its high-affinity receptor. Functional cloning identified the other subunit of the receptor for IL23, a subunit known as IL23R (text adapted from CA Hunter 2003). It was also found that IL-23 plays an important role in proliferation of Th17 cells.

IL27 is another heterodimeric cytokine related to IL12 composed of EBI3 and IL27p28. Epstein–Barr virus (EBV)-induced molecule 3 (EBI3) had been identified as an IL-12p40 homologue. In 2002, the p28 subunit of IL-27 (IL-27p28) was discovered as a protein with homology to IL-12p35 and IL-6.

Recently, the existence of a further heterodimeric cytokine belonging to the IL-12 family, called IL-35, has been described (Collison et al., Nature, 22 November 2007, 566). This heterodimeric cytokine is described as contributing to regulatort T-cell function and is composed of the IL12p35 and EBI-3 subunits.

Thirty-four known type I cytokine receptors have been described, and although the ligands are more difficult to identify, there are at least 27 that can be clustered into 5 distinct families (see Boulay et al 2003). One of these groupings is composed of the ligands for a series of cytokine receptors that use gp130 (glycoprotein 130) or one of several gp130-related proteins. These include the receptors for IL6 and the receptors for the heterodimeric cytokines IL-12, IL-23 and IL-27 (Hunter, supra).

The IL12 receptor is a heterodimer of IL12Rbeta1 and IL12Rbeta2.

The IL23 receptor is a heterodimer of IL12Rbeta1 and IL23R. IL12Rbeta1 is a used by both IL12 and IL-23 for signalling. Targeting this receptor will lead to a blockade of both IL-12 and IL-23 signaling.

The IL27 receptor is a hetero dimer composed of WSX1 (Identified on the basis of a homology search for gp130-like proteins) and gp130 which is a common element of the receptor for IL-6 (which comprises IL-6Rα and gp130) and the receptor for IL27 (which comprises WSX1 and gp130), which is consistent with the close familial relationship of these cytokines.

For further information on heterodimeric cytokines and their receptors, as well as the pathways, signalling, biological mechanisms and biological effects in which they are involved, and also the diseases in which they are associated, reference is made to the

following prior art: Oppmann, 2000, Immunity, 13:751-725; Gubler et al., 1991, PNAS, 88: 4143-4147; Hunter, Nature Rev., Vol.5, July 2003, 521; Watford et al., Cytokine and Growth Factor Reviews 14 (2003), 361-368; Boulay, Immunity, Vol.19, 159-163 (2003); Goriely and Goldmann, American Journal of Transplantation 2007; 7: 208-284; Langrish et al., Immunological Reviews 2004, 202, 96-105; Kaufmann et al., J. Invest. Dermatol., 123: 1037-1044, 2004; Neurath, Nature Medecine, Vol.13, January 2007, 26; Collison et al., Nature, 22 November 2007, 566; Parham et al., The Journal of Immunology, 2002, 5699; EP 433 827; EP 1 210 434; EP 790 308; EP 790 309; EP 1 175 446; EP 0 969 867; EP 1 309 692; EP 1 002 084; EP 1 587 178; EP 1 589 998; WO 04/071517; EP 1 601 695; WO 05/079837; WO 06/068987; WO 07/027761; WO/2007/024846; WO 02/09748 and WO 06/069036; as well as the further prior art cited in these references and in the present specification. Some of the above references also describe antagonists of heterodimeric cytokines (such as conventional monoclonal antibodies) and mention diseases and disorders that can be prevented and/or treated by the use of such antagonists.

For the sequences of the various subunits of the heterodimeric cytokines and their receptors, reference is made to following Genbank accession numbers, which also mention additional information on as the pathways, signalling, biological mechanisms and biological effects in which they are involved, and also the diseases in which they are associated:

P19 : NM_016584

P40 : NM_002187

IL12Rbeta1 : NM_005535

IL23R NM_144701

IL12Rbeta2 NM_001559

WSX1: IL27RA: NM_004843

Gp130: NM_002184 and NM_175767

P35 (IL12A): NM_000882

P28: NM_145659

EBI3: NM_005755

From the above, it will also be clear that the aforementioned heterodimeric cytokines and their receptors have some subunits in common, with for example IL12p40 being present in both IL-12 and IL-23, and for example IL-12Rbeta1 being present in both the (cognate) receptor for IL-12 as well as the (cognate) receptor for IL-23. Also, some of the other

subunits present in the heterodimeric cytokines or the receptors, although not identical, are structurally and/or functionally similar, and on the basis of these similarities can be grouped as follows:

- the p19, p35 and p28 subunits (and their present and future homologs), which will also be collectively referred to herein as the "*p19-like subunits*", it being understood that the p19-like subunit of IL-12 is p35, the p19-like subunit of IL-23 is p19, the p19-like subunit of IL-27 is p28, and the p19-like subunit of IL-35 is p35. P19-like subunits (such as the p35) are also homologous to type I cytokines, such as IL6 and oncostatin M, and for example share the "four helix bundle" that is common to type I cytokines;
- the p40 and EBI3 subunits (and their present and future homologs), which will also be collectively referred to herein as the "*p40-like subunits*", it being understood that the p40-like subunit of IL-12 is p40, the p40-like subunit of IL-23 is p40, the p40-like subunit of IL-27 is EBI3, and the p40-like subunit of IL-35 is EBI3. P40-like subunits (such as IL12p40) are structurally related to the soluble IL-6 receptor (IL-6Rα);
- the gp130 and IL-12beta-1 subunits (and their present and future homologs), which will also be collectively referred to herein as the "*gp130-like subunits*", it being understood that the gp130-like subunit of the IL-12 receptor is IL-12Rbeta-1, the gp130-like subunit of the IL-23 receptor is IL-12Rbeta-1, and the gp130-like subunit of the IL-27 receptor is gp130.
- the IL-12Rbeta-2, IL-23R and WSX-1 subunits (and their present and future homologs), which will also be collectively referred to herein as the "*IL-23 subunits*", it being understood that the IL-23 subunit of the IL-12 receptor is IL-12Rbeta-2, the IL-23-like subunit of the IL-23 receptor is IL-23R, and the IL-23-like subunit of the IL-27 receptor is WSX-1.

It is generally known that cytokines and their receptors are critical players in (the pathways) regulating all aspects of immune responses. This is also the case for the heterodimeric cytokines that belong to the interleukin-12 (IL12)-related family and for their receptors. For example, IL12 - the prototypical heterodimeric member of the IL-12 family - induces interferon-□ (IFN-□) production by NK, T cells, dendritic cells (DC), and macrophages. IL-12 also promotes the differentiation of naive $CD4^+$ T cells into T helper 1 (T_H1) cells that produce IFN-□ and aid in cell-mediated immunity. Therefore the central role

of IL12 in the generation of T_H1 cells (cell-mediated immune response) has long been appreciated. For example, mouse models established that IL12 is required for the development of protective innate and adaptive immune response to intracellular pathogens.

IL23 and IL27 - two of the other heterodimeric cytokines from the IL-12 family - also regulate T_H1-cell response, albeit with distinct functions. The ability of IL-23 to stimulate $CD4^+$ T cells to produce IL-17 has a dominant role in the development and maintenance of autoimmune inflammation. By contrast, a principal function of IL-27 *in vivo* is to limit the intensity and duration of innate and adaptive immune responses.

In addition IL12p40 can be found as a monomers or homodimers which have antagonistic activities.

Recently, IL23 was shown to be responsible for the chronic inflammation observed in inflammatory bowel disease. This was confirmed by the fact that the IL23R gene was identified as being involved in inflammatory bowel disease. It has also been found that p19 knock out mice are resistant to collagen-induced arthritis and colitis, whereas comparable p35 knock out mice were found to be more susceptible to collagen-induced arthritis. Also, when p19 knock out mice were crossed with IL-10 knock out mice, the resulting offspring were resistant to colitis, whereas similar crosses of p19 knock out mice with IL-10 knock out mice resulted in offspring that was susceptible to colitis. It was further found that a monoclonal antibody against p19 inhibits the development of EAE, a preclinical animal model for multiple sclerosis, and reduces serum levels of IL-17 (which is not regulated by IL-12). Also, IL-23 rather than IL-12 appears to be the essential cytokine in CNS autoimmune inflammation. All this results suggests that IL-23/p19 may be a more attractive target for the treatment of colitis, Crohn's diseases, IBD, multiple sclerosis, rheumatoid arthritis and some of the other diseases and disorders mentioned herein that IL-12/p35 or p40 (as a compound directed against p40 will probably modulate both IL-12 and IL-23). It should also be noted that the monoclonal antibodies CNTO 1275 and ABT-874 (see below) that are currently under clinical development are both directed against p40. Thus, one specific object of the invention is to provide amino acid sequences and polypeptides that are directed against p19, and in particular amino acid sequences and polypeptides that are specific for (as defined herein) p19 compared to both p35 and p40 and/or that are specific for (as defined herein) IL-23 compared to IL-12. Examples of such amino acid sequences and polypeptides will become clear from the description herein.

As further described herein, the amino acid sequences, polypeptides and compositions of the present invention can generally be used to modulate (as defined herein) the signalling that is mediated by heterodimeric cytokines and/or their receptors, to modulate (as defined herein) the biological pathways in which heterodimeric cytokines and/or their receptors are involved, and/or to modulate (as defined herein) the biological mechanisms, responses and effects associated with heterodimeric cytokines, their receptors, such signalling and/or these pathways (all the foregoing is also collectively referred to herein as "*heterodimeric cytokine-mediated signalling*").

As such, the amino acid sequences, polypeptides and compositions of the present invention can generally be used to modulate the immune system and/or one or more specific immune responses in a subject to which one or more of the amino acid sequences, polypeptides and compositions of the present invention are administered (i.e. in therapeutically relevant amounts).

The term "heterodimeric cytokines" as used herein in its broadest sense generally includes any heterodimeric cytokine, i.e. a cytokine that comprises at least two, and more preferably only two, subunits.

In particular, the term "heterodimeric cytokine" as used herein encompasses heterodimeric cytokines that are associated with cell-mediated (T_H1) immunity, although the invention is its broadest sense is not limited thereto and also encompasses heterodimeric cytokines associated with humoral (T_H2) immunity.

According to one specific, but non-limiting aspect, the amino acid sequences and polypeptides of invention are directed against a heterodimeric cytokine that is chosen from heterodimeric cytokines that comprise a p40 subunit or p40-like subunit, such as a p40 subunit (present in for example IL-12 and IL-23) or Epstein-Barr virus (EBV)-induced molecule 3 (EBI3, present in for example IL-27 and IL-35).

According to another specific, but non-limiting aspect, the amino acid sequences and polypeptides of invention are directed against a heterodimeric cytokine that is chosen from heterodimeric cytokines that comprise a p19 subunit or a p19-like subunit, such as a p19 subunit (present in for example IL-23), a p35 subunit (present in for example IL-12 and IL-35), or a p28 subunit (present in for example IL-27) or a homolog thereof.

For example, the amino acid sequences and polypeptides of invention may be directed against a heterodimeric cytokine that will comprise at least one p19 subunit or p19-like subunit and at least one p40 subunit or p40-like subunit.

According to an even more specific, but non-limiting aspect, the amino acid sequences and polypeptides of invention are directed against a heterodimeric cytokine that is chosen from IL-12, IL-23, IL-27 and/or IL-35.

In one specific aspect, but non-limiting aspect, the amino acid sequences and polypeptides of the invention are directed against IL-23 (i.e. against p40, p19 or both). Such amino acid sequences and polypeptides of the invention (as well as compositions comprising the same), can be used for preventing and treating disorders associated with IL-23.

In another specific aspect, but non-limiting aspect, the amino acid sequences and polypeptides of the invention are directed against IL-12 (i.e. against p40, p35 or both). Such amino acid sequences and polypeptides of the invention (as well as compositions comprising the same), may be as further described herein, and can be used for preventing and treating disorders associated with IL-12.

The amino acid sequences, polypeptides and compositions can be used to modulate (as defined herein, and for example as an agonist or an antagonist) heterodimeric cytokines and their receptors, and/or the signaling, pathways, biological mechanisms and effects in which these are involved.

The amino acid sequences and polypeptides that are antagonists of heterodimeric cytokines and their receptors (and/or of the signaling, pathways, biological mechanisms and effects in which these are involved) can also be used to reduce or inhibit the agonistic effects of heterodimeric cytokines.

More generally, the amino acid sequences (such as the p19+ sequences, p19- sequences, p40+ sequences, p40- sequences, p35 sequences, IL-27 sequences, IL-12Rb1 sequences, IL-12Rb2 sequences and IL-23 sequences described herein), polypeptides (such as the - for example multivalent, multispecific and/or biparatopic - constructs described herein that comprise at least one p19+ sequence, p19- sequence, p40+ sequence, p40- sequence, p35 sequence, IL-27 sequence, IL-12Rb1 sequence, IL-12Rb2 sequence and/or IL-23 sequence) and compositions of the present invention can be used for the prevention and treatment (as defined herein) of diseases and disorders associated with heterodimeric cytokines and their receptors (and/or with the signaling, pathways, biological mechanisms and effects in which

these are involved). Generally, "diseases and disorders associated with heterodimeric cytokines and their receptors" can be defined as diseases and disorders that can be prevented and/or treated, respectively, by suitably administering to a subject in need thereof (i.e. having the disease or disorder or at least one symptom thereof and/or at risk of attracting or developing the disease or disorder) of either a polypeptide or composition of the invention (and in particular, of a pharmaceutically active amount thereof) and/or of a known active principle active against heterodimeric cytokines and/or their receptors or a biological pathway or mechanism in which heterodimeric cytokines and/or their receptors is involved (and in particular, of a pharmaceutically active amount thereof). Examples of such diseases and disorders associated with heterodimeric cytokines and their receptors will be clear to the skilled person based on the disclosure herein, and for example include the following diseases and disorders: inflammation and inflammatory disorders such as bowel diseases (colitis, Crohn'disease, IBD), infectious diseases, psioriasis, cancer, autoimmune diseases (such as MS), carcoidis, transplant rejection, cystic fibrosis, asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, viral infection, common variable immunodeficiency, and the various diseases and disorders mentioned in the prior art cited herein. Based thereon, it will also be clear to the skilled person with heterodimeric cytokines (and/or receptors thereof) are involved in which specific diseases and disorders.

In particular, the polypeptides and compositions of the present invention can be used for the prevention and treatment of diseases and disorders associated with heterodimeric cytokines and their receptors which are characterized by excessive and/or unwanted signalling mediated by heterodimeric cytokines and/or their receptors or by the pathway(s) in which heterodimeric cytokines and/or their receptors is involved. Examples of such diseases and disorders associated with heterodimeric cytokines and their receptors will again be clear to the skilled person based on the disclosure herein. For this purpose, usually antagonists of heterodimeric cytokines and their receptors (and/or with the signaling, pathways, biological mechanisms and effects in which these are involved) will be used.

Agonists of heterodimeric cytokines and their receptors (and/or with the signaling, pathways, biological mechanisms and effects in which these are involved) can be used to stimulate or enhance one or more immune response in a human or animal, for example for the prevention and/or treatment of diseases that are characterized by a weakened immune system or that may occur as a result of having a weakened immune system. Reference is for example

made to Hunter (supra), Table 1, which lists several mice knock-outs in which various heterodimeric cytokines and receptors thereof (and in particular subunits thereof) have been knock-out, and the inflammatory phenotypes associated therewith.

IL12p40 has also been shown to have an essential role in autoimmune inflammation as shown in disease model system as EAE (Experimental Allergic Encephalomyelitis) or CIA (Collagen-induced arthritis).

Thus, without being limited thereto, the amino acid sequences and polypeptides of the invention can for example be used to prevent and/or to treat all diseases and disorders that are currently being prevented or treated with active principles that can modulate heterodimeric cytokines and/or their receptors-mediated signalling, such as those mentioned in the prior art cited above (for example, the monoclonal antibody CNTO 1275 that is described in WO 02/09748 and WO 06/069036; ABT-874, a monoclonal against p40 that is being developed by Abbott; as well as the small molecule Apilimod®, Syntha Pharmaceuticals). It is also envisaged that the polypeptides of the invention can be used to prevent and/or to treat all diseases and disorders for which treatment with such active principles is currently being developed, has been proposed, or will be proposed or developed in future. In addition, it is envisaged that, because of their favourable properties as further described herein, the polypeptides of the present invention may be used for the prevention and treatment of other diseases and disorders than those for which these known active principles are being used or will be proposed or developed; and/or that the polypeptides of the present invention may provide new methods and regimens for treating the diseases and disorders described herein.

As will be clear from the further description herein, the amino acid sequences of the invention may be in a so-called "monovalent" format (i.e. comprising or essentially consisting of a single antigen binding domain or binding unit) or in a "multivalent" format (i.e. comprising or essentially consisting of two or more binding domains or binding units – which may be the same or different - that are linked to each other, optionally via one or more suitable linkers). As also further described herein, such multivalent amino acid sequences and polypeptides of the invention may for example, without limitation, be multispecific (such as bispecific or trispecific) or multiparatopic (such as biparatopic) constructs (or be both multiparatopic and multispecific, such as a biparatopic construct against the p19 subunit that contains a further binding domain for binding to a serum protein, as exemplified herein); and may for example be constructs that comprise at least two binding domains or binding units

that are each directed towards a different epitope on the same subunit of a heterodimeric cytokine, constructs that comprise at least two binding domains or binding units that each have a different biological function (for example one binding domain that can block or inhibit receptor-ligand interaction, and one binding domain that does not block or inhibit receptor-ligand interaction), or constructs that comprise at least two binding domains or binding units that are each directed towards a different subunit of a heterodimeric cytokine.

Examples of such constructs will become clear from the further disclosure herein.

It will also become clear from the further description herein that such constructs can generally be provided (and in particular, purposefully designed for a specific biological action) by suitably linking (optionally via suitable linkers) or combining two or more "monovalent" amino acid sequences of the invention (or by suitably linking or combining nucleotide sequences encoding such monovalent amino acid sequences to provide a nucleic acid that encodes the desired multivalent construct, and then suitably expressing said multivalent construct). Thus, it should be clear that the invention not only makes available the monovalent and multivalent amino acid sequences and polypeptides described herein, but also provides - by making available the monovalent amino acid sequences and polypeptides described herein - the skilled person with a range of different binding domains and binding units that can be used as "building blocks" to provide a range of different multivalent, multispecific and/or multiparatopic (and in particular, biparatopic) constructs (which may have different binding affinities, avidities, specificities, potencies and/or efficacies), which through the use of suitable "building blocks" as described herein can be purposefully designed for use in different aspects of the invention (as further described herein).

Consequently, the use of the various monovalent amino acid sequences of the invention as "building blocks" for providing the proteins and polypeptides of the invention (or nucleotide sequences/nucleic acids encoding the same, which can then be expressed to provide such proteins and polypeptides) form an important aspect of the invention.

For this purpose and for the other purposes described herein, the invention in a particular aspect provides a number of different amino acid sequences that each can be used as a single binding domain or binding unit, either as such (i.e. as a monovalent amino acid sequence as further described herein) or as part of (and/or as a "building block") for, a multivalent, multispecific and/or multispecific construct, as further described herein.

In their monovalent form, these amino acid sequences may for example be classified as follows:

- "p19 sequences", i.e. amino acid sequences of the invention that are directed against (as defined herein) the p19 subunit (as present in for example IL-23). The p19 sequences described herein may be further subdivided into "p19+ sequences" (i.e. p19 sequences that are directed against the p19 subunt and that are capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p19 subunit to its (cognate) receptor, and in particular capable of are capable of modulating, neutralizing, blocking and/or inhibiting the binding of IL-23 to its (cognate) receptor, for example in the alpha-screen assay of Example 19 or 22)and "p19- sequences" (i.e. p19 sequences that are directed against the p19 subunit but that (per se/as such) are (essentially) not capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p19 subunit to its (cognate) receptor);
- "*p40 sequences*", i.e. amino acid sequences of the invention that are directed against (as defined herein) the p40 subunit (as present in for example IL-12 and IL-23). The p40 sequences described herein may be further subdivided into "p40+ sequences" (i.e. p40 sequences that are directed against the p40 subunt and that are capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p40 subunit to its (cognate) receptor, and in particular capable of are capable of modulating, neutralizing, blocking and/or inhibiting the binding of IL-23 to its (cognate) receptor, for example in the alpha-screen assay of Example 19 or 22), and/or of modulating, neutralizing, blocking and/or inhibiting the binding of IL-12 to its (cognate) receptor) and "p40- sequences" (i.e. p40 sequences that are directed against the p40 subunit but that (per se/as such) are (essentially) not capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p40 subunit to its (cognate) receptor);
- "*p35 sequences*", i.e. amino acid sequences of the invention that are directed against (as defined herein) the p35 subunit (as present in for example IL-12);
- "*IL-27 sequences*", i.e. amino acid sequences of the invention that are directed against (as defined herein) IL-27. The IL-27 sequences described herein may be directed against the EBI-3 subunit or against the IL-27p28 subunit;

- "*IL-12Rb1 sequences*", i.e. amino acid sequences of the invention that are directed against the Rbeta1 subunit of IL-12R and/or of IL-23R;
- "*IL-12Rb2 sequences*", i.e. amino acid sequences of the invention that are directed against the Rbeta2 subunit of IL-12R)
- "*IL-23R sequences*", i.e. amino acid sequences of the invention that are directed against the IL-23R subunit of the IL-23 receptor.

Each of the p19+ sequences, p19- sequences, p40+ sequences, p40- sequence, p35 sequences, IL-27 sequences, IL-12Rb1 sequences, IL-12Rb2 sequences and IL-23R sequences may be as further described herein and each class of amino acid sequences of the invention forms a further aspect of the invention.

The invention also relates to the use of such p19+ sequences, p19- sequences, p40+ sequences, p40- sequences, p35 sequences, IL-27 sequences, IL-12Rb1 sequences, IL-12Rb2 sequences and IL-23R sequences (and/or of nucleotide sequences and/or nucleic acids encoding the same) as "building blocks" (i.e. as single antigen binding domains or units) in or for multivalent, multispecific and/or multiparatopic constructs, as further described herein.

In this respect, it should for example be noted that amino acid sequences of the invention that are not capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine to its cognate receptor (such as the p19- sequences or p40- sequences) may still find use as binding domains and/or binding units in multivalent, multispecific and/or multiparatopic polypeptides of the invention, for example in order to provide/improve specificity and/or to provide/improve affinity and/or avidity. Examples thereof will become clear to the skilled person from the disclosure herein.

Thus, further aspects of the invention relate to:

- the use of an amino acid sequence of the invention that comprises or essentially consists of a single binding domain or binding unit (as defined herein) in providing, constructing, and/or as part of a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that comprises said amino acid sequence of the invention (one or more) and at least one further binding domain or binding unit;
- the use of a nucleotide sequence and/or nucleic acid that encodes an amino acid sequence of the invention that comprises or essentially consists of a single binding domain or binding unit (as defined herein) in providing, constructing, and/or as part of

a nucleotide sequence and/or nucleic acid that encodes a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that comprises said amino acid sequence of the invention (one or more) and at least one further binding domain or binding unit;

- the use of an amino acid sequence of the invention that comprises or essentially consists of a single binding domain or binding unit (as defined herein) in providing, constructing, and/or as part of a biparatopic construct, protein and/or polypeptide that comprises said amino acid sequence of the invention (one or more) and at least one further binding domain or binding unit;
- the use of a nucleotide sequence and/or nucleic acid that encodes an amino acid sequence of the invention that comprises or essentially consists of a single binding domain or binding unit (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a biparatopic construct, protein and/or polypeptide that comprises said amino acid sequence of the invention (one or more) and at least one further binding domain or binding unit;
- the use of an amino acid sequence of the invention that comprises or essentially consists of a single binding domain or binding unit (as defined herein) in providing, constructing, and/or as part of a multispecific (and in particular, bispecific) construct, protein and/or polypeptide that is directed against a heterodimeric protein, polypeptide, ligand or receptor (or other heterodimeric "target"), wherein said construct, protein and/or polypeptide comprises said amino acid sequence of the invention (one or more) and at least one further binding domain or binding unit, and wherein said one or more amino acid sequences of the invention are directed against a first subunit of the heterodimeric protein, polypeptide, ligand or receptor and at least one of said further binding domains or binding units is directed against a second subunit of the heterodimeric protein, polypeptide, ligand or receptor different from the first;
- the use of a nucleotide sequence and/or nucleic acid that encodes an amino acid sequence of the invention that comprises or essentially consists of a single binding domain or binding unit (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a multispecific (and in particular, bispecific) construct, protein and/or polypeptide that is directed against a heterodimeric protein, polypeptide, ligand or receptor (or other heterodimeric "target"),

wherein said construct, protein and/or polypeptide comprises said amino acid sequence of the invention (one or more) and at least one further binding domain or binding unit, and wherein said one or more amino acid sequences of the invention are directed against a first subunit of the heterodimeric protein, polypeptide, ligand or receptor and at least one of said further binding domains or binding units is directed against a second subunit of the heterodimeric protein, polypeptide, ligand or receptor different from the first;

- the use of an amino acid sequence of the invention that comprises or essentially consists of a single binding domain or binding unit (as defined herein) in providing, constructing and/or as part of a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that is directed against a heterodimeric cytokine or a (cognate) receptor for a heterodimeric cytokine and that comprises said amino acid sequence of the invention and at least one further binding domain or binding unit;
- the use of a nucleotide sequence and/or nucleic acid that encodes an amino acid sequence of the invention that comprises or essentially consists of a single binding domain or binding unit (as defined herein) in providing, constructing and/or as part of a nucleotide sequence and/or nucleic acid that encodes a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that is directed against a heterodimeric cytokine or a (cognate) receptor for a heterodimeric cytokine and that comprises said amino acid sequence of the invention and at least one further binding domain or binding unit;
- the use of an amino acid sequence of the invention that comprises or essentially consists of a single binding domain or binding unit (as defined herein) in providing, constructing and/or as part of a biparatopic construct, protein and/or polypeptide that is directed against (a subunit of) a heterodimeric cytokine or (a subunit of) a (cognate) receptor for a heterodimeric cytokine and that comprises said amino acid sequence of the invention and at least one further binding domain or binding unit;
- the use of a nucleotide sequence and/or nucleic acid that encodes an amino acid sequence of the invention that comprises or essentially consists of a single binding domain or binding unit (as defined herein) in providing, constructing and/or as part of a nucleotide sequence and/or nucleic acid that encodes a biparatopic construct, protein and/or polypeptide that is directed against (a subunit of) a heterodimeric cytokine or (a

subunit of) a (cognate) receptor for a heterodimeric cytokine and that comprises said amino acid sequence of the invention and at least one further binding domain or binding unit;

- the use of an amino acid sequence of the invention that comprises or essentially consists of a single binding domain or binding unit (as defined herein) in providing, constructing, and/or as part of a multispecific (and in particular, bispecific) construct, protein and/or polypeptide that is directed against a heterodimeric cytokine, wherein said construct, protein and/or polypeptide comprises said amino acid sequence of the invention (one or more) and at least one further binding domain or binding unit, and wherein said one or more amino acid sequences of the invention are directed against a first subunit of the heterodimeric cytokine and at least one of said further binding domains or binding units is directed against a second subunit of the same heterodimeric cytokine (i.e. different from the first subunit);

- the use of a nucleotide sequence and/or nucleic acid that encodes an amino acid sequence of the invention that comprises or essentially consists of a single binding domain or binding unit (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a multispecific (and in particular, bispecific) construct, protein and/or polypeptide that is directed against a heterodimeric cytokine, wherein said construct, protein and/or polypeptide comprises said amino acid sequence of the invention (one or more) and at least one further binding domain or binding unit, and wherein said one or more amino acid sequences of the invention are directed against a first subunit of the heterodimeric cytokine and at least one of said further binding domains or binding units is directed against a second subunit of the same heterodimeric cytokine (i.e. different from the first subunit);

- the use of a p19+ sequence (as defined herein) in providing, constructing, and/or as part of a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that comprises said p19+ sequence (one or more) and one or more further binding domains or binding units;

- the use of a nucleotide sequence and/or nucleic acid that encodes a p19+ sequence (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a multivalent, multispecific and/or multiparatopic

construct, protein and/or polypeptide that comprises said p19+ sequence (one or more) and one or more further binding domains or binding units;

- the use of a p19+ sequence (as defined herein) in providing, constructing, and/or as part of a biparatopic construct, protein and/or polypeptide that is directed against p19 and/or against a heterodimeric cytokine that comprises a p19 subunit (such as IL-23) and that comprises said p19+ sequence (one or more) and at least one further binding domain or binding unit that is also directed against p19 (but to a different epitope or antigenic determinant of p19), and optionally one or more further binding domains or binding units;
- the use of a nucleotide sequence and/or nucleic acid that encodes a p19+ sequence (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a biparatopic construct, protein and/or polypeptide that is directed against p19 and/or against a heterodimeric cytokine that comprises a p19 subunit (such as IL-23) and that comprises said p19+ sequence (one or more) and at least one further binding domain or binding unit that is also directed against p19 (but to a different epitope or antigenic determinant of p19), and optionally one or more further binding domains or binding units;
- the use of a p19+ sequence (as defined herein) in providing, constructing, and/or as part of a multispecific (and in particular, bispecific) construct, protein and/or polypeptide that is directed against a heterodimeric cytokine that comprises a p19 subunit (such as IL-23), wherein said construct, protein and/or polypeptide comprises said p19+ sequence (one or more) and one or more further binding domains or binding units, and wherein at least one of said further binding domains or binding units is directed against a second subunit of the said heterodimeric cytokine different from p19 (such as p40 in IL-23);
- the use of a nucleotide sequence and/or nucleic acid that encodes a p19+ sequence (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a multispecific (and in particular, bispecific) construct, protein and/or polypeptide that is directed against a heterodimeric cytokine that comprises a p19 subunit (such as IL-23), wherein said construct, protein and/or polypeptide comprises said p19+ sequence (one or more) and one or more further binding domains or binding units, and wherein at least one of said further binding

domains or binding units is directed against a second subunit of the said heterodimeric cytokine different from p19 (such as p40 in IL-23);

- the use of a p19- sequence (as defined herein) in providing, constructing, and/or as part of a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that comprises said p19- sequence (one or more) and one or more further binding domains or binding units;
- the use of a nucleotide sequence and/or nucleic acid that encodes a p19- sequence (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that comprises said p19- sequence (one or more) and one or more further binding domains or binding units;
- the use of a p19- sequence (as defined herein) in providing, constructing, and/or as part of a biparatopic construct, protein and/or polypeptide that is directed against p19 and/or against a heterodimeric cytokine that comprises a p19 subunit (such as IL-23) and that comprises said p19- sequence (one or more) and at least one further binding domain or binding unit that is also directed against p19 (but to a different epitope or antigenic determinant of p19), and optionally one or more further binding domains or binding units;
- the use of a nucleotide sequence and/or nucleic acid that encodes a p19- sequence (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a biparatopic construct, protein and/or polypeptide that is directed against p19 and/or against a heterodimeric cytokine that comprises a p19 subunit (such as IL-23) and that comprises said p19- sequence (one or more) and at least one further binding domain or binding unit that is also directed against p19 (but to a different epitope or antigenic determinant of p19), and optionally one or more further binding domains or binding units;
- the use of a p19- sequence (as defined herein) in providing, constructing, and/or as part of a multispecific (and in particular, bispecific) construct, protein and/or polypeptide that is directed against a heterodimeric cytokine that comprises a p19 subunit (such as IL-23), wherein said construct, protein and/or polypeptide comprises said p19-sequence (one or more) and one or more further binding domains or binding units, and wherein at least one of said further binding domains or binding units is directed against

a second subunit of the said heterodimeric cytokine different from p19 (such as p40 in IL-23);

- the use of a nucleotide sequence and/or nucleic acid that encodes a p19- sequence (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a multispecific (and in particular, bispecific) construct, protein and/or polypeptide that is directed against a heterodimeric cytokine that comprises a p19 subunit (such as IL-23), wherein said construct, protein and/or polypeptide comprises said p19- sequence (one or more) and one or more further binding domains or binding units, and wherein at least one of said further binding domains or binding units is directed against a second subunit of the said heterodimeric cytokine different from p19 (such as p40 in IL-23);
- the use of a p40+ sequence (as defined herein) in providing, constructing, and/or as part of a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that comprises said p40+ sequence (one or more) and one or more further binding domains or binding units;
- the use of a nucleotide sequence and/or nucleic acid that encodes a p40+ sequence (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that comprises said p40+ sequence (one or more) and one or more further binding domains or binding units;
- the use of a p40+ sequence (as defined herein) in providing, constructing, and/or as part of a biparatopic construct, protein and/or polypeptide that is directed against p40 and/or against a heterodimeric cytokine that comprises a p40 subunit (such as IL-23 or IL-12) and that comprises said p40+ sequence (one or more) and at least one further binding domain or binding unit that is also directed against p40 (but to a different epitope or antigenic determinant of p40), and optionally one or more further binding domains or binding units;
- the use of a nucleotide sequence and/or nucleic acid that encodes a p40+ sequence (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a biparatopic construct, protein and/or polypeptide that is directed against p40 and/or against a heterodimeric cytokine that comprises a p40 subunit (such as IL-23) and that comprises said p40+ sequence (one or more) and at

least one further binding domain or binding unit that is also directed against p40 (but to a different epitope or antigenic determinant of p40), and optionally one or more further binding domains or binding units;

- the use of a p40+ sequence (as defined herein) in providing, constructing, and/or as part of a multispecific (and in particular, bispecific) construct, protein and/or polypeptide that is directed against a heterodimeric cytokine that comprises a p40 subunit (such as IL-23), wherein said construct, protein and/or polypeptide comprises said p40+ sequence (one or more) and one or more further binding domains or binding units, and wherein at least one of said further binding domains or binding units is directed against a second subunit of the said heterodimeric cytokine different from p40 (such as p19 in IL-23 or p35 in IL-12);
- the use of a nucleotide sequence and/or nucleic acid that encodes a p40+ sequence (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a multispecific (and in particular, bispecific) construct, protein and/or polypeptide that is directed against a heterodimeric cytokine that comprises a p40 subunit (such as IL-23 or IL-12), wherein said construct, protein and/or polypeptide comprises said p40+ sequence (one or more) and one or more further binding domains or binding units, and wherein at least one of said further binding domains or binding units is directed against a second subunit of the said heterodimeric cytokine different from p40 (such as p40 in IL-23 or p35 in IL-12);
- the use of a p40- sequence (as defined herein) in providing, constructing, and/or as part of a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that comprises said p40- sequence (one or more) and one or more further binding domains or binding units;
- the use of a nucleotide sequence and/or nucleic acid that encodes a p40- sequence (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that comprises said p40- sequence (one or more) and one or more further binding domains or binding units;
- the use of a p40- sequence (as defined herein) in providing, constructing, and/or as part of a biparatopic construct, protein and/or polypeptide that is directed against p40 and/or against a heterodimeric cytokine that comprises a p40 subunit (such as IL-23 or IL-12)

and that comprises said p40- sequence (one or more) and at least one further binding domain or binding unit that is also directed against p40 (but to a different epitope or antigenic determinant of p40), and optionally one or more further binding domains or binding units;

- the use of a nucleotide sequence and/or nucleic acid that encodes a p40- sequence (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a biparatopic construct, protein and/or polypeptide that is directed against p40 and/or against a heterodimeric cytokine that comprises a p40 subunit (such as IL-23 or IL-12) and that comprises said p40- sequence (one or more) and at least one further binding domain or binding unit that is also directed against p40 (but to a different epitope or antigenic determinant of p40), and optionally one or more further binding domains or binding units;
- the use of a p40- sequence (as defined herein) in providing, constructing, and/or as part of a multispecific (and in particular, bispecific) construct, protein and/or polypeptide that is directed against a heterodimeric cytokine that comprises a p40 subunit (such as IL-23 or IL-12), wherein said construct, protein and/or polypeptide comprises said p40- sequence (one or more) and one or more further binding domains or binding units, and wherein at least one of said further binding domains or binding units is directed against a second subunit of the said heterodimeric cytokine different from p40 (such as p19 in IL-23 or p35 in IL-12);
- the use of a nucleotide sequence and/or nucleic acid that encodes a p40- sequence (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a multispecific (and in particular, bispecific) construct, protein and/or polypeptide that is directed against a heterodimeric cytokine that comprises a p40 subunit (such as IL-23 or IL-12), wherein said construct, protein and/or polypeptide comprises said p40- sequence (one or more) and one or more further binding domains or binding units, and wherein at least one of said further binding domains or binding units is directed against a second subunit of the said heterodimeric cytokine different from p40 (such as p40 in IL-23 or p35 in IL-12);
- the use of a p35 sequence (as defined herein) in providing, constructing, and/or as part of a multivalent, multispecific and/or multiparatopic construct, protein and/or

polypeptide that comprises said p35 sequence (one or more) and one or more further binding domains or binding units;

- the use of a nucleotide sequence and/or nucleic acid that encodes a p35 sequence (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that comprises said p35 sequence (one or more) and one or more further binding domains or binding units;
- the use of a p35 sequence (as defined herein) in providing, constructing, and/or as part of a biparatopic construct, protein and/or polypeptide that is directed against p35 and/or against a heterodimeric cytokine that comprises a p35 subunit (such as IL-12) and that comprises said p35 sequence (one or more) and at least one further binding domain or binding unit that is also directed against p35 (but to a different epitope or antigenic determinant of p35), and optionally one or more further binding domains or binding units;
- the use of a nucleotide sequence and/or nucleic acid that encodes a p35 sequence (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a biparatopic construct, protein and/or polypeptide that is directed against p35 and/or against a heterodimeric cytokine that comprises a p35 subunit (such as IL-12) and that comprises said p35 sequence (one or more) and at least one further binding domain or binding unit that is also directed against p35 (but to a different epitope or antigenic determinant of p35), and optionally one or more further binding domains or binding units;
- the use of a p35 sequence (as defined herein) in providing, constructing, and/or as part of a multispecific (and in particular, bispecific) construct, protein and/or polypeptide that is directed against a heterodimeric cytokine that comprises a p35 subunit (such as IL-12), wherein said construct, protein and/or polypeptide comprises said p35 sequence (one or more) and one or more further binding domains or binding units, and wherein at least one of said further binding domains or binding units is directed against a second subunit of the said heterodimeric cytokine different from p35 (such as p40 in IL-12);
- the use of a nucleotide sequence and/or nucleic acid that encodes a p35 sequence (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a multispecific (and in particular, bispecific) construct,

protein and/or polypeptide that is directed against a heterodimeric cytokine that comprises a p35 subunit (such as IL-12), wherein said construct, protein and/or polypeptide comprises said p35 sequence (one or more) and one or more further binding domains or binding units, and wherein at least one of said further binding domains or binding units is directed against a second subunit of the said heterodimeric cytokine different from p35 (such as p40 in IL-12);

- the use of an IL-27 sequence (as defined herein) in providing, constructing, and/or as part of a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that comprises said IL-27 sequence (one or more) and one or more further binding domains or binding units;
- the use of a nucleotide sequence and/or nucleic acid that encodes an IL-27 sequence (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that comprises said IL-27 sequence (one or more) and one or more further binding domains or binding units;
- the use of an IL-27 sequence (as defined herein) in providing, constructing, and/or as part of a biparatopic construct, protein and/or polypeptide that is directed against IL-27 and that comprises said IL-27 sequence (one or more) and at least one further binding domain or binding unit that is also directed against IL-27 (but to a different epitope or antigenic determinant of IL-27), and optionally one or more further binding domains or binding units;
- the use of a nucleotide sequence and/or nucleic acid that encodes a IL-27 sequence (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a biparatopic construct, protein and/or polypeptide that is directed against IL-27 and that comprises said IL-27 sequence (one or more) and at least one further binding domain or binding unit that is also directed against IL-27 (but to a different epitope or antigenic determinant of IL-27), and optionally one or more further binding domains or binding units;
- the use of an IL-27 sequence (as defined herein) in providing, constructing, and/or as part of a multispecific (and in particular, bispecific) construct, protein and/or polypeptide that is directed against IL-27, wherein said construct, protein and/or polypeptide comprises said IL-27 sequence (one or more) and one or more further

binding domains or binding units, and wherein at least one of said further binding domains or binding units is directed against a another subunit of IL-27 different from the subunit against which said IL-27 sequence is directed;

- the use of a nucleotide sequence and/or nucleic acid that encodes an IL-27 sequence (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a multispecific (and in particular, bispecific) construct, protein and/or polypeptide that is directed against IL-27, wherein said construct, protein and/or polypeptide comprises said IL-27 sequence (one or more) and one or more further binding domains or binding units, and wherein at least one of said further binding domains or binding units is directed against another subunit of IL-27 different from the subunit against which said IL-27 sequence is directed;
- the use of an IL-12RB1 sequence (as defined herein) in providing, constructing, and/or as part of a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that comprises said IL-12RB1 sequence (one or more) and one or more further binding domains or binding units;
- the use of a nucleotide sequence and/or nucleic acid that encodes an IL-12RB1 sequence (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that comprises said IL-12RB1 sequence (one or more) and one or more further binding domains or binding units;
- the use of an IL-12RB1 sequence (as defined herein) in providing, constructing, and/or as part of a biparatopic construct, protein and/or polypeptide that is directed against IL-12RB1 and/or against a receptor that comprises an IL-12Rb1 subunit (such as the cognate receptors for IL-12 and IL-23) and that comprises said IL-12RB1 sequence (one or more) and at least one further binding domain or binding unit that is also directed against IL-12RB1 (but to a different epitope or antigenic determinant of IL-12RB1), and optionally one or more further binding domains or binding units;
- the use of a nucleotide sequence and/or nucleic acid that encodes a IL-12RB1 sequence (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a biparatopic construct, protein and/or polypeptide that is directed against IL-12RB1 and/or against a receptor that comprises an IL-12Rb1 subunit (such as the cognate receptors for IL-12 and IL-23) and that comprises said IL-

12RB1 sequence (one or more) and at least one further binding domain or binding unit that is also directed against IL-12RB1 (but to a different epitope or antigenic determinant of IL-12RB1), and optionally one or more further binding domains or binding units;

- the use of an IL-12RB1 sequence (as defined herein) in providing, constructing, and/or as part of a multispecific (and in particular, bispecific) construct, protein and/or polypeptide that is directed against a heterodimeric receptor that comprises an IL-12RB1 subunit (such as the cognate receptors for IL-12 and IL-23), wherein said construct, protein and/or polypeptide comprises said IL-12RB1 sequence (one or more) and one or more further binding domains or binding units, and wherein at least one of said further binding domains or binding units are directed against another subunit of said heterodimeric receptor different from IL-12RB1;
- the use of a nucleotide sequence and/or nucleic acid that encodes an IL-12RB1 sequence (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a multispecific (and in particular, bispecific) construct, protein and/or polypeptide that is directed against a heterodimeric receptor that comprises an IL-12RB1 subunit (such as the cognate receptors for IL-12 and IL-23), wherein said construct, protein and/or polypeptide comprises said IL-12RB1 sequence (one or more) and one or more further binding domains or binding units, and wherein at least one of said further binding domains or binding units are directed against another subunit of said heterodimeric receptor different from IL-12RB1;
- the use of an IL-12RB2 sequence (as defined herein) in providing, constructing, and/or as part of a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that comprises said IL-12RB2 sequence (one or more) and one or more further binding domains or binding units;
- the use of a nucleotide sequence and/or nucleic acid that encodes an IL-12RB2 sequence (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that comprises said IL-12RB2 sequence (one or more) and one or more further binding domains or binding units;
- the use of an IL-12RB2 sequence (as defined herein) in providing, constructing, and/or as part of a biparatopic construct, protein and/or polypeptide that is directed against IL-

12RB2 and/or against a receptor that comprises an IL-12Rb2 subunit (such as the cognate receptor for IL-12) and that comprises said IL-12RB2 sequence (one or more) and at least one further binding domain or binding unit that is also directed against IL-12RB2 (but to a different epitope or antigenic determinant of IL-12RB2), and optionally one or more further binding domains or binding units;

- the use of a nucleotide sequence and/or nucleic acid that encodes a IL-12RB2 sequence (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a biparatopic construct, protein and/or polypeptide that is directed against IL-12RB2 and/or against a receptor that comprises an IL-12Rb2 subunit (such as the cognate receptor for IL-12) and that comprises said IL-12RB2 sequence (one or more) and at least one further binding domain or binding unit that is also directed against IL-12RB2 (but to a different epitope or antigenic determinant of IL-12RB2), and optionally one or more further binding domains or binding units;
- the use of an IL-12RB2 sequence (as defined herein) in providing, constructing, and/or as part of a multispecific (and in particular, bispecific) construct, protein and/or polypeptide that is directed against a heterodimeric receptor that comprises an IL-12RB2 subunit (such as the cognate receptor for IL-12), wherein said construct, protein and/or polypeptide comprises said IL-12RB2 sequence (one or more) and one or more further binding domains or binding units, and wherein at least one of said further binding domains or binding units are directed against another subunit of said heterodimeric receptor different from IL-12RB2;
- the use of a nucleotide sequence and/or nucleic acid that encodes an IL-12RB2 sequence (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a multispecific (and in particular, bispecific) construct, protein and/or polypeptide that is directed against a heterodimeric receptor that comprises an IL-12RB2 subunit (such as the cognate receptor for IL-12), wherein said construct, protein and/or polypeptide comprises said IL-12RB2 sequence (one or more) and one or more further binding domains or binding units, and wherein at least one of said further binding domains or binding units are directed against another subunit of said heterodimeric receptor different from IL-12RB2;
- the use of an IL-23R sequence (as defined herein) in providing, constructing, and/or as part of a multivalent, multispecific and/or multiparatopic construct, protein and/or

polypeptide that comprises said IL-23R sequence (one or more) and one or more further binding domains or binding units;

- the use of a nucleotide sequence and/or nucleic acid that encodes an IL-23R sequence (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that comprises said IL-23R sequence (one or more) and one or more further binding domains or binding units;
- the use of an IL-23R sequence (as defined herein) in providing, constructing, and/or as part of a biparatopic construct, protein and/or polypeptide that is directed against IL-23R and/or against a receptor that comprises an IL-23R subunit (such as the cognate receptor for IL-23) and that comprises said IL-23R sequence (one or more) and at least one further binding domain or binding unit that is also directed against IL-23R (but to a different epitope or antigenic determinant of IL-23R), and optionally one or more further binding domains or binding units;
- the use of a nucleotide sequence and/or nucleic acid that encodes a IL-23R sequence (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a biparatopic construct, protein and/or polypeptide that is directed against IL-23R and/or against a receptor that comprises an IL-23R subunit (such as the cognate receptor for IL-23) and that comprises said IL-23R sequence (one or more) and at least one further binding domain or binding unit that is also directed against IL-23R (but to a different epitope or antigenic determinant of IL-23R), and optionally one or more further binding domains or binding units;
- the use of an IL-23R sequence (as defined herein) in providing, constructing, and/or as part of a multispecific (and in particular, bispecific) construct, protein and/or polypeptide that is directed against a heterodimeric receptor that comprises an IL-23R subunit (such as the cognate receptor for IL-23), wherein said construct, protein and/or polypeptide comprises said IL-23R sequence (one or more) and one or more further binding domains or binding units, and wherein at least one of said further binding domains or binding units are directed against another subunit of said heterodimeric receptor different from IL-23R;
- the use of a nucleotide sequence and/or nucleic acid that encodes an IL-23R sequence (as defined herein) in providing, constructing, and/or as part of a nucleotide sequence

and/or nucleic acid that encodes a multispecific (and in particular, bispecific) construct, protein and/or polypeptide that is directed against a heterodimeric receptor that comprises an IL-23R subunit (such as the cognate receptor for IL-23), wherein said construct, protein and/or polypeptide comprises said IL-23R sequence (one or more) and one or more further binding domains or binding units, and wherein at least one of said further binding domains or binding units are directed against another subunit of said heterodimeric receptor different from IL-23R.

Where any of the above aspects/uses comprises the use of a nucleotide sequence and/or nucleic acid that encodes a monovalent amino acid sequence in in providing, constructing, and/or as part of a nucleotide sequence and/or nucleic acid that encodes a multivalent, multispecific and/or multiparatopic constructs (such as a biparatopic construct), said aspect/use optionally further comprises the use of the a nucleotide sequence and/or nucleic acid thus obtained in preparing (e.g. by suitable expression, as further described herein) the multivalent, multispecific and/or multiparatopic construct encoded by said nucleotide sequence and/or nucleic acid.

More generally, in one aspect of the invention, there is provided a ("multispecific", as defined herein) polypeptide construct that is directed against (as defined herein) a heterodimeric protein, polypeptide, ligand or receptor (or other "target") that comprises:

- at least a first subunit;

and

- at least a second subunit;

wherein said polypeptide construct at least comprises a first binding domain or binding unit that is directed against said first subunit and a second binding domain or binding unit that is directed against said second subunit.

In particular, in this aspect of the invention, there is provided a ("multispecific", as defined herein) polypeptide construct that is directed against (as defined herein) a first heterodimeric protein, polypeptide, ligand or receptor that comprises:

- at least a first subunit that is shared between said first heterodimeric protein, polypeptide, ligand or receptor and at least a second, different heterodimeric protein, polypeptide, ligand or receptor;

and

- at least a second subunit that is not shared between said first heterodimeric protein, polypeptide, ligand or receptor and said second, different heterodimeric protein, polypeptide, ligand or receptor;

wherein said polypeptide construct at least comprises a first binding domain or binding unit that is directed against said first (i.e. shared) subunit and a second binding domain or binding unit that is directed against said second (i.e. not shared) subunit.

In another aspect of the invention, there is provided a polypeptide construct that is directed against (as defined herein) a heterodimeric protein, polypeptide, ligand or receptor (or other "target") that comprises:

- at least a first subunit;

and

- at least a second subunit;

wherein said polypeptide construct is a (biparatopic - as defined herein) construct that at least comprises a first binding domain or binding unit that is directed against said first subunit and a second binding domain or binding unit different from said first binding domain or binding unit that is also directed against said first subunit, but against a different epitope, antigenic determinant or binding site on said first subunit.

In another aspect of the invention, there is provided a polypeptide construct that is directed against (as defined herein) a heterodimeric protein that is a ligand for a receptor and that comprises:

- at least a first subunit;

and

- at least a second subunit;

wherein said polypeptide construct is a (biparatopic - as defined herein) construct that at least comprises a first binding domain or binding unit that is directed against said first subunit and a second binding domain or binding unit different from said first binding domain or binding unit that is also directed against said first subunit, but against a different epitope, antigenic determinant or binding site on said first subunit. In particular, but without limitation, in such a (biparatopic) contruct, the first binding domain or binding unit may be such that it modulates (as defined herein), blocks, inhibits and/or neutralizes the binding of said heterodimeric protein to its (cognate) receptor, and the second binding domain or binding unit may be such that it essentially does not modulate (as defined herein), block,

inhibit and/or neutralize the binding of said heterodimeric protein to its (cognate) receptor (or visa versa).

In another aspect of the invention, there is provided a polypeptide construct that is directed against (as defined herein) a heterodimeric protein that is a ligand for a receptor and that comprises:

- at least a first subunit that is shared between said first heterodimeric protein, polypeptide, ligand or receptor and at least a second, different heterodimeric protein, polypeptide, ligand or receptor;

and

- at least a second subunit that is not shared between said first heterodimeric protein, polypeptide, ligand or receptor and said second, different heterodimeric protein, polypeptide, ligand or receptor;

wherein said polypeptide construct is a (biparatopic - as defined herein) construct that at least comprises a first binding domain or binding unit that is directed against said second (i.e. not shared) subunit and a second binding domain or binding unit different from said first binding domain or binding unit that is also directed against said second (i.e. not shared) subunit, but against a different epitope, antigenic determinant or binding site on said second subunit. In particular, but without limitation, in such a (biparatopic) contruct, the first binding domain or binding unit may be such that it modulates (as defined herein), blocks, inhibits and/or neutralizes the binding of said heterodimeric protein to its (cognate) receptor, and the second binding domain or binding unit may be such that it essentially does not modulate (as defined herein), block, inhibit and/or neutralize the binding of said heterodimeric protein to its (cognate) receptor (or visa versa).

In another aspect of the invention, there is provided a polypeptide construct that is directed against (as defined herein) a heterodimeric protein, polypeptide, ligand or receptor that comprises:

- at least a first subunit;

and

- at least a second subunit;

wherein said polypeptide construct is a (biparatopic - as defined herein) construct that at least comprises a first binding domain or binding unit that is directed against said first subunit and a second binding domain or binding unit different from said first binding domain

or binding unit that is also directed against said first subunit, but against a different epitope, antigenic determinant or binding site on said first subunit.

In the above multispecific (and in particular, bispecific) and multiparatopic (and in particular biparatopic) constructs, the first and second binding domain may be as generally described herein (for example, in terms of affinity, specificity etc. for the subunit against which they are directed) for the amino acid sequences of the invention in general. Also, as described herein for the amino acid sequences of the invention, the first, second and optionally further binding domains or binding units present in said constructs are preferably such that they form or are capable of forming (optionally after suitable folding) a single antigen binding domain or antigen binding unit, and may for example be amino acid sequences that comprise an immunoglobulin fold, amino acid sequences that are comprises of four framework regions and three CDR's, and may in particular be domain antibodies, single domain antibodies, VHH's, "dAb's" or Nanobodies (all as further described herein), or suitable fragments thereof.

Suitable heterodimeric "targets" for the above multispecific (and in particular, bispecific) and multiparatopic (and in particular biparatopic) constructs will be clear to the skilled person based on the disclosure herein; as will be the advantages of the use of the above constructs against such targets.

For example, but without limitation, the heterodimeric protein, polypeptide, ligand or receptor may be a heterodimeric protein that is a ligand for a heterodimeric receptor, and may in particular be a heterodimeric cytokine (for example, IL-12, IL-23, IL-27 or IL-35). Also, for example, the heterodimeric protein, polypeptide, ligand or receptor may be a heterodimeric ligand that is a receptor for a heterodimeric ligand, and may in particular be a receptor for a heterodimeric cytokine (for example, a receptor for IL-12, IL-23, IL-27 or IL-35).

In particular, according to the invention, said heterodimeric protein, ligand or polypeptide may be a heterodimeric cytokine or a (heterodimeric) receptor for a cytokine (and in particular for a heterodimeric cytokine).

Other uses and advantages of the above constructs will become clear to the skilled person based on the disclosure herein.

Some preferred, but non-limiting constructs of the invention are:

a) a construct comprising at least one p19+ sequence (as defined herein) and at least one p19- sequence (as defined herein);

b) a construct comprising at least one p19+ sequence (as defined herein) and at least one p40+ sequence (as defined herein);

c) a construct comprising at least one p19+ sequence (as defined herein) and at least one p40- sequence (as defined herein);

d) a construct comprising at least one p19- sequence (as defined herein) and at least one p40+ sequence (as defined herein);

e) a construct comprising at least one p35 sequence (as defined herein) and at least one p40+ sequence (as defined herein);

f) a construct comprising at least one p35 sequence (as defined herein) and at least one p40- sequence (as defined herein);

g) a construct comprising at least one p40+ sequence (as defined herein) and at least one p40- sequence (as defined herein);

h) a construct comprising at least two (the same or different) p19- sequences (as defined herein), that is such that it capable (for example, but without limitation, through steric interaction and/or courtesy of the linker(s) present therein) of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p19 subunit to its receptor, and in particular capable of are capable of modulating, neutralizing, blocking and/or inhibiting the binding of IL-23 to IL-23R (for example in the alpha-screen assay of Example 19 or 22)

i) a construct comprising at least two (the same or different) p40- sequences, that is such that it capable (for example, but without limitation, through steric interaction and/or courtesy of the linker(s) present therein) of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p40 subunit to its receptor, and in particular capable of are capable of modulating, neutralizing, blocking and/or inhibiting the binding of IL-23 to IL-23R (for example in the alpha-screen assay of Example 19 or 22) and/or of modulating, neutralizing, blocking and/or inhibiting the binding of IL-12 to its receptor (for example in the alpha-screen assay of Example 19 or 22);

j) a construct comprising at least one IL-12Rb1 sequence (as defined herein) and at least one IL-12Rb2 sequence (as defined herein);

k) a construct comprising at least one IL-12Rb1 sequence (as defined herein) and at least one IL-23R sequence (as defined herein);

and such constructs, nucleotide sequences encoding the same, formulations and preparations comprising the same, and their preparation and various uses (all as further described herein) form further aspects of the invention.

Examples of such constructs (and/or of amino acid sequences of the invention that can be used as binding domains and/or binding units to provide such constructs), as well as possible uses and advantages of the above constructs will become clear to the skilled person based on the disclosure herein. For example, and without limitation:

- the constructs referred to under a) above: (i) will be capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p19 subunit to its receptor, and in particular be capable of are capable of modulating, neutralizing, blocking and/or inhibiting the binding of IL-23 to IL-23R (for example in the alpha-screen assay of Example 19 or 22); and/or (ii) will generally be specific for (as defined herein) IL-23 compared to heterodimeric cytokines that do not comprise a p19 subunit (such as IL-12, IL-27 or IL-35); and/or (iii) will bind to p19 with greater avidity and specificity than the corresponding p19+ sequence (or another p19+ sequence) per se; and/or
- the constructs referred to under b), c) and d) above (i) will be capable of modulating, neutralizing, blocking and/or inhibiting the binding of IL-23 to the (cognate) receptor for IL-23 (for example in the alpha-screen assay of Example 19 or 22); and/or (ii) will generally be specific for (as defined herein) IL-23 compared to IL-12 (and are also expected to be specific for IL-23 compared to other heterodimeric cytokines that might comprise a p19 or p40 subunit); and/or (iii) bind to IL-23 with greater avidity and specificity than the corresponding p19+ sequence (or another p19+ sequence) per se; and/or (iv) generally be preferred over similar constructs comprising only p19-sequences and p40- sequences;
- the constructs referred to under e) and f) above: (i) will be capable of modulating, neutralizing, blocking and/or inhibiting the binding of IL-12 to the (cognate) receptor for IL-12 (for example in the alpha-screen assay of Example 19 or 22) ; and/or (ii) will generally be specific for (as defined herein) IL-12 compared to IL-23 (and are also expected to be specific for IL-12 compared to other heterodimeric cytokines that might

comprise a p35 or p40 subunit); and/or (iii) bind to IL-12 with greater avidity and specificity than the corresponding p35 sequence (or another p35 sequence) per se;

- the constructs referred to under g) above: (i) will be capable of modulating, neutralizing, blocking and/or inhibiting both the binding of IL-23 to the (cognate) receptor for IL-23 for example in the alpha-screen assay of Example 19 or 22)) as well as binding of IL-12 to the (cognate) receptor for IL-12 (for example in the alpha-screen assay of Example 19 or 22); (ii) will bind to p40 with greater avidity and specificity than the corresponding p40+ sequence (or another p40+ sequence) per se
- the constructs referred to under h) above: (i) will be capable of modulating, neutralizing, blocking and/or inhibiting the binding of IL-23 to the (cognate) receptor for IL-23 (for example in the alpha-screen assay of Example 19 or 22); and/or (ii) will generally be specific for (as defined herein) IL-23 compared to heterodimeric cytokines that do not comprise a p19 subunit (such as IL-12, IL-27 or IL-35); and/or (iii) bind to IL-23 with greater avidity and specificity than each of the corresponding p19-sequences (or another monomeric p19- sequence or p19+ sequence) per se;
- the constructs referred to under i) above: (i) will be capable of modulating, neutralizing, blocking and/or inhibiting both the binding of IL-23 to the (cognate) receptor for IL-23 (for example in the alpha-screen assay of Example 19 or 22) as well as binding of IL-12 to the (cognate) receptor for IL-12 (for example in the alpha-screen assay of Example 19 or 22); and (ii) bind to p40 with greater avidity and specificity than each of the corresponding p40- sequences (or another monomeric p40- sequences or p40+ sequence) per se;
- the construct referred to under j) above: (i) will be specific for the cognate receptor for IL-12 compared to the cognate receptor for IL-23; and (ii) will bind to the cognate receptor for IL-12 with greater avidity and specificity compared to a monomeric IL-12Rb2 sequence;
- the construct referred to under k) above: (i) will be specific for the cognate receptor for IL-23 compared to the cognate receptor for IL-12; and (ii) will bind to the cognate receptor for IL-23 with greater avidity and specificity compared to a monomeric IL-23R sequence;

Also, as further described herein, a construct as referred to under j) above: (i) may act as an agonist for the signalling that is mediated by the cognate receptor for IL-12 (in which

case, the construct is expected to be specific for the signalling that is mediated by the cognate receptor for IL-12 compared to the signalling that is mediated by the cognate receptor for IL-23 mediated signalling, or may essentially not even be capable of acting as agonist for the signalling that is mediated by the cognate receptor for IL-23); and/or (ii) may be capable of modulating, neutralizing, blocking and/or inhibiting the binding of a IL-12 to its cognate receptor and/or may otherwise be capable of preventing, modulating, neutralizing, blocking and/or inhibiting the receptor-mediated signalling that, without the presence of said construct, would be triggered by binding of IL-12 to its cognate receptor (i.e. act as an antagonist for IL-12 and/or for the signalling that is mediated by the cognate receptor for IL-12), and as such be specific for the cognate receptor for IL-12 compared to the cognate receptor for IL-23 (and/or bind with higher avidity and/or specificity to the cognate receptor for IL-12 compared to the cognate receptor for IL-23).

Similarly, as further described herein, a construct as referred to under k) above: (i) may act as an agonist for the signalling that is mediated by the cognate receptor for IL-23 (in which case, the construct is expected to be specific for the signalling that is mediated by the cognate receptor for IL-23 compared to the signalling that is mediated by the cognate receptor for IL-12 mediated signalling, or may essentially not even be capable of acting as agonist for the signalling that is mediated by the cognate receptor for IL-12); and/or (ii) may be capable of modulating, neutralizing, blocking and/or inhibiting the binding of a IL-23 to its cognate receptor and/or may otherwise be capable of preventing, modulating, neutralizing, blocking and/or inhibiting the receptor-mediated signalling that, without the presence of said construct, would be triggered by binding of IL-23 to its cognate receptor (i.e. act as an antagonist for IL-23 and/or for the signalling that is mediated by the cognate receptor for IL-23), and as such be specific for the cognate receptor for IL-23 compared to the cognate receptor for IL-12 (and/or bind with higher avidity and/or specificity to the cognate receptor for IL-23 compared to the cognate receptor for IL-12).

Other applications and uses of the amino acid sequences and polypeptides of the invention will become clear to the skilled person from the further disclosure herein.

Generally, it is an object of the invention to provide pharmacologically active agents, as well as compositions comprising the same, that can be used in the diagnosis, prevention and/or treatment of diseases and disorders associated with heterodimeric cytokines and their

receptors and of the further diseases and disorders mentioned herein; and to provide methods for the diagnosis, prevention and/or treatment of such diseases and disorders that involve the administration and/or use of such agents and compositions.

In particular, it is an object of the invention to provide such pharmacologically active agents, compositions and/or methods that have certain advantages compared to the agents, compositions and/or methods that are currently used and/or known in the art. These advantages will become clear from the further description below.

More in particular, it is an object of the invention to provide therapeutic proteins that can be used as pharmacologically active agents, as well as compositions comprising the same, for the diagnosis, prevention and/or treatment of diseases and disorders associated with heterodimeric cytokines and their receptors and of the further diseases and disorders mentioned herein; and to provide methods for the diagnosis, prevention and/or treatment of such diseases and disorders that involve the administration and/or the use of such therapeutic proteins and compositions.

Accordingly, it is a specific object of the present invention to provide amino acid sequences that are directed against (as defined herein) heterodimeric cytokines and/or their receptors, in particular against heterodimeric cytokines and/or their receptors from a warm-blooded animal, more in particular against heterodimeric cytokines and/or their receptors from a mammal, and especially against human heterodimeric cytokines and/or their receptors; and to provide proteins and polypeptides comprising or essentially consisting of at least one such amino acid sequence.

In particular, it is a specific object of the present invention to provide such amino acid sequences and such proteins and/or polypeptides that are suitable for prophylactic, therapeutic and/or diagnostic use in a warm-blooded animal, and in particular in a mammal, and more in particular in a human being.

More in particular, it is a specific object of the present invention to provide such amino acid sequences and such proteins and/or polypeptides that can be used for the prevention, treatment, alleviation and/or diagnosis of one or more diseases, disorders or conditions associated with heterodimeric cytokines and/or their receptors and/or mediated by heterodimeric cytokines and/or their receptors (such as the diseases, disorders and conditions mentioned herein) in a warm-blooded animal, in particular in a mammal, and more in particular in a human being.

It is also a specific object of the invention to provide such amino acid sequences and such proteins and/or polypeptides that can be used in the preparation of pharmaceutical or veterinary compositions for the prevention and/or treatment of one or more diseases, disorders or conditions associated with and/or mediated by heterodimeric cytokines and/or their receptors (such as the diseases, disorders and conditions mentioned herein) in a warm-blooded animal, in particular in a mammal, and more in particular in a human being.

In the invention, generally, these objects are achieved by the use of the amino acid sequences, proteins, polypeptides and compositions that are described herein.

In general, the invention provides amino acid sequences that are directed against (as defined herein) and/or can specifically bind (as defined herein) to heterodimeric cytokines and/or their receptors; as well as compounds and constructs, and in particular proteins and polypeptides, that comprise at least one such amino acid sequence. Said amino acid sequence preferably form and/or essentially consist of a single (antigen) binding domain or binding unit, and/or are capable of forming and/or of functioning as a single (antigen) binding domain or binding unit (optionally after suitable folding), either as such and/or as part of a protein or polypeptide of the invention as further described herein.

More in particular, the invention provides amino acid sequences (such as the p19+ sequences, p19- sequences, p40+ sequences, p40- sequences, p35 sequences, IL-27 sequences, IL-12Rb1 sequences, IL-12Rb2 sequences and IL-23 sequences described herein) that can bind to heterodimeric cytokines and/or their receptors with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value, as further described herein) that is as defined herein; as well as compounds and constructs, and in particular proteins and polypeptides, that comprise at least one such amino acid sequence.

In particular, the amino acid sequences and polypeptides of the invention are preferably such that they:

- bind to heterodimeric cytokines and/or their receptors with a dissociation constant (K_D) of 10^{-5} to 10^{-12} moles/liter or less, and preferably 10^{-7} to 10^{-12} moles/liter or less and more preferably 10^{-8} to 10^{-12} moles/liter (i.e. with an association constant (K_A) of 10^{5} to 10^{12} liter/ moles or more, and preferably 10^{7} to 10^{12} liter/moles or more and more preferably 10^{8} to 10^{12} liter/moles);

and/or such that they:

- bind to heterodimeric cytokines and/or their receptors with a k_{on}-rate of between 10^2 $M^{-1}s^{-1}$ to about 10^7 $M^{-1}s^{-1}$, preferably between 10^3 $M^{-1}s^{-1}$ and 10^7 $M^{-1}s^{-1}$, more preferably between 10^4 $M^{-1}s^{-1}$ and 10^7 $M^{-1}s^{-1}$, such as between 10^5 $M^{-1}s^{-1}$ and 10^7 $M^{-1}s^{-1}$;

and/or such that they:

- bind to heterodimeric cytokines and/or their receptors with a k_{off} rate between $1s^{-1}$ ($t_{1/2}$=0.69 s) and 10^{-6} s^{-1} (providing a near irreversible complex with a $t_{1/2}$ of multiple days), preferably between 10^{-2} s^{-1} and 10^{-6} s^{-1}, more preferably between 10^{-3} s^{-1} and 10^{-6} s^{-1}, such as between 10^{-4} s^{-1} and 10^{-6} s^{-1}.

Preferably, a monovalent amino acid sequence of the invention (or a polypeptide that essentially contains only one amino acid sequence of the invention) is preferably such that it will bind to heterodimeric cytokines and/or their receptors with an affinity less than 500 nM, preferably less than 200 nM, more preferably less than 10 nM, such as less than 500 pM.

Some preferred IC50 values for binding of the amino acid sequences or polypeptides of the invention to heterodimeric cytokines and/or their receptors will become clear from the further description and examples herein.

For binding to heterodimeric cytokines and/or their receptors, an amino acid sequence of the invention will usually contain within its amino acid sequence one or more amino acid residues or one or more stretches of amino acid residues (i.e. with each "stretch" comprising two or amino acid residues that are adjacent to each other or in close proximity to each other, i.e. in the primary or tertiary structure of the amino acid sequence) via which the amino acid sequence of the invention can bind to heterodimeric cytokines and/or their receptors, which amino acid residues or stretches of amino acid residues thus form the "site" for binding to heterodimeric cytokines and/or their receptors (also referred to herein as the "*antigen binding site*").

The amino acid sequences provided by the invention are preferably in essentially isolated form (as defined herein), or form part of a protein or polypeptide of the invention (as defined herein), which may comprise or essentially consist of one or more amino acid sequences of the invention and which may optionally further comprise one or more further amino acid sequences (all optionally linked via one or more suitable linkers). For example, and without limitation, the one or more amino acid sequences of the invention may be used as a binding unit in such a protein or polypeptide, which may optionally contain one or more further amino acid sequences that can serve as a binding unit (i.e. against one or more other

targets than heterodimeric cytokines and/or their receptors), so as to provide a monovalent, multivalent or multispecific polypeptide of the invention, respectively, all as described herein. Such a protein or polypeptide may also be in essentially isolated form (as defined herein).

The amino acid sequences (such as the p19+ sequences, p19- sequences, p40+ sequences, p40- sequences, p35 sequences, IL-27 sequences, IL-12Rb1 sequences, IL-12Rb2 sequences and IL-23 sequences described herein) and polypeptides (such as the – for example multivalent, multispecific and/or biparatopic - constructs described herein that comprise at least one p19+ sequence, p19- sequence, p40+ sequence, p40- sequence, p35 sequence, IL-27 sequence, IL-12Rb1 sequence, IL-12Rb2 sequence and/or IL-23 sequence) of the invention as such preferably essentially consist of a single amino acid chain that is not linked via disulphide bridges to any other amino acid sequence or chain (but that may or may not contain one or more intramolecular disulphide bridges. For example, it is known that Nanobodies – as described herein - may sometimes contain a disulphide bridge between CDR3 and CDR1 or FR2). However, it should be noted that one or more amino acid sequences of the invention may be linked to each other and/or to other amino acid sequences (e.g. via disulphide bridges) to provide peptide constructs that may also be useful in the invention (for example Fab' fragments, $F(ab')_2$ fragments, ScFv constructs, "diabodies" and other multispecific constructs. Reference is for example made to the review by Holliger and Hudson, Nat Biotechnol. 2005 Sep;23(9):1126-36).

Generally, when an amino acid sequence of the invention (or a compound, construct or polypeptide comprising the same) is intended for administration to a subject (for example for therapeutic and/or diagnostic purposes as described herein), it is preferably either an amino acid sequence that does not occur naturally in said subject; or, when it does occur naturally in said subject, in essentially isolated form (as defined herein).

It will also be clear to the skilled person that for pharmaceutical use, the amino acid sequences of the invention (as well as compounds, constructs and polypeptides comprising the same) are preferably directed against human heterodimeric cytokines and/or their receptors; whereas for veterinary purposes, the amino acid sequences and polypeptides of the invention are preferably directed against heterodimeric cytokines and/or their receptors from the species to be treated, or at at least cross-reactive with heterodimeric cytokines and/or their receptors from the species to be treated.

Furthermore, an amino acid sequence of the invention may optionally, and in addition to the at least one binding site for binding against heterodimeric cytokines and/or their receptors, contain one or more further binding sites for binding against other antigens, proteins or targets.

The efficacy of the amino acid sequences and polypeptides of the invention, and of compositions comprising the same, can be tested using any suitable in vitro assay, cell-based assay, in vivo assay and/or animal model known per se, or any combination thereof, depending on the specific disease or disorder involved. Suitable assays and animal models will be clear to the skilled person, and for example include in vitro assays such as Biacore (see for example Example 12, 20 or 23), Alpha-screen (see for example Example 14, Example 20 or Example22), FLIPR, ELISA (see for example Example 10) and competitive ELISA (see for example Example 11), cell-based assays such as proliferation of activated PBMCs (for measuring modulation of IL-12 mediated signalling,) IL17 production of activated spleen cells (for measuring modulation of IL-23 mediated signalling, see for example Aggarwal, Journal of Biological Chemistry, 278, 3, 2003, 1910-1914); and assays for measuring differentiation of TH1 and/or inhibition of TH17 cells (for for measuring modulation of IL-23 mediated signalling), and various animal models for inflammatory diseases and disorders, such as models for autoimmune inflammation such as EAE (Experimental Allergic Encephalomyelitis), CIA (Collagen-induced arthritis), IL12-induced neopterin release, and mouse spleen IL17 production; IBD models in mice and rats such as Dextran Sulphate Salt induced Ulcerative Colitis and Dinitrofluorobenzene induced Crohn's disease, as well as the assays and animal models used in the experimental part below and in the prior art cited herein. Based on the disclosure herein, and depending on the heterodimeric cytokine(s) and/or receptor(s) involved, the skilled person will generally be able to select a suitable in vitro assay, cellular assay or animal model to test the amino acid sequences and polypeptides of the invention to a heterodimeric cytokine or a receptor thereof, for their capacity to modulate heterodimeric cytokines and their receptors, and/or the signaling, pathways, biological mechanisms and effects in which these are involved; and for their therapeutic and/or prophylactic effect in respect of one or more diseases and disorders that are associate with a heterodimeric cytokine and/or a receptors thereof.

Also, according to the invention, amino acid sequences and polypeptides that are directed against heterodimeric cytokines and/or their receptors from a first species of warm-

blooded animal may or may not show cross-reactivity with heterodimeric cytokines and/or their receptors from one or more other species of warm-blooded animal. For example, amino acid sequences and polypeptides directed against human heterodimeric cytokines and/or their receptors may or may not show cross reactivity with heterodimeric cytokines and/or their receptors from one or more other species of primates (such as, without limitation, monkeys from the genus *Macaca* (such as, and in particular, cynomologus monkeys (*Macaca fascicularis*) and/or rhesus monkeys (*Macaca mulatta*)) and baboon (*Papio ursinus*)) and/or with heterodimeric cytokines and/or their receptors from one or more species of animals that are often used in animal models for diseases (for example mouse, rat, rabbit, pig or dog), and in particular in animal models for diseases and disorders associated with heterodimeric cytokines and/or their receptors (such as the species and animal models mentioned herein). In this respect, it will be clear to the skilled person that such cross-reactivity, when present, may have advantages from a drug development point of view, since it allows the amino acid sequences and polypeptides against human heterodimeric cytokines and/or their receptors to be tested in such disease models.

More generally, amino acid sequences and polypeptides of the invention that are cross-reactive with heterodimeric cytokines and/or their receptors from multiple species of mammal will usually be advantageous for use in veterinary applications, since it will allow the same amino acid sequence or polypeptide to be used across multiple species. Thus, it is also encompassed within the scope of the invention that amino acid sequences and polypeptides directed against heterodimeric cytokines and/or their receptors from one species of animal (such as amino acid sequences and polypeptides against human heterodimeric cytokines and/or their receptors) can be used in the treatment of another species of animal, as long as the use of the amino acid sequences and/or polypeptides provide the desired effects in the species to be treated.

The present invention is in its broadest sense also not particularly limited to or defined by a specific antigenic determinant, epitope, part, domain, subunit or confirmation (where applicable) of heterodimeric cytokines and/or their receptors against which the amino acid sequences and polypeptides of the invention are directed. In one particular aspect of the invention, the amino acid sequences and polypeptides are (at least) directed against an interaction site (as defined herein) on the heterodimeric cytokine or the receptor.

As further described herein, a polypeptide of the invention may contain two or more amino acid sequences of the invention that are directed against their intended (cognate) cognate target (such as a heterodimeric cytokine, a receptor for the same, or a subunit of either). Generally, such polypeptides will bind to said said target with increased avidity compared to a single amino acid sequence of the invention. Such a polypeptide may for example comprise two amino acid sequences of the invention that are directed against the same antigenic determinant, epitope, part, domain, subunit or confirmation (where applicable) of said target (which may or may not be an interaction site); or comprise at least one "first" amino acid sequence of the invention that is directed against a first same antigenic determinant, epitope, part, domain, subunit or confirmation (where applicable) of said target (which may or may not be an interaction site); and at least one "second" amino acid sequence of the invention that is directed against a second antigenic determinant, epitope, part, domain, subunit or confirmation (where applicable) different from the first (and which again may or may not be an interaction site). Preferably, in such "biparatopic" polypeptides of the invention, at least one amino acid sequence of the invention is directed against an interaction site (as defined herein), although the invention in its broadest sense is not limited thereto.

Also, when the target is part of a binding pair (for example, a receptor-ligand binding pair), the amino acid sequences and polypeptides may be such that they compete with the cognate binding partner (e.g. the ligand, receptor or other binding partner, as applicable) for binding to the target, and/or such that they (fully or partially) neutralize binding of the binding partner to the target.

It is also within the scope of the invention that, where applicable, an amino acid sequence of the invention can bind to two or more antigenic determinants, epitopes, parts, domains, subunits or confirmations of heterodimeric cytokines and/or their receptors. In such a case, the antigenic determinants, epitopes, parts, domains or subunits of heterodimeric cytokines and/or their receptors to which the amino acid sequences and/or polypeptides of the invention bind may be essentially the same (for example, if heterodimeric cytokines and/or their receptors contains repeated structural motifs or occurs in a multimeric form) or may be different (and in the latter case, the amino acid sequences and polypeptides of the invention may bind to such different antigenic determinants, epitopes, parts, domains, subunits of heterodimeric cytokines and/or their receptors with an affinity and/or specificity which may

be the same or different). Also, for example, when heterodimeric cytokines and/or their receptors exists in an activated conformation and in an inactive conformation, the amino acid sequences and polypeptides of the invention may bind to either one of these confirmation, or may bind to both these confirmations (i.e. with an affinity and/or specificity which may be the same or different). Also, for example, the amino acid sequences and polypeptides of the invention may bind to a conformation of heterodimeric cytokines and/or their receptors in which it is bound to a pertinent ligand, may bind to a conformation of heterodimeric cytokines and/or their receptors in which it not bound to a pertinent ligand, or may bind to both such conformations (again with an affinity and/or specificity which may be the same or different).

It is also expected that the amino acid sequences and polypeptides of the invention will generally bind to all naturally occurring or synthetic analogs, variants, mutants, alleles, parts and fragments of heterodimeric cytokines and/or their receptors; or at least to those analogs, variants, mutants, alleles, parts and fragments of heterodimeric cytokines and/or their receptors that contain one or more antigenic determinants or epitopes that are essentially the same as the antigenic determinant(s) or epitope(s) to which the amino acid sequences and polypeptides of the invention bind in heterodimeric cytokines and/or their receptors (e.g. in wild-type heterodimeric cytokines and/or their receptors). Again, in such a case, the amino acid sequences and polypeptides of the invention may bind to such analogs, variants, mutants, alleles, parts and fragments with an affinity and/or specificity that are the same as, or that are different from (i.e. higher than or lower than), the affinity and specificity with which the amino acid sequences of the invention bind to (wild-type) heterodimeric cytokines and/or their receptors. It is also included within the scope of the invention that the amino acid sequences and polypeptides of the invention bind to some analogs, variants, mutants, alleles, parts and fragments of heterodimeric cytokines and/or their receptors, but not to others.

The amino acid sequences, polypeptides and compositions of the present invention can generally be used to modulate (as defined herein) the signalling that is mediated by heterodimeric cytokines and/or their receptors, to modulate (as defined herein) the biological pathways in which heterodimeric cytokines and/or their receptors are involved, and/or to modulate (as defined herein) the biological mechanisms, responses and effects associated with heterodimeric cytokines, their receptors, such signalling and/or these pathways (all the

foregoing is also collectively referred to herein as "*heterodimeric cytokine-mediated signalling*").

As such, the amino acid sequences, polypeptides and compositions of the present invention can generally be used to modulate the immune system and/or one or more specific immune responses in a subject to which one or more of the amino acid sequences, polypeptides and compositions of the present invention are administered (i.e. in therapeutically relevant amounts).

The term "heterodimeric cytokines" as used herein in its broadest sense generally includes any heterodimeric cytokine, i.e. a cytokine that comprises at least two, and more preferably only two, subunits.

In particular, the term "heterodimeric cytokine" as used herein encompasses heterodimeric cytokines that are associated with cell-mediated (T_H1) immunity, although the invention is its broadest sense is not limited thereto and also encompasses heterodimeric cytokines associated with humoral (T_H2) immunity.

According to one specific, but non-limiting aspect, the amino acid sequences and polypeptides of invention are directed against a heterodimeric cytokine that is chosen from heterodimeric cytokines that comprise a p40 subunit or p40-like subunit, such as a p40 subunit (present in for example IL-12 and IL-23) or Epstein-Barr virus (EBV)-induced molecule 3 (EBI3, present in for example IL-27 and IL-35).

According to another specific, but non-limiting aspect, the amino acid sequences and polypeptides of invention are directed against a heterodimeric cytokine that is chosen from heterodimeric cytokines that comprise a p19 subunit or a p19-like subunit, such as a p19 subunit (present in for example IL-23), a p35 subunit (present in for example IL-12 and IL-35), or a p28 subunit (present in for example IL-27) or a homolog thereof.

For example, the amino acid sequences and polypeptides of invention may be directed against a heterodimeric cytokine that will comprise at least one p19 subunit or p19-like subunit and at least one p40 subunit or p40-like subunit.

According to an even more specific, but non-limiting aspect, the amino acid sequences and polypeptides of invention are directed against a heterodimeric cytokine that is chosen from IL-12, IL-23, IL-27 and/or IL-35.

In one specific aspect, but non-limiting aspect, the amino acid sequences and polypeptides of the invention are directed against IL-23 (i.e. against p40, p19 or both). Such

amino acid sequences and polypeptides of the invention (as well as compositions comprising the same) may be as further described herein and can be used for preventing and treating disorders associated with IL-23, the IL-23 receptor and/or IL-23 mediated signalling. Reference is again made to the prior art cited above. Also, as mentioned herein, the amino acid sequences and polypeptides of the invention that are directed against IL-23, and in particular those that are specific for (as defined herein) IL-23 compared to IL-12, may have advantages for therapeutic use over the amino acid sequences and polypeptides of the invention that are directed against IL-12. Also, as mentioned herein, the amino acid sequences and polypeptides of the invention that are directed against p19, and in particular those that are specific for (as defined herein) p19 compared to p35 and p40, may have advantages for therapeutic use over the amino acid sequences and polypeptides of the invention that are directed against p35 or p40.

According to another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against at least one subunit of a heterodimeric cytokine (as defined herein). These amino acid sequences and/or polypeptides may be as further described herein.

In another specific, but non-limiting aspect, the invention provides "bispecific" (as defined herein) polypeptides that are directed against both subunits of a heterodimeric cytokine. These polypeptides may be as further described herein.

In another specific, but non-limiting aspect, the invention provides "biparatopic" (as defined herein) polypeptides that are directed against one subunit of a heterodimeric cytokine. These polypeptides may be as further described herein.

In particular, but without limitation, the invention provides amino acid sequences and polypeptides that are directed against at least one subunit of a heterodimeric cytokine, wherein said heterodimeric cytokine is associated with cell-mediated (T_H1) immunity.

For example, in one specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against at least one subunit of a heterodimeric cytokine, wherein said heterodimeric cytokine is chosen from heterodimeric cytokines that comprise a p40 subunit or p40-like subunit, such as a p40 subunit (present in for example IL-12 and IL-23) or Epstein-Barr virus (EBV)-induced molecule 3 (EBI3, present in for example IL-27 and IL-35).

In another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against a p40 subunit or a p40-like subunit, such as against one of the following subunits: p40 and/or EBI3, or a mutant, variant, allele or homolog of each of the foregoing.

In another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against at least one subunit of a heterodimeric cytokine, wherein said heterodimeric cytokine is chosen from heterodimeric cytokines that comprise a p19 subunit or p19-like subunit, such as a p19 subunit (present in for example IL-23), a p35 subunit (present in for example IL-12 and IL-35), a p28 subunit (present in for example IL-27), or a mutant, variant, allele or homolog of each of the foregoing. These amino acid sequences and/or polypeptides may be as further described herein.

In another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against a p19 subunit or p19-like subunit, such as against one of the following subunits: p19, p35 and/or p28, or a mutant, variant, allele or homolog of each of the foregoing. These amino acid sequences and/or polypeptides may be as further described herein.

In another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against at least one subunit of one of the following heterodimeric cytokines: IL-12, IL-23, IL-27 and/or IL-35. These amino acid sequences and/or polypeptides may be as further described herein.

In another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against IL-12 or at least one subunit of IL-12, which amino acid sequences and/or polypeptides may be as further described herein.

In another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against IL-23 or at least one subunit of IL-23, which amino acid sequences and/or polypeptides may be as further described herein.

In another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against IL-27 or at least one subunit of IL-27, which amino acid sequences and/or polypeptides may be as further described herein.

In another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against IL-35 or at least one subunit of IL-35, which amino acid sequences and/or polypeptides may be as further described herein.

For example, such a polypeptide against IL-12, IL-23, IL-27 or IL-35 may comprise or essentially consist of a single amino acid sequence of the invention (such as a Nanobody) that is directed against IL-12, IL-23, IL-27 or IL-35, respectively, and in particular against an interaction site (as defined herein) on IL-12, IL-23, IL-27 or IL-35. When such a polypeptide comprises two or more amino acid sequences of the invention (optionally linked to each other via one or more suitable linkers, as described herein) that are directed against IL-12, IL-23, IL-27 or IL-35 respectively, these amino acid sequences may be directed against the same epitope, antigenic determinant, part, domain or stretch of amino acid residues on IL-12, IL-23, IL-27 or IL-35, respectively, or against different epitopes, antigenic determinants, parts, domains or stretches of amino acid residues on IL-12, IL-23, IL-27 or IL-35. For example, such a polypeptide may comprise one or more amino acid sequences of the invention that are directed against an interaction site (as defined herein, and in particular the receptor binding site) on IL-12, IL-23, IL-27 or IL-35, respectively, and one or more amino acid sequences of the invention that are directed against a site, epitope, antigenic determinant, part, domain or stretch of amino acid residues on IL-12, IL-23, IL-27 or IL-35, respectively, that is not an interaction site. Such a polypeptide may also comprise one or more amino acid sequences of the invention that are directed against an interaction site (as defined herein, and in particular the receptor binding site) on IL-12, IL-23, IL-27 or IL-35, respectively, and one or more amino acid sequences that are directed against a different interaction site (as defined herein) on IL-12, IL-23, IL-27 or IL-35, respectively. It is also possible that such a polypeptide comprises two or more amino acid sequences of the invention that are directed against the same interaction site (as defined herein, and in particular the receptor binding site) on IL-12, IL-23, IL-27 or IL-35, respectively.

For example, such a polypeptide may comprise one or more amino acid sequences of the invention (such as one or more Nanobodies) that can modulate binding of IL-12, IL-23, IL-27 or IL-35, respectively, to its receptor; and/or one or more amino acid sequences of the invention (such as one or more Nanobodies) that do not modulate (and in particular inhibit) binding of IL-12, IL-23, IL-27 or IL-35, respectively, to its receptor. For example, such a polypeptide may comprise one amino acid sequence of the invention (such as a Nanobodies) that can modulate binding of IL-12, IL-23, IL-27 or IL-35, respectively, to its receptor and one amino acid sequence of the invention (such as a Nanobody) that does not modulate binding of IL-12, IL-23, IL-27 or IL-35, respectively, to its receptor.

Examples of such polypeptides of the invention will become clear from the further description herein.

In another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against p19 (also referred to herein as "p19 sequences"). Such amino acid sequences and/or polypeptides may be as further described herein (for example, such amino acid sequences may be may be "p19+ sequences" or "p19-sequences"). For example, such a polypeptide may be a polypeptide that contains one or more amino acid sequences against p19, such as one or more Nanobodies against p19. It is expected that such a polypeptide of the invention will be selective for IL-23 and other heterodimeric cytokines that contain p19 compared to IL-12, IL-27 and/or IL-35..

In another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against p35. Such amino acid sequences and/or polypeptides may be as further described herein. For example, such a polypeptide may be a polypeptide that contains one or more amino acid sequences against p35, such as one or more Nanobodies against p35. It is expected that such a polypeptide of the invention will be selective for IL-12 and/or IL-35 and other heterodimeric cytokines that contain p40 compared to IL-12 and/or IL-27.

In another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against p28. Such amino acid sequences and/or polypeptides may be as further described herein. For example, such a polypeptide may be a polypeptide that contains one or more amino acid sequences against p28, such as one or more Nanobodies against p28. It is expected that such a polypeptide of the invention will be selective for IL-27 and other heterodimeric cytokines that contain p28 compared to IL-12, IL-23 and/or IL-35.

In another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against p40. Such amino acid sequences and/or polypeptides may be as further described herein (for example, such amino acid sequences may be may be "p40+ sequences" or "p40-sequences"). For example, such a polypeptide may be a polypeptide that contains one or more amino acid sequences against p40, such as one or more Nanobodies against p40. It is expected that such a polypeptide of the invention will be selective for IL-12 and/or IL-23 and other heterodimeric cytokines that contain p40 compared to IL-27 and/or IL-35.

In another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against EBI3. Such amino acid sequences and/or polypeptides may be as further described herein. For example, such a polypeptide may be a polypeptide that contains one or more amino acid sequences against EBI3, such as one or more Nanobodies against EBI3. It is expected that such a polypeptide of the invention will be selective for IL-27 and/or IL-23 and other heterodimeric cytokines that contain EBI3 compared to IL-12 and/or IL-23.

For example, such a polypeptide against p19, p35, p28, p40 or EBI3, respectively, may comprise or essentially consist of a single amino acid sequence of the invention (such as a Nanobody) that is directed against p19, p35, p28, p40 or EBI3, respectively, and in particular against an interaction site (as defined herein) on p19, p35, p28, p40 or EBI3. When such a polypeptide comprises two or more amino acid sequences of the invention (optionally linked to each other via one or more suitable linkers, as described herein) that are directed against p19, p35, p28, p40 or EBI3, respectively, these amino acid sequences may be directed against the same epitope, antigenic determinant, part, domain or stretch of amino acid residues on p19, p35, p28, p40 or EBI3, respectively, or against different epitopes, antigenic determinants, parts, domains or stretches of amino acid residues on p19, p35, p28, p40 or EBI3. For example, such a polypeptide may comprise one or more amino acid sequences of the invention that are directed against an interaction site (as defined herein, and in particular a site that is involved in binding of the heterodimeric cytokine in which said subunit is present to its receptor) on p19, p35, p28, p40 or EBI3, respectively, and one or more amino acid sequences of the invention that are directed against a site, epitope, antigenic determinant, part, domain or stretch of amino acid residues on p19, p35, p28, p40 or EBI3, respectively, that is not an interaction site. Such a polypeptide may also comprise one or more amino acid sequences of the invention that are directed against an interaction site (as defined herein, and in particular the receptor binding site) on p19, p35, p28, p40 or EBI3, respectively, and one or more amino acid sequences that are directed against a different interaction site (as defined herein) on p19, p35, p28, p40 or EBI3, respectively. It is also possible that such a polypeptide comprises two or more amino acid sequences of the invention that are directed against the same interaction site (as defined herein, and in particular a site that is involved in binding of the heterodimeric cytokine in which said subunit is present to its receptor) on p19, p35, p28, p40 or EBI3, respectively.

For example, such a polypeptide may comprise one or more amino acid sequences of the invention (such as one or more Nanobodies) that are directed against p19, p35, p28, p40 or EBI3, respectively, and that can modulate (and in particular inhibit) binding of the heterodimeric cytokine in which said subunit is present to its receptor; and/or one or more amino acid sequences of the invention (such as one or more Nanobodies) that are directed against p19, p35, p28, p40 or EBI3, respectively, but that are not capable of modulate binding of the heterodimeric cytokine in which said subunit is present to its receptor.

Again, examples of such polypeptides of the invention will become clear from the further description herein.

In another specific, but non-limiting aspect, the invention provides amino acid sequences and (in particular) polypeptides that are directed against two different subunits that occur in heterodimeric cytokines. In particular, the invention provides amino acid sequences and (in particular) polypeptides that are directed against two different subunits that occur in heterodimeric cytokines (and in particular in heterodimeric cytokines from the IL-12 family, such as in IL-12, IL-23, IL-27 and IL-35). For example, such an amino acid sequence or polypeptide may be directed (a) against p19 or a p19-like subunit, such as against p19, p35 or p28; and against at least one other subunit that occurs in a heterodimeric cytokine (such as in IL-12, IL-23, IL-27 and IL-35); or (b) against p40 or a p40-like subunit, such as against p40 or EBI-3 and against at least one other subunit that occurs in a heterodimeric cytokine (such as in IL-12, IL-23, IL-27 and IL-35).

More in particular, the invention provides amino acid sequences and (in particular) polypeptides that are directed against (i) at least one p19 or p19-like subunit, such as against p19, p35 or p28; and (ii) at least one p40 or p40-like subunit, such as against p40 or EBI-3.

Such an amino acid sequence or polypeptide of the invention may for example also be an amino acid sequence or polypeptide of the invention that is directed towards the interface of two subunits that occur in a heterodimeric cytokine, such as towards the p19/p40 interface in IL-23, against the p35/p40 interface in IL-12, against the p28/EBI3 interface in IL-27, or against the p35/EBI3 interface in IL-35.

In a specifically preferred aspect, such a polypeptide of the invention may be a "bispecific" and in particular "biparatopic" polypeptide of the invention (as further described herein) that comprises at least one amino acid sequence of the invention (such as a Nanobody) that is directed against at least one p19 or p19-like subunit (such as against p19,

p35 or p28), and at least one amino acid sequence of the invention (such as a Nanobody) that is directed against at least one p40 or p40-like subunit (such as against p40 or EBI-3).

For example, the invention provides:

– amino acid sequences and (in particular) polypeptides that are directed against p19 and p40, which are expected to be selective for IL-23 compared to IL-12, IL-27 and IL-35. For example, such a biparatopic polypeptide may comprise at least one amino acid sequence of the invention that is directed against p19 and at least one amino acid sequence of the invention that is directed against p40;

– amino acid sequences and (in particular) polypeptides that are directed against p35 and p40, which are expected to be selective for IL-12 compared to IL-23, IL-27 and IL-35. For example, such a biparatopic polypeptide may comprise at least one amino acid sequence of the invention that is directed against p35 and at least one amino acid sequence of the invention that is directed against p40;

– amino acid sequences and (in particular) polypeptides that are directed against p35 and EBI3, which are expected to be selective for IL-35 compared to IL-12, IL-23 and IL-27. For example, such a biparatopic polypeptide may comprise at least one amino acid sequence of the invention that is directed against p35 and at least one amino acid sequence of the invention that is directed against EBI3;

– amino acid sequences and (in particular) polypeptides that are directed against p28 and EBI3, which are expected to be selective for IL-27 compared to IL-12, IL-23 and IL-35. For example, such a biparatopic polypeptide may comprise at least one amino acid sequence of the invention that is directed against p28 and at least one amino acid sequence of the invention that is directed against EBI3.

Again, all such amino acid sequences and/or polypeptides may be as further described herein, and some examples of such polypeptides of the invention will become clear from the further description herein.

For example, such a polypeptide may comprise:

– one or more amino acid sequences of the invention that are directed against an interaction site (as defined herein, and in particular a site that is involved in binding of the heterodimeric cytokine in which said subunit is present to its receptor) on the p19 or p19-like subunit; and one or more amino acid sequences of the invention that are

directed against a site, epitope, antigenic determinant, part, domain or stretch of amino acid residues on the p40 or p40-like subunit that is not an interaction site;

- one or more amino acid sequences of the invention that are directed against an interaction site (as defined herein, and in particular a site that is involved in binding of the heterodimeric cytokine in which said subunit is present to its receptor) on the p40 or p40-like subunit; and one or more amino acid sequences of the invention that are directed against a site, epitope, antigenic determinant, part, domain or stretch of amino acid residues on the p19 or p19-like subunit that is not an interaction site; or
- one or more amino acid sequences of the invention that are directed against an interaction site (as defined herein) on the p40 or p40-like subunit; and one or more amino acid sequences of the invention that are directed against an interaction site on the p19 or p19-like subunit;
- one or more amino acid sequences of the invention that are directed against the p19 or p19-like subunit and that can modulate (and in particular inhibit) binding of the heterodimeric cytokine in which said p19 or p19-like subunit is present to its receptor; and/or one or more amino acid sequences of the invention that are directed against the p40 or p40-like subunit but that are not capable of modulating binding of the heterodimeric cytokine in which said p40 or p40-like subunit is present to its receptor;
- one or more amino acid sequences of the invention that are directed against the p40 or p40-like subunit and that can modulate (and in particular inhibit) binding of the heterodimeric cytokine in which said p40 or p40-like subunit is present to its receptor; and/or one or more amino acid sequences of the invention that are directed against the p19 or p19-like subunit but that are not capable of modulating binding of the heterodimeric cytokine in which said p19 or p19-like subunit is present to its receptor;
- one or more amino acid sequences of the invention that are directed against the p19 or p19-like subunit and that can modulate (and in particular inhibit) binding of the heterodimeric cytokine in which said p19 or p19-like subunit is present to its receptor; and one or more amino acid sequences of the invention that are directed against the p40 or p40-like subunit and that can modulate (and in particular inhibit) binding of the heterodimeric cytokine in which said p40 or p40-like subunit is present to its receptor.

Again, all such amino acid sequences and/or polypeptides may be as further described herein, and some examples of such polypeptides of the invention will become clear from the further description herein.

Accordingly, in a specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against two or more subunits of heterodimeric cytokines. For example, the invention comprises multispecific proteins and polypeptides (as described herein) that comprise at least one binding unit against a first subunit of a heterodimeric cytokine and at least one binding unit against a second subunit of a heterodimeric cytokine that is different from said first subunit. For example, the invention comprises such multispecific proteins and polypeptides which comprise at least one binding unit against a first subunit of a heterodimeric cytokine and at least one binding unit against a second subunit of a heterodimeric cytokine that is different from said first subunit, in which said first and second subunit form part of the same heterodimeric cytokine (in other words, such multispecific proteins or polypeptides are "biparatopic" with respect to said heterodimeric cytokine, in that they are capable of binding to two different epitopes on said heterodimeric cytokine. Alternatively, and without limitation, a protein or polypeptide as described herein may for example be biparatopic in respect of one of the subunits mentioned herein, i.e. comprise at least one binding unit against a first epitope on said subunit and at least one binding unit against a second epitope on said subunit). Some non-limiting examples of such multispecific proteins and polypeptides are multispecific proteins and polypeptides that are directed against p35 and p40 (which are both present in IL-12, so that such a multivalent protein or polypeptide is expected to be specific for IL-12), against p19 and p40 (both present in IL-23), or against p28 and EBI3 (both present in IL-27).

More generally, the invention comprises such multispecific proteins and polypeptides which comprise at least one binding unit against a first subunit of a heterodimeric cytokine and at least one binding unit against a second subunit of a heterodimeric cytokine that is different from said first subunit, in which said first and second subunit are chosen from p19, p35, p28, p40 and/or EBI3; and/or mutants, variants, alleles or homologs of each of the foregoing. For example, such multispecific proteins and polypeptides may comprise at least one binding unit which is directed against a p19-like subunit such as p19, p35 or p 28 and at least one binding unit that is directed against a p40-like subunit such as p40 or EBI3 (it should also be noted that the invention even more generally relates to any multispecific

protein and polypeptide which comprises at least one binding unit that is directed against a heterodimeric cytokine or a subunit thereof – such as p19, p35, p28, p40 and/or EBI3 – and at least one further binding unit that is directed against any other (e.g. non-heterodimeric cytokine) desired target, antigenic determinant or epitope).

It will also be clear to the skilled person that an amino acid sequence or polypeptide as described herein may be directed against the interface between the two subunits that form a heterodimeric cytokine (usually the interface between a p19-like subunit and a p40-like subunit). Thus, such an amino acid sequence and polypeptide will often be able to (simultaneously) bind to both subunits that form the heterodimeric cytokine, so as to span the interface between said two subunits. For example, the amino acid sequences and polypeptides described herein may be directed against the p35/p40 interface of IL-12, against the p19/p40 interface of IL-23, or against the p28/EBI-3 interface of IL-28.

Thus, from the above, it will be clear to the skilled person that the amino acid sequences and polypeptides described herein may be directed against a single heterodimeric cytokine (or against a single subunit of a heterodimeric cytokine), but may also be directed against multiple heterodimeric cytokines (or against multiple subunits thereof, that either form part of the same heterodimeric cytokine or even of different heterodimeric cytokines).

In one specific, but non-limiting aspect, the amino acid sequences and polypeptides described herein are specific for (as defined herein) IL-23, compared to IL-12, IL-27 and IL-35.

In another specific, but non-limiting aspect, the amino acid sequences and polypeptides described herein are specific for (as defined herein) IL-12, compared to IL-23, IL-27 and IL-35.

In another specific, but non-limiting aspect, the amino acid sequences and polypeptides described herein are specific for (as defined herein) IL-27, compared to IL-12, IL-23 and IL-35.

In another specific, but non-limiting aspect, the amino acid sequences and polypeptides described herein are specific for (as defined herein) IL-35, compared to IL-12, IL-23 and IL-27.

In another specific, but non-limiting aspect, the amino acid sequences and polypeptides described herein are specific for (as defined herein) the p19 subunit, compared

to the p35 or p28 subunits. Such amino acid sequences and polypeptides are expected to be specific for IL-23 (i.e. compared to IL-12, IL-27 and IL-35).

In another specific, but non-limiting aspect, the amino acid sequences and polypeptides described herein are specific for (as defined herein) the p28 subunit, compared to the p35 or p19 subunits. Such amino acid sequences and polypeptides are expected to be specific for IL-27 (i.e. compared to IL-12, IL-23 and IL-35).

In another specific, but non-limiting aspect, the amino acid sequences and polypeptides described herein are specific for (as defined herein) the p35 subunit, compared to the p28 or p19 subunits. Such amino acid sequences and polypeptides are expected to be specific for IL-12 and IL-35 (i.e. compared to IL-23 and IL-27).

In another specific, but non-limiting aspect, the amino acid sequences and polypeptides described herein are specific for (as defined herein) the p40 subunit, compared to EBI-3. Such amino acid sequences and polypeptides are expected to be specific for IL-12 and IL-23 (i.e. compared to IL-27 and IL-35).

In another specific, but non-limiting aspect, the amino acid sequences and polypeptides described herein are specific for (as defined herein) the EBI-3 subunit, compared to the p40 subunit. Such amino acid sequences and polypeptides are expected to be specific for IL-27 and IL-35 (i.e. compared to IL-12 and IL-23).

In another specific, but non-limiting aspect, the amino acid sequences and polypeptides described herein are specific for both the p19 and p40 subunits (compared to other subunits), and in particular directed against (as defined herein, i.e. capable of specifically binding to) the p19 and p40 subunits, but not directed against (i.e. not capable of specifically binding to) any of the subunits p35, p28 and/or EBI3 (or, according to an even more specific aspect, not directed to any p19-like subunit other than p19 and not directed to any p40-like subunit other than p40). Such amino acid sequences (which may for example span the p19/p40 interface in IL-23 as described herein) or polypeptides (which may for example be bispecific polypeptides with at least one binding unit directed against p19 and at least one binding unit directed against p40) are expected to be specific for IL-23 compared to IL-27, and are expected to bind with higher avidity (and preferably also selectivity) to IL-23 compared to IL-12.

In another specific, but non-limiting aspect, the amino acid sequences and polypeptides described herein are specific for both the p35 and p40 subunits (compared to

other subunits), and in particular directed against (as defined herein, i.e. capable of specifically binding to) the p35 and p40 subunits, but not directed against (i.e. not capable of specifically binding to) any of the subunits p19, p28 and/or EBI3 (or, according to an even more specific aspect, not directed to any p19-like subunit other than p35 and not directed to any p40-like subunit other than p40). Such amino acid sequences (which may for example span the p35/p40 interface in IL-12 as described herein) or polypeptides (which may for example be bispecific polypeptides with at least one binding unit directed against p35 and at least one binding unit directed against p40) are expected to be specific for IL-12 compared to IL-27, and are expected to bind with higher avidity (and preferably also selectivity) to IL-12 compared to IL-23.

In another specific, but non-limiting aspect, the amino acid sequences and polypeptides described herein are specific for both the p28 and EBI-3 subunits (compared to other subunits), and in particular directed against (as defined herein, i.e. capable of specifically binding to) the p28 subunit and EBI-3, but not directed against (i.e. not capable of specifically binding to) any of the subunits p19, p35 and/or p40 (or, according to an even more specific aspect, not directed to any p19-like subunit other than p28 and not directed to any p40-like subunit other than EBI-3). Such amino acid sequences (which may for example span the p28/EBI-3 interface in IL-27 as described herein) or polypeptides (which may for example be bispecific polypeptides with at least one binding unit directed against p28 and at least one binding unit directed against EBI3) are expected to be specific for IL-27 compared to IL-12 and IL-23.

The invention also provides amino acid sequences and polypeptides that are directed against receptors for heterodimeric cytokines, in particular for receptors of the heterodimeric cytokines described herein.

More in particular, the invention provides amino acid sequences and polypeptides that are directed against receptors for heterodimeric cytokines, wherein said receptors are receptors for heterodimeric cytokines that are associated with cell-mediated (T_H1) immunity.

In one specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against receptors for heterodimeric cytokines, wherein said receptors are receptors for heterodimeric cytokines that contain one or more p19-like subunits, and/or that contain one or more p40-like subunits, and in particular contain one or

more of the following subunits: p19, p35, p28, p40 and/or EBI3; or a mutant, variant, allele or homolog of each of the foregoing.

In another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against receptors for heterodimeric cytokines, wherein said receptors are receptors for heterodimeric cytokines that at least contain the p19 subunit.

In another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against receptors for heterodimeric cytokines, wherein said receptors are receptors for heterodimeric cytokines that at least contain the p35 subunit.

In another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against receptors for heterodimeric cytokines, wherein said receptors are receptors for heterodimeric cytokines that at least contain the p28 subunit.

In another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against receptors for heterodimeric cytokines, wherein said receptors are receptors for heterodimeric cytokines that at least contain the p40 subunit.

In another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against receptors for heterodimeric cytokines, wherein said receptors are receptors for heterodimeric cytokines that at least contain EBI3.

In another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against a receptor for IL-12, IL-23, IL-27 and/or IL-35, respectively, and preferably against a high-affinity receptor for IL-12, IL-23, IL-27 and/or IL-35, respectively.

In another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against a receptor for IL-12, and preferably against a high-affinity receptor for IL-12, or against at least one subunit thereof. More preferably, such amino acid sequences and polypeptides are specific for (as defined herein) the (cognate) receptor of IL-12 compared the (cognate) receptor of IL-23R and/or the (cognate) receptor of IL-27.

In another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against a receptor for IL-23, and preferably against a high-affinity receptor for IL-23, or against at least one subunit thereof. More preferably, such amino acid sequences and polypeptides are specific for (as defined herein) the (cognate) receptor of IL-23 compared to the (cognate) receptor of IL-12 and/or the (cognate) receptor of IL-27.

In another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against a receptor for IL-27, and preferably against a high-affinity receptor for IL-27, or against at least one subunit thereof. More preferably, such amino acid sequences and polypeptides are specific for (as defined herein) the (cognate) receptor of IL-27 compared to the (cognate) receptor of IL-12 and the (cognate) receptor of IL-23.

In another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against a receptor for IL-35, and preferably against a high-affinity receptor for IL-35, or against at least one subunit thereof.

The above amino acid sequences and polypeptides may all be as further described herein.

In another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against at least one subunit of a receptor for IL-12, IL-23, IL-27 and/or IL-35, and that preferably are directed against a subunit of a high-affinity receptor for IL-12, IL-23, IL-27 and/or IL-35. Such amino acid sequences and polypeptides of the invention may for example be directed against a IL-23-like subunit of such a receptor, against a gp130-like subunit of such a receptor, or both (e.g. in the case of bispecific/biparatopic polypeptides of the invention).

Preferably, such amino acid sequences and polypeptides are directed against a IL-23-like subunit of such a receptor such as IL-12Rbeta-2, IL-23R and WSX-1 (with amino acid sequences and polypeptides against gp-130 like subunits such as the IL-12Rbeta-1 subunit or against gp130, although not excluded from the scope of the invention, being less preferred).

In another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against at least one subunit of a receptor for IL-12, preferably against a high-affinity receptor for IL-12. Preferably, said amino acid sequences and polypeptides are directed against the IL-12Rbeta-2 subunit. More preferably,

such amino acid sequences and polypeptides are specific for (as defined herein) the IL-12Rbeta-2 subunit compared to the IL-23R subunit and the WSX-1 subunit. It is expected that such amino acid sequences and polypeptides will be specific for the (cognate) receptor of IL-12 compared to the (cognate) receptor of IL-23 and/or the (cognate) receptor of IL-27.

In another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against at least one subunit of a receptor for IL-23, and preferably against a high-affinity receptor for IL-23. Preferably, said amino acid sequences and polypeptides are directed against the IL-23R subunit. More preferably, such amino acid sequences and polypeptides are specific for (as defined herein) the IL-23R subunit compared to the IL-12Rbeta-2 subunit and the WSX-1 subunit. It is expected that such amino acid sequences and polypeptides will be specific for the (cognate) receptor of IL-23 compared to the (cognate) receptor of IL-12 and/or the (cognate) receptor of IL-27.

In another specific, but non-limiting aspect, the invention provides amino acid sequences and polypeptides that are directed against at least one subunit of a receptor for IL-27, and preferably against a high-affinity receptor for IL-27. Preferably, said amino acid sequences and polypeptides are directed against the WSX-1 subunit. More preferably, such amino acid sequences and polypeptides are specific for (as defined herein) the WSX-1 subunit IL-23R subunit compared to the IL-12Rbeta-2 subunit and the IL-23R subunit. It is expected that such amino acid sequences and polypeptides will be specific for the (cognate) receptor of IL-27 compared to the (cognate) receptor of IL-12 and/or the (cognate) receptor of IL-23.

The above amino acid sequences and polypeptides may all be as further described herein.

The invention also provides amino acid sequences and polypeptides that are directed against IL-12Rbeta-1. Preferably, such amino acid sequences and polypeptides are specific for (as defined herein) IL-12Rbeta-1 compared to gp130.

The invention also provides amino acid sequences and polypeptides that are directed against gp130. Preferably, such amino acid sequences and polypeptides are specific for (as defined herein) gp130 compared to IL-12Rbeta-1.

These amino acid sequences and polypeptides may all be as further described herein.

In another specific, but non-limiting aspect, the invention provides bispecific polypeptides that are directed against a first subunit of a receptor for a heterodimeric

cytokine, and against a second subunit of a receptor for a heterodimeric cytokine different from said first subunit.

For example, such a bispecific polypeptide of the invention may comprise at least one amino acid sequence of the invention (such as a Nanobody) that is directed against a gp130-like subunit (such as the gp130 or IL-12beta-1 subunit, or variants, mutants, alleles or homologs thereof), and at least one amino acid sequence of the invention (such as a Nanobody) that is directed against an IL-23 like subunit (such as IL-12Rbeta-2, IL-23, or WSX-1). Preferably, such a bispecific polypeptide is such that it is directed against a gp130-like subunit and an IL-23 like subunit that form part of the same receptor. Such bispecific polypeptides may for example trigger, facilitate and/or enhance activation and/or association of the receptor (or more generally receptor-mediated signalling), for example by mimicking the effects of ligand binding; and thus act as an agonist for the receptor, its ligand and/or the relevant heterodimeric cytokine-mediated signalling (in this respect, it should also be noted that in another aspect, the invention comprises polypeptides of the invention that comprise one or more, such as two, three or four, amino acid sequences of the invention that are directed against a single cytokine receptor chain so as to induce dimerisation or oligomerization and leading to activation of the receptor).

Alternatively, such bispecific polypeptides may for example block, inhibit or reduce binding of the ligand to the receptor, or block, inhibit or reduce activation and/or association of the receptor after binding of the ligand, and/or more generally act as an agonist for the receptor, its ligand and/or the relevant heterodimeric cytokine-mediated signalling

For example, the invention provides:

- amino acid sequences and (in particular) polypeptides that are directed against IL12Rbeta1 and IL12Rbeta2, which are expected to be (and preferably are) selective for the IL-12 receptor compared to the IL-23 receptor and the IL-27 receptor. For example, such a biparatopic polypeptide may comprise at least one amino acid sequence of the invention that is directed against IL12Rbeta1 and at least one amino acid sequence of the invention that is directed against IL12Rbeta2;
- amino acid sequences and (in particular) polypeptides that are directed against IL12Rbeta1 and IL23R, which are expected to be (and preferably are) selective for the IL-23 receptor compared to the IL-12 receptor and the IL-27 receptor. For example,

such a biparatopic polypeptide may comprise at least one amino acid sequence of the invention that is directed against IL12Rbeta1 and at least one amino acid sequence of the invention that is directed against IL23R;

– amino acid sequences and (in particular) polypeptides that are directed against WSX-1 and gp130, which are expected to be (and preferably are) selective for the IL-27 receptor compared to the IL-12 receptor and the IL-23 receptor. For example, such a biparatopic polypeptide may comprise at least one amino acid sequence of the invention that is directed against WSX-1 and at least one amino acid sequence of the invention that is directed against gp130.

Again, such amino acid sequences and polypeptides may all be as further described herein.

In another non-limiting aspect of the invention, a polypeptide of the invention may be a bispecific polypeptide that comprises at least one amino acid sequence of the invention that is directed against a heterodimeric cytokine (or against at least one subunit thereof), and at least one amino acid sequence of the invention that is directed against a receptor for a heterodimeric cytokine (or against at least one subunit thereof). In particular, in this aspect of the invention, a polypeptide of the invention may comprise at least amino acid sequence of the invention that is directed against a heterodimeric cytokine (or at least one subunit thereof), and at least one amino acid sequence of the invention that is directed against a receptor for said heterodimeric cytokine (or at least one subunit thereof), i.e. against the cognate receptor for said heterodimeric cytokine.

It is expected that such bispecific polypeptides may act as agonists of heterodimeric cytokines, their receptors, and heterodimeric cytokine-mediated signalling, i.e. by promoting or facilitating binding of the heterodimeric cytokine to its receptor, and/or by stabilizing the ligand/receptor complex upon binding of the heterodimeric cytokine to its receptor. For this purpose, such bispecific polypeptides preferably comprise amino acid sequences that do not neutralize binding of the heterodimeric cytokine to the receptor.

Depending on the amino acid sequences that are chosen to form the construct, it is further expected that such bispecific polypeptides may also be designed to act as an antagonists, i.e. link the cytokine to the receptor without activating it, act as a dominant negative regulator since the receptor is then occupied and inactive).

Bispecific polypeptides as described herein can also be linked to a Fc portion as described in Applicant's copending application entitled "Immunoglobulin constructs", which has the same filing date as this application, December 4, 2007.

Also, a bispecific polypeptide that is directed against a heterodimeric cytokine and against a receptor that is not the cognate receptor for said heterodimeric cytokine, may also be used to modulate the signalling that is mediated by the cytokine against which it is directed and (in particular) by the receptor against which it is directed. For example, a bispecific anti-IL12p35 and anti-IL23R polypeptide of the invention could link IL12 to the IL23 receptor and trigger a IL23 signal.

For example, the above bispecific polypeptides may comprise:

- at least one amino acid sequence of the invention that is directed against IL-12 (or at least one subunit thereof, and preferably the p35 subunit), and at least one amino acid sequence of the invention that that is directed against the receptor for IL-12 (or at least one subunit thereof, and preferably the IL-12Rbeta-2 subunit).
- at least one amino acid sequence of the invention that that is directed against IL-23 (or at least one subunit thereof, and preferably the p19 subunit), and at least one amino acid sequence of the invention that that is directed against the receptor for IL-23 (or at least one subunit thereof, and preferably the IL-23 subunit); or
- at least one amino acid sequence of the invention that that is directed against IL-27 (or at least one subunit thereof, and preferably the p28 subunit), and at least one amino acid sequence of the invention that that is directed against the receptor for IL-27 (or at least one subunit thereof, and preferably the WSX-1 subunit).

Again, such amino acid sequences and polypeptides may all be as further described herein.

When an amino acid sequence or polypeptide of the invention is directed against a heterodimeric cytokine, it may modulate (as defined herein) heterodimeric cytokine-mediated signalling (as defined herein) in several different ways. For example, and although the invention in its broadest sense is not limited to any specific explanation, hypothesis or mechanism, it may be that such an amino acid sequence or polypeptide, upon binding to the heterodimeric cytokine (or to at least one subunit thereof):

- prevents, reduces or inhibits (in part or in full) binding of said heterodimeric cytokine to its receptor (or to at least one subunit thereof);
- prevents, reduces, inhibits the association (i.e. the heterodimerization) of the heterodimeric cytokine (e.g. of its subunits);
- destabilizes the heterodimeric cytokine or otherwise influences the conformation of the heterodimeric cytokine or prevents or reduces the ability of the heterodimeric cytokine to change its confirmation, in particular so as to fully or partially reduce its ability to bind to its receptor (or to at least one subunit thereof) or, upon binding to its receptor, to trigger receptor-mediated signalling;
- still allows the heterodimeric cytokine to bind to its receptor (or to at least one subunit thereof), but upon such binding prevents, reduces, inhibits (in part or in full) the activation and/or dimerization of the receptor (i.e. where the receptor associates upon ligand binding, as is for example the case for the IL-23 receptor, see Parham et al., supra) ;
- or otherwise prevents, reduces or inhibits the signalling that is caused by binding of the heterodimeric cytokine to its receptor

Thus, according to one non-limiting aspect, an amino acid sequence or polypeptide of the invention that is directed against a heterodimeric cytokine (and that may further be as described herein) is such that, upon binding to the heterodimeric cytokine, it prevents, reduces or inhibits binding of said heterodimeric cytokine to its receptor or to at least one subunit thereof (i.e. compared to the binding of the heterodimeric cytokine to the same receptor without the presence of the amino acid sequence or polypeptide, and by at least 1%, such as by at least 5%, for example by at least 10%, at least 30%, at least 50%, at least 70% and up to 90% or more, as determined by a suitable assay, such as one of the assays mentioned herein and/or used in the Experimental Part).

According to another non-limiting aspect, an amino acid sequence or polypeptide of the invention that is directed against a heterodimeric cytokine (and that may further be as described herein) is such that, upon binding to the heterodimeric cytokine and following binding of the heterodimeric cytokine to its receptor (or to at least one subunit of the receptor), it prevents, reduces or inhibits activation and/or association of its receptor (i.e. compared to the association of the receptor mediated by the heterodimeric cytokine without

the presence of the amino acid sequence or polypeptide, and by at least 1%, such as by at least 5%, for example by at least 10%, at least 30%, at least 50%, at least 70% and up to 90% or more, as determined by a suitable assay, such as one of the assays mentioned herein and/or used in the Experimental Part).

According to another non-limiting aspect, an amino acid sequence or polypeptide of the invention that is directed against a heterodimeric cytokine (and that may further be as described herein) is such that, upon binding to the heterodimeric cytokine, it prevents, reduces or inhibits the signalling of the receptor that is triggered by the heterodimeric cytokine-mediated association of the receptor (i.e. compared to the signalling following heterodimeric cytokine-mediated association of the receptor without the presence of the amino acid sequence or polypeptide, and by at least 1%, such as by at least 5%, for example by at least 10%, at least 30%, at least 50%, at least 70% and up to 90% or more, as determined by a suitable assay, such as one of the assays mentioned herein and/or used in the Experimental Part).

Generally, according to a preferred aspect, an amino acid sequence or polypeptide of the invention that is directed against a heterodimeric cytokine (and that may further be as described herein) is such that, upon binding to the heterodimeric cytokine, it prevents, reduces or inhibits the heterodimeric cytokine-mediated signalling (as defined herein) associated with said heterodimeric cytokine and/or with its receptor (i.e. compared to the heterodimeric cytokine-mediated signalling mediated by the heterodimeric cytokines without the presence of the amino acid sequence or polypeptide, and by at least 1%, such as by at least 5%, for example by at least 10%, at least 30%, at least 50%, at least 70% and up to 90% or more, as determined by a suitable assay, such as one of the assays mentioned herein and/or used in the Experimental Part).

Again, such amino acid sequences and polypeptides may all be as further described herein.

When an amino acid sequence (such as the p19+ sequences, p19- sequences, p40+ sequences, p40- sequences, p35 sequences, IL-27 sequences, IL-12Rb1 sequences, IL-12Rb2 sequences and IL-23 sequences described herein) or polypeptide (such as the – for example multivalent, multispecific and/or biparatopic - constructs described herein that comprise at least one p19+ sequence, p19- sequence, p40+ sequence, p40- sequence, p35 sequence, IL-27 sequence, IL-12Rb1 sequence, IL-12Rb2 sequence and/or IL-23 sequence) of the invention

is directed against a receptor for a heterodimeric cytokine, it may modulate (as defined herein) heterodimeric cytokine-mediated signalling (as defined herein) in several different ways. For example, and although the invention in its broadest sense is not limited to any specific explanation, hypothesis or mechanism, it may be that such an amino acid sequence or polypeptide, upon binding to the receptor (or to at least one subunit thereof):

- prevents, reduces or inhibits (in part or in full) binding of the ligand (i.e. of the heterodimeric cytokine that is the ligand of the receptor) to the receptor (or to at least one subunit thereof);
- still allows the ligand to bind to the receptor, but prevents, reduces or inhibits the signalling that would normally be triggered by binding of the ligand to the receptor (for example, and without limitation, influencing the conformation of the receptor or by reducing the ability of the receptor to change its confirmation)
- prevents, reduces, inhibits the activation and/orassociation (e.g. dimerization) of the receptor (e.g. of its subunits), and in particular the association of the receptor that is triggered by binding of the ligand (i.e. of the heterodimeric cytokine that is the ligand of the receptor) to the receptor (or to at least one subunit thereof), as is for example the case for the the IL-23 receptor, see Parham et al., supra;
- still allows ligand-mediated association (e.g. dimerization) of the receptor, but prevents, reduces or inhibits the signalling that would normally be triggered by such association (for example, and without limitation, influencing the conformation of the associated receptor or by reducing the ability of the associated receptor to change its confirmation) or otherwise prevents, reduces or inhibits the signalling that is caused by binding of the heterodimeric cytokine to its receptor or by ligand-mediated association of the receptor.

Thus, according to one non-limiting aspect, an amino acid sequence or polypeptide of the invention that is directed against a receptor for a heterodimeric cytokine (and that may further be as described herein) is such that, upon binding to the receptor (e.g. to at least one subunit thereof), it prevents, reduces or inhibits binding of its ligand to said receptor or to at least one subunit thereof (i.e. compared to the binding of the ligand to said receptor without the presence of the amino acid sequence or polypeptide, and by at least 1%, such as by at least 5%, for example by at least 10%, at least 30%, at least 50%, at least 70% and up to 90%

or more, as determined by a suitable assay, such as one of the assays mentioned herein and/or used in the Experimental Part).

According to one non-limiting aspect, an amino acid sequence or polypeptide of the invention that is directed against a receptor for a heterodimeric cytokine (and that may further be as described herein) is such that, upon binding to the receptor (e.g. to at least one subunit thereof), allows the ligand to bind to the receptor, but prevents, reduces or inhibits the signalling that is (or normally would be) triggered by binding of the ligand to the receptor or to at least one subunit thereof (i.e. compared to the signalling upon binding of the ligand to said receptor without the presence of the amino acid sequence or polypeptide, and by at least 1%, such as by at least 5%, for example by at least 10%, at least 30%, at least 50%, at least 70% and up to 90% or more, as determined by a suitable assay, such as one of the assays mentioned herein and/or used in the Experimental Part).

According to another non-limiting aspect, an amino acid sequence or polypeptide of the invention that is directed against a receptor for a heterodimeric cytokine (and that may further be as described herein) is such that, upon binding to the receptor (or to at least one subunit thereof), it prevents, reduces or inhibits activation and/or association of the receptor, and in particular ligand-mediated association of the receptor (i.e. compared to the ligand-mediated association of the receptor without the presence of the amino acid sequence or polypeptide, and by at least 1%, such as by at least 5%, for example by at least 10%, at least 30%, at least 50%, at least 70% and up to 90% or more, as determined by a suitable assay, such as one of the assays mentioned herein and/or used in the Experimental Part).

According to another non-limiting aspect, an amino acid sequence or polypeptide of the invention that is directed against a receptor for a heterodimeric cytokine (and that may further be as described herein) is such that, upon binding to the receptor, it prevents, reduces or inhibits the signalling that is triggered by ligand-mediated association of the receptor (i.e. compared to the signalling following binding of the ligand to the receptor without the presence of the amino acid sequence or polypeptide, and by at least 1%, such as by at least 5%, for example by at least 10%, at least 30%, at least 50%, at least 70% and up to 90% or more, as determined by a suitable assay, such as one of the assays mentioned herein and/or used in the Experimental Part).

Generally, according to a preferred aspect, an amino acid sequence or polypeptide of the invention that is directed against a receptor for heterodimeric cytokine (and that may

further be as described herein) is such that, upon binding to the receptor, it prevents, reduces or inhibits heterodimeric cytokine-mediated signalling (as defined herein) associated with said receptor and/or with its ligand (i.e. compared to the heterodimeric cytokine-mediated signalling without the presence of the amino acid sequence or polypeptide, and by at least 1%, such as by at least 5%, for example by at least 10%, at least 30%, at least 50%, at least 70% and up to 90% or more, as determined by a suitable assay, such as one of the assays mentioned herein and/or used in the Experimental Part).

Again, such amino acid sequences and polypeptides may all be as further described herein.

It will be clear to the skilled person that the above amino acid sequences and polypeptides of the invention will generally act as antagonists of heterodimeric cytokine-mediated signalling (by which is generally meant herein the signalling associated with the heterodimeric cytokine and/or with the receptor for the heterodimeric cytokine, and in particular the signalling that is caused by binding of a heterodimeric cytokine to its receptor, as well as the biological mechanisms and effects that are triggered by such signalling).

However, the invention also relates to amino acid sequences and polypeptides of the invention that act as agonists of heterodimeric cytokine-mediated signalling. For example, such agonists may be amino acid sequences or polypeptides of the invention that can bind to a receptor for a heterodimeric cytokine (such as the receptor for IL-12, IL-23, IL-27 or IL-35) or to at least one subunit thereof so as to trigger receptor mediated signalling. It is also expected that the some of the above-described bispecific polypeptides that comprise at least one amino acid sequence of the invention that is directed against a heterodimeric cytokine (or against at least one subunit thereof) and at least one amino acid sequence of the invention that is directed against a receptor for said heterodimeric cytokine (or against at least one subunit thereof) may act as agonists for heterodimeric cytokine-mediated signalling, as further described herein.. For this purpose, such bispecific polypeptides preferably comprise amino acid sequences that do not neutralize binding of the heterodimeric cytokine to the receptor.

It is also within the scope of the invention to use parts, fragments, analogs, mutants, variants, alleles and/or derivatives of the amino acid sequences and polypeptides of the invention, and/or to use proteins or polypeptides comprising or essentially consisting of one or more of such parts, fragments, analogs, mutants, variants, alleles and/or derivatives, as long as these are suitable for the uses envisaged herein. Such parts, fragments, analogs,

mutants, variants, alleles and/or derivatives will usually contain (at least part of) a functional antigen-binding site for binding against heterodimeric cytokines and/or their receptors; and more preferably will be capable of specific binding to heterodimeric cytokines and/or their receptors, and even more preferably capable of binding to heterodimeric cytokines and/or their receptors with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value, as further described herein) that is as defined herein. Some non-limiting examples of such parts, fragments, analogs, mutants, variants, alleles, derivatives, proteins and/or polypeptides will become clear from the further description herein. Additional fragments or polypeptides of the invention may also be provided by suitably combining (i.e. by linking or genetic fusion) one or more (smaller) parts or fragments as described herein.

In one specific, but non-limiting aspect of the invention, which will be further described herein, such analogs, mutants, variants, alleles, derivatives have an increased half-life in serum (as further described herein) compared to the amino acid sequence from which they have been derived. For example, an amino acid sequence of the invention may be linked (chemically or otherwise) to one or more groups or moieties that extend the half-life (such as PEG), so as to provide a derivative of an amino acid sequence of the invention with increased half-life.In one specific, but non-limiting aspect, the amino acid sequences of the invention (such as the p19+ sequences, p19- sequences, p40+ sequences, p40- sequences, p35 sequences, IL-27 sequences, IL-12Rb1 sequences, IL-12Rb2 sequences and IL-23 sequences described herein) may be amino acid sequences that comprise an immunoglobulin fold or may be amino acid sequences that, under suitable conditions (such as physiological conditions) are capable of forming an immunoglobulin fold (i.e. by folding). Reference is inter alia made to the review by Halaby et al., J. (1999) Protein Eng. 12, 563-71. Preferably, when properly folded so as to form an immunoglobulin fold, such an amino acid sequence is capable of specific binding (as defined herein) to heterodimeric cytokines and/or their receptors; and more preferably capable of binding to heterodimeric cytokines and/or their receptors with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value, as further described herein) that is as defined herein. Also, parts, fragments, analogs, mutants, variants, alleles and/or derivatives of such amino acid sequences are

preferably such that they comprise an immunoglobulin fold or are capable for forming, under suitable conditions, an immunoglobulin fold.

In particular, but without limitation, the amino acid sequences of the invention (such as the p19+ sequences, p19- sequences, p40+ sequences, p40- sequences, p35 sequences, IL-27 sequences, IL-12Rb1 sequences, IL-12Rb2 sequences and IL-23 sequences described herein) may be amino acid sequences that essentially consist of 4 framework regions (FR1 to FR4 respectively) and 3 complementarity determining regions (CDR1 to CDR3 respectively); or any suitable fragment of such an amino acid sequence (which will then usually contain at least some of the amino acid residues that form at least one of the CDR's, as further described herein).

The amino acid sequences of the invention (such as the p19+ sequences, p19- sequences, p40+ sequences, p40- sequences, p35 sequences, IL-27 sequences, IL-12Rb1 sequences, IL-12Rb2 sequences and IL-23 sequences described herein) may in particular be an immunoglobulin sequence or a suitable fragment thereof, and more in particular be an immunoglobulin variable domain sequence or a suitable fragment thereof, such as light chain variable domain sequence (e.g. a V_L-sequence) or a suitable fragment thereof; or a heavy chain variable domain sequence (e.g. a V_H-sequence) or a suitable fragment thereof. When the amino acid sequence of the invention is a heavy chain variable domain sequence, it may be a heavy chain variable domain sequence that is derived from a conventional four-chain antibody (such as, without limitation, a V_H sequence that is derived from a human antibody) or be a so-called V_{HH}-sequence (as defined herein) that is derived from a so-called "heavy chain antibody" (as defined herein).

However, it should be noted that the invention is not limited as to the origin of the amino acid sequence of the invention (or of the nucleotide sequence of the invention used to express it), nor as to the way that the amino acid sequence or nucleotide sequence of the invention is (or has been) generated or obtained. Thus, the amino acid sequences of the invention may be naturally occurring amino acid sequences (from any suitable species) or synthetic or semi-synthetic amino acid sequences. In a specific but non-limiting aspect of the invention, the amino acid sequence is a naturally occurring immunoglobulin sequence (from any suitable species) or a synthetic or semi-synthetic immunoglobulin sequence, including but not limited to "humanized" (as defined herein) immunoglobulin sequences (such as partially or fully humanized mouse or rabbit immunoglobulin sequences, and in particular

partially or fully humanized V_{HH} sequences or Nanobodies), "camelized" (as defined herein) immunoglobulin sequences, as well as immunoglobulin sequences that have been obtained by techniques such as affinity maturation (for example, starting from synthetic, random or naturally occurring immunoglobulin sequences), CDR grafting, veneering, combining fragments derived from different immunoglobulin sequences, PCR assembly using overlapping primers, and similar techniques for engineering immunoglobulin sequences well known to the skilled person; or any suitable combination of any of the foregoing. Reference is for example made to the standard handbooks, as well as to the further description and prior art mentioned herein.

Similarly, the nucleotide sequences of the invention may be naturally occurring nucleotide sequences or synthetic or semi-synthetic sequences, and may for example be sequences that are isolated by PCR from a suitable naturally occurring template (e.g. DNA or RNA isolated from a cell), nucleotide sequences that have been isolated from a library (and in particular, an expression library), nucleotide sequences that have been prepared by introducing mutations into a naturally occurring nucleotide sequence (using any suitable technique known per se, such as mismatch PCR), nucleotide sequence that have been prepared by PCR using overlapping primers, or nucleotide sequences that have been prepared using techniques for DNA synthesis known per se.

The amino acid sequences of the invention (such as the p19+ sequences, p19- sequences, p40+ sequences, p40- sequences, p35 sequences, IL-27 sequences, IL-12Rb1 sequences, IL-12Rb2 sequences and IL-23 sequences described herein) may in particular be a domain antibody (or an amino acid sequence that is suitable for use as a domain antibody), a single domain antibody (or an amino acid sequence that is suitable for use as a single domain antibody), a "dAb" (or an amino acid sequence that is suitable for use as a dAb) or a Nanobody™ (as defined herein, and including but not limited to a V_{HH} sequence); other single variable domains, or any suitable fragment of any one thereof. For a general description of (single) domain antibodies, reference is also made to the prior art cited above, as well as to EP 0 368 684. For the term "dAb's", reference is for example made to Ward et al. (Nature 1989 Oct 12; 341 (6242): 544-6), to Holt et al., Trends Biotechnol., 2003, 21(11):484-490; as well as to for example WO 06/030220, WO 06/003388 and other published patent applications of Domantis Ltd. It should also be noted that, although less preferred in the context of the present invention because they are not of mammalian origin,

single domain antibodies or single variable domains can be derived from certain species of shark (for example, the so-called "IgNAR domains", see for example WO 05/18629).

In particular, the amino acid sequence of the invention may be a Nanobody™ (as defined herein) or a suitable fragment thereof. *[Note: Nanobody™, Nanobodies™ and Nanoclone™ are registered trademarks of Ablynx N.V.]* Such Nanobodies directed against heterodimeric cytokines and/or their receptors will also be referred to herein as "*Nanobodies of the invention*".

For a general description of Nanobodies, reference is made to the further description below, as well as to the prior art cited herein. In this respect, it should however be noted that this description and the prior art mainly described Nanobodies of the so-called "V_H3 class" (i.e. Nanobodies with a high degree of sequence homology to human germline sequences of the V_H3 class such as DP-47, DP-51 or DP-29), which Nanobodies form a preferred aspect of this invention. It should however be noted that the invention in its broadest sense generally covers any type of Nanobody directed against heterodimeric cytokines and/or their receptors, and for example also covers the Nanobodies belonging to the so-called "V_H4 class" (i.e. Nanobodies with a high degree of sequence homology to human germline sequences of the V_H4 class such as DP-78), as for example described in the US provisional application 60/792,279 by Ablynx N.V. entitled "*DP-78-like Nanobodies*" filed on April 14, 2006 (see also PCT/EP2007/003259 and WO 07/118670).

Generally, Nanobodies (in particular V_{HH} sequences and partially humanized Nanobodies) can in particular be characterized by the presence of one or more "*Hallmark residues*" (as described herein) in one or more of the framework sequences (again as further described herein).

Thus, generally, a Nanobody can be defined as an amino acid sequence with the (general) structure

FR1 - CDR1 - FR2 - CDR2 - FR3 - CDR3 - FR4

in which FR1 to FR4 refer to framework regions 1 to 4, respectively, and in which CDR1 to CDR3 refer to the complementarity determining regions 1 to 3, respectively, and in which one or more of the Hallmark residues are as further defined herein.

In particular, a Nanobody can be an amino acid sequence with the (general) structure

FR1 - CDR1 - FR2 - CDR2 - FR3 - CDR3 - FR4

in which FR1 to FR4 refer to framework regions 1 to 4, respectively, and in which CDR1 to CDR3 refer to the complementarity determining regions 1 to 3, respectively, and in which the framework sequences are as further defined herein.

More in particular, a Nanobody can be an amino acid sequence with the (general) structure

FR1 - CDR1 - FR2 - CDR2 - FR3 - CDR3 - FR4

in which FR1 to FR4 refer to framework regions 1 to 4, respectively, and in which CDR1 to CDR3 refer to the complementarity determining regions 1 to 3, respectively, and in which:

i) preferably one or more of the amino acid residues at positions 11, 37, 44, 45, 47, 83, 84, 103, 104 and 108 according to the Kabat numbering are chosen from the Hallmark residues mentioned in Table A-4 below;

and in which:

ii) said amino acid sequence has at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1 to 22, in which for the purposes of determining the degree of amino acid identity, the amino acid residues that form the CDR sequences (indicated with X in the sequences of SEQ ID NO's: 1 to 22) are disregarded.

In these Nanobodies, the CDR sequences are generally as further defined herein.

Thus, the invention also relates to such Nanobodies that can bind to (as defined herein) and/or are directed against heterodimeric cytokines and/or their receptors, to suitable fragments thereof, as well as to polypeptides that comprise or essentially consist of one or more of such Nanobodies and/or suitable fragments.

- Some (other) examples of suitable framework sequences are:
- For framework 1: the framework 1 sequences of FR1 Sequences Group 1; FR1 Sequences Group 8; FR1 Sequences Group 15; FR1 Sequences Group 22; FR1 Sequences Group 29; FR1 Sequences Group 36; FR1 Sequences Group 43; FR1

Sequences Group 50 and/or FR1 Sequences Group 57 (see Table A-1 below), or amino acid sequences that have no more than 5, such as 4, 3, 2, or only 1 amino acid difference (as defined herein) with one or more of said framework I sequences (in which case Optional Condition I. Optional Condition II and/or Optional Condition IV (as defined herein) may apply);

- For framework 2: the framework 2 sequences of FR2 Sequences Group 3; FR2 Sequences Group 10; FR2 Sequences Group 17; FR2 Sequences Group 24; FR2 Sequences Group 31; FR2 Sequences Group 38; FR2 Sequences Group 45; FR2 Sequences Group 52 and/or FR2 Sequences Group 59 (see Table A-1 below), or amino acid sequences that have no more than 5, such as 4, 3, 2, or only 1 amino acid difference (as defined herein) with one or more of said framework I sequences (in which case Optional Condition I. Optional Condition II and/or Optional Condition IV (as defined herein) may apply);
- For framework 3: the framework 3 sequences of FR3 Sequences Group 5; FR3 Sequences Group 12; FR3 Sequences Group 19; FR3 Sequences Group 26; FR3 Sequences Group 33; FR3 Sequences Group 40; FR3 Sequences Group 47; FR3 Sequences Group 54 and/or FR3 Sequences Group 61 (see Table A-1 below), or amino acid sequences that have no more than 5, such as 4, 3, 2, or only 1 amino acid difference (as defined herein) with one or more of said framework I sequences(in which case Optional Condition I. Optional Condition II and/or Optional Condition IV (as defined herein) may apply);
- For framework 4: the framework 4 sequences of FR4 Sequences Group 7; FR4 Sequences Group 14; FR4 Sequences Group 21; FR4 Sequences Group 28; FR4 Sequences Group 35; FR4 Sequences Group 42; FR4 Sequences Group 49; FR4 Sequences Group 56 and/or FR4 Sequences Group 63 (see Table A-1 below), or amino acid sequences that have no more than 5, such as 4, 3, 2, or only 1 amino acid difference (as defined herein) with one or more of said framework I sequences (in which case Optional Condition I. Optional Condition II and/or Optional Condition IV (as defined herein) may apply);

In the further description herein, reference will be made to certain groups of amino acid sequences (i.e. framework sequences and CDR sequences). These groups of amino acid sequences (63 in total) are defined in Table A-1 below:

Table A-1: Framework sequences and CDR sequences referred to in this specification. The SEQ ID NO's refer to the SEQ ID NO's given in the sequence listing and in Figure 11 to 19, respectively.

Framework sequences and CDR sequences derived from p19+ Nanobodies (see also Figure 11)
FR1 Sequences Group 1: SEQ ID NO's: 126 to 136 and 2170 to 2175
CDR1 Sequences Group 2 : SEQ ID NO's: 378 to 388 and 2215 to 2220
FR2 Sequences Group 3: SEQ ID NO's: 630 to 640 and 2260 to 2265
CDR2 Sequences Group 4: SEQ ID NO's: 882 to 892 and 2305 to 2310
FR3 Sequences Group 5: SEQ ID NO's: 1134 to 1144 and 2350 to 2355
CDR3 Sequences Group 6: SEQ ID NO's: 1386 to 1396 and 2395 to 2400
FR4 Sequences Group 7: SEQ ID NO's: 1638 to 1648 and 2440 to 2445
Framework sequences and CDR sequences derived from p19- Nanobodies (see also Figure 12)
FR1 Sequences Group 8: SEQ ID NO's: 137 to 175 and 2187 to 2188
CDR1 Sequences Group 9: SEQ ID NO's: 389 to 427 and 2232 to 2233
FR2 Sequences Group 10: SEQ ID NO's: 641 to 679 and 2277 to 2278
CDR2 Sequences Group 11: SEQ ID NO's: 893 to 931 and 2322 to 2323
FR3 Sequences Group 12: SEQ ID NO's: 1145 to 1183 and 2367 to 2368
CDR3 Sequences Group 13: SEQ ID NO's: 1397 to 1435 and 2412 to 2413
FR4 Sequences Group 14: SEQ ID NO's: 1649 to 1687 and 2457 to 2458
Framework sequences and CDR sequences derived from p40- Nanobodies (see also Figure 13)
FR1 Sequences Group 15: SEQ ID NO's: 176 to 181 and 191; 194 ; 204; 207; 208; 210 to 216; 219; 222; 225; 227; 228; 232; 238; 240; 242; 243; 259 ; 260; 264; 269 and 2189 to 2194

Table A-1 (continued):

CDR1 Sequences Group 16: SEQ ID NO's: 428 to 433 and 443; 446; 456; 459; 460; 462 to 468; 471; 474; 477; 479; 480; 484; 490; 492; 494; 495; 511; 512; 516; 521 and 2234 to 2239
FR2 Sequences Group 17: SEQ ID NO's: 680 to 685 and 695; 698; 708; 711; 712; 714 to 720; 723; 726; 729; 731; 732; 736; 742; 744; 746; 747; 763; 764; 768; 773 and 2279 to 2284
CDR2 Sequences Group 18: SEQ ID NO's: 932 to 937 and 947; 950; 960; 963; 964; 966 to 972; 975; 978; 981; 983; 984; 988; 994; 996; 998; 999; 1015; 1016; 1020; 1025 and 2324 to 2329
FR3 Sequences Group 19: SEQ ID NO's: 1184 to 1189 and 1199; 1202; 1212; 1215; 1216; 1218 to 1224; 1227; 1230; 1233; 1235; 1236; 1240; 1246; 1248; 1250; 1251; 1267; 1268; 1272; 1277 and 2369 to 2374
CDR3 Sequences Group 20: SEQ ID NO's: 1436 to 1441 and 1451; 1454; 1464; 1467; 1468; 1470 to 1476; 1479; 1482; 1485; 1487; 1488; 1492; 1498; 1500; 1502; 1503; 1519; 1520; 1524; 1529 and 2414 to 2419
FR4 Sequences Group 21: SEQ ID NO's: 1688 to 1693 and 1703; 1706; 1716; 1719; 1720; 1722 to 1728; 1731; 1734; 1737; 1739; 1740; 1744; 1750; 1752; 1754; 1755; 1771; 1772; 1776; 1781 and 2459 to 2464
Framework sequences and CDR sequences derived from p40+ Nanobodies (see also Figure 13)
FR1 Sequences Group 22: SEQ ID NO's: 178; 182; 184; 186; 188; 189; 190; 192; 193; 195; 198 to 201; 203; 205; 206; 209; 217; 218; 220; 221; 223; 224; 226; 229; 230; 231; 233 to 237; 239; 241; 266 and 2195 to 2213
CDR1 Sequences Group 23: SEQ ID NO's: 430; 434; 436; 438; 440; 441; 442; 444; 445; 447; 450 to 453; 455; 457; 458; 461; 469; 470; 472; 473; 475; 476; 478; 481; 482; 483; 485 to 489; 491; 493; 518 and 2240 to 2258

Table A-1 (continued):

FR2 Sequences Group 24: SEQ ID NO's: 682; 686; 688; 690; 692; 693; 694; 696; 697; 699; 702 to 705; 707; 709; 710; 713; 721; 722; 724; 725; 727; 728; 730; 733; 734; 735; 737 to 741; 743; 745; 770 and 2285 to 2303
CDR2 Sequences Group 25: SEQ ID NO's: 934; 938; 940; 942; 944; 945; 946; 948; 949; 951; 954 to 957; 959; 961; 962; 965; 973; 974; 976; 977; 979; 980; 982; 985; 986; 987; 989 to 993; 995; 997; 1022 and 2330 to 2348
FR3 Sequences Group 26: SEQ ID NO's: 1186; 1190; 1192; 1194; 1196; 1197; 1198; 1200; 1201; 1203; 1206 to 1209; 1211; 1213; 1214; 1217; 1225; 1226; 1228; 1229; 1231; 1232; 1234; 1237; 1238; 1239; 1241 to 1245; 1247; 1249; 1274 and 2375 to 2393
CDR3 Sequences Group 27: SEQ ID NO's: 1438; 1442; 1444; 1446; 1448; 1449; 1450; 1452; 1453; 1455; 1458 to 1461; 1463; 1465; 1466; 1469; 1477; 1478; 1480; 1481; 1483; 1484; 1486; 1489; 1490; 1491; 1493 to 1497; 1499; 1501; 1526 and 2420 to 2438
FR4 Sequences Group 28: SEQ ID NO's: 1690; 1694; 1696; 1698; 1700; 1701; 1702; 1704 ; 1705; 1707; 1710 to 1713; 1715; 1717; 1718; 1721; 1729; 1730; 1732; 1733; 1735; 1736; 1738; 1741; 1742; 1743; 1745 to 1749; 1751; 1753; 1778 and 2465 to 2483
Framework sequences and CDR sequences derived from p35 Nanobodies (see also Figure 15)
FR1 Sequences Group 29: SEQ ID NO's: 183; 185; 187; 196; 197; 202; 244 to 258; 261 to 263; 265; 267; 268; 270 to 273 and 2214
CDR1 Sequences Group 30: SEQ ID NO's: 435; 437; 439; 448; 449; 454; 496 to 510; 513 to 515; 517; 519; 520; 522 to 525 and 2259
FR2 Sequences Group 31: SEQ ID NO's: 687; 689; 691; 700; 701; 706; 748 to 762; 765 to 767; 769; 771; 772; 774 to 777 and 2304
CDR2 Sequences Group 32: SEQ ID NO's: 939; 941; 943; 952; 953; 958; 1000 to 1014; 1017 to 1019; 1021; 1023; 1024; 1026 to 1029 and 2349

Table A-1 (continued):

FR3 Sequences Group 33: SEQ ID NO's: 1191; 1193; 1195; 1204; 1205; 1210; 1252 to 1266; 1269 to 1271; 1273; 1275; 1276; 1278 to 1281 and 2394
CDR3 Sequences Group 34: SEQ ID NO's: 1443; 1445; 1447; 1456; 1457; 1462; 1504 to 1518; 1521 to 1523; 1525; 1527; 1528; 1530 to 1533 and 2439
FR4 Sequences Group 35: SEQ ID NO's: 1695; 1697; 1699; 1708; 1709; 1714; 1756 to 1770; 1773 to 1775; 1777; 1779; 1780; 1782 to 1785 and 2484
FR sequences and CDR sequences derived from Nanobodies against IL-27 (see also Figure 16)
FR1 Sequences Group 36: SEQ ID NO's: 274 to 312
CDR1 Sequences Group 37: SEQ ID NO's: 526 to 564
FR2 Sequences Group 38: SEQ ID NO's: 778 to 816
CDR2 Sequences Group 39: SEQ ID NO's: 1030 to 1068
FR3 Sequences Group 40: SEQ ID NO's: 1282 to 1320
CDR3 Sequences Group 41: SEQ ID NO's: 1534 to 1572
FR4 Sequences Group 42: SEQ ID NO's: 1786 to 1824
FR sequences and CDR sequences derived from Nanobodies against IL-12Rb1 (see also Figure 17)
FR1 Sequences Group 43: SEQ ID NO's: 313 to 339
CDR1 Sequences Group 44: SEQ ID NO's: 565 to 591
FR2 Sequences Group 45: SEQ ID NO's: 817 to 843
CDR2 Sequences Group 46: SEQ ID NO's: 1069 to 1095
FR3 Sequences Group 47: SEQ ID NO's: 1321 to 1347
CDR3 Sequences Group 48: SEQ ID NO's: 1573 to 1599
FR4 Sequences Group 49: SEQ ID NO's: 1825 to 1851
FR sequences and CDR sequences derived from Nanobodies against IL-12Rb2 (see also Figure 18)
FR1 Sequences Group 50: SEQ ID NO's: 340 to 360

Table A-1 (continued):

CDR1 Sequences Group 51: SEQ ID NO's: 592 to 612
FR2 Sequences Group 52: SEQ ID NO's: 844 to 864
CDR2 Sequences Group 53: SEQ ID NO's: 1096 to 1116
FR3 Sequences Group 54: SEQ ID NO's: 1348 to 1368
CDR3 Sequences Group 55: SEQ ID NO's: 1600 to 1620
FR4 Sequences Group 56: SEQ ID NO's: 1852 to 1872
FR sequences and CDR sequences derived from Nanobodies against IL-23R (see also Figure 19)
FR1 Sequences Group 57: SEQ ID NO's: 361 to 377
CDR1 Sequences Group 58: SEQ ID NO's: 613 to 629
FR2 Sequences Group 59: SEQ ID NO's: 865 to 881
CDR2 Sequences Group 60: SEQ ID NO's: 1117 to 1133
FR3 Sequences Group 61: SEQ ID NO's: 1369 to 1385
CDR3 Sequences Group 62: SEQ ID NO's: 1621 to 1637
FR4 Sequences Group 63: SEQ ID NO's: 1873 to 1889

Also, in the description herein, reference will be made to certain groups of amino acid sequences that form complete single antigen-binding domains (in this particular case, Nanobody sequences). These groups of sequences are defined in Table A-2 below:

Table A-2: Non-limiting examples of P19+ sequences, p19-sequences, P40-sequences, P40+ sequences, P35 sequences, IL-27 sequences, IL-12Rb1 sequences, IL-12Rb2 sequences and IL-23R sequences of the invention. The SEQ ID NO's refer to the SEQ ID NO's given in the sequence listing and in Figures 20 to 27, respectively.

Group name	**SEQ ID NO's**
"*P19+ sequences*" (see also Figure 20)	SEQ ID NO's: 1890; 1891; 1892; 1893; 1894; 1895; 1896; 1897; 1898; 1899; 1900; 2485; 2486; 2487; 2488; 2489 and/or 2490
"*P19-sequences*" (see also Figure 21)	SEQ ID NO's: 1901; 1902; 1903; 1904; 1905; 1906; 1907; 1908; 1909; 1910; 1911; 1912; 1913; 1914; 1915; 1916; 1917; 1918; 1919; 1920; 1921; 1922; 1923; 1924; 1925; 1926; 1927; 1928; 1929; 1930; 1931; 1932; 1933; 1934; 1935; 1936; 1937; 1938; 1939; 2502 and/or 2503
"*P40- sequences*" (see also Figure 22)	SEQ ID NO's: 1940; 1941; 1942; 1943; 1944; 1945; 1955; 1958; 1968; 1971; 1972; 1974; 1975; 1976; 1977; 1978; 1979; 1980; 1983; 1986; 1989; 1991; 1992; 1996; 2002; 2004; 2006; 2007; 2023; 2024; 2028; 2033; 2504; 2505; 2506; 2507; 2508 and/or 2509

Table A-2: (continued):

"P40+ sequences" (see also Figure 23)	SEQ ID NO's: 1942; 1946; 1948; 1950; 1952; 1953; 1954; 1956; 1957; 1959; 1962; 1963; 1964; 1965; 1967; 1969; 1970; 1973; 1981; 1982; 1984; 1985; 1987; 1988; 1990; 1993; 1994; 1995; 1997; 1998; 1999; 2000; 2001; 2003; 2005; 2030; 2510; 2511; 2512; 2513; 2514; 2515; 2516; 2517; 2518; 2519; 2520; 2521; 2522; 2523; 2524; 2525; 2526; 2527 and/or 2528
"P35 sequences" (see also Figure 24)	SEQ ID NO's: 1947; 1949; 1951; 1960; 1961; 1966; 2008; 2009; 2010; 2011; 2012; 2013; 2014; 2015; 2016; 2017; 2018; 2019; 2020; 2021; 2022; 2025; 2026; 2027; 2029; 2031; 2032; 2034; 2035; 2036; 2037 and/or 2529
"IL-27 sequences" (see also Figure 26)	SEQ ID NO's: 2038; 2039; 2040; 2041; 2042; 2043; 2044; 2045; 2046; 2047; 2048; 2049; 2050; 2051; 2052; 2053; 2054; 2055; 2056; 2057; 2058; 2059; 2060; 2061; 2062; 2063; 2064; 2065; 2066; 2067; 2068; 2069; 2070; 2071; 2072; 2073; 2074; 2075 and/or 2076

Table A-2: (continued):

"IL-12Rb1 sequences" (see also Figure 27)	SEQ ID NO's: 2077; 2078; 2079; 2080; 2081; 2082; 2083; 2084; 2085; 2086; 2087; 2088; 2089; 2090; 2091; 2092; 2093; 2094; 2095; 2096; 2097; 2098; 2099; 2100; 2101; 2102 and/or 2103
"IL-12Rb2 sequences" (see also Figure 28)	SEQ ID NO's: 2104; 2105; 2106; 2107; 2108; 2109; 2110; 2111; 2112; 2113; 2114; 2115; 2116; 2117; 2118; 2119; 2120; 2121; 2122; 2123 and/or 2124
"IL-23R sequences" (see also Figure 29)	SEQ ID NO's: 2125; 2126; 2127; 2128; 2129; 2130; 2131; 2132; 2133; 2134; 2135; 2136; 2137; 2138; 2139; 2140 and/or 2141

In particular, the invention in some specific aspects provides:

- amino acid sequences that are directed against (as defined herein) p19 and that have at least 80%, preferably at least 85%, such as 90% or 95% or more sequence identity with at least one of the p19+ sequences listed in Table A-2 above. These amino acid sequences are preferably such that they neutralize binding of IL-23 to its receptor;
- amino acid sequences that cross-block (as defined herein) the binding of at least one of the p19+ sequences listed in Table A-2 above to p19 and/or that compete with at least one of the p19+ sequences listed in Table A-2 abovefor binding to p19.
- amino acid sequences that are directed against (as defined herein) p19 and that have at least 80%, preferably at least 85%, such as 90% or 95% or more sequence identity with at least one of the p19- sequences listed in Table A-2 above. These amino acid

sequences are preferably such that they essentially do not block or neutralize binding of IL-23 to its receptor;

- amino acid sequences that cross-block (as defined herein) the binding of at least one of the p19- sequences listed in Table A-2 above to p19 and/or that compete with at least one of the p19- sequences listed in Table A-2 above for binding to p19.
- amino acid sequences that are directed against (as defined herein) p40 and that have at least 80%, preferably at least 85%, such as 90% or 95% or more sequence identity with at least one of the p40+ sequences listed in Table A-2 above. These amino acid sequences are preferably such that they neutralize binding of IL-23 and/or IL-12 to its receptor;
- amino acid sequences that cross-block (as defined herein) the binding of at least one of the p40+ sequences listed in Table A-2 above to p40 and/or that compete with at least one of the p40+ sequences listed in Table A-2 above for binding to p40.
- amino acid sequences that are directed against (as defined herein) p40 and that have at least 80%, preferably at least 85%, such as 90% or 95% or more sequence identity with at least one of the p40- sequences listed in Table A-2 above. These amino acid sequences are preferably such that they essentially do not block or neutralize binding of IL-23 or of IL-12 to its receptor;
- amino acid sequences that cross-block (as defined herein) the binding of at least one of the p40- sequences listed in Table A-2 above to p40 and/or that compete with at least one of the p40- sequences listed in Table A-2 above for binding to p40.
- amino acid sequences that are directed against (as defined herein) p35 and that have at least 80%, preferably at least 85%, such as 90% or 95% or more sequence identity with at least one of the p35 sequences listed in Table A-2 above.
- amino acid sequences that cross-block (as defined herein) the binding of at least one of the p35 sequences listed in Table A-2 above to p35 and/or that compete with at least one of the p35 sequences listed in Table A-2 above for binding to p35.
- amino acid sequences that are directed against (as defined herein) IL-12 and that have at least 80%, preferably at least 85%, such as 90% or 95% or more sequence identity with at least one of the p35 sequences, p40+ sequences and/or p40- sequences listed in Table A-2 above;

- amino acid sequences that cross-block (as defined herein) the binding of at least one of the p35 sequences, p40+ sequences and/or p40- sequences listed in Table A-2 above to IL-12 and/or that compete with at least one of the p35 sequences, p40+ sequences and/or p40- sequences listed in Table A-2 above for binding to IL-12.
- amino acid sequences that are directed against (as defined herein) IL-23 and that have at least 80%, preferably at least 85%, such as 90% or 95% or more sequence identity with at least one of the p19+ sequences, p19- sequences, p40+ sequences and/or p40- sequences listed in Table A-2 above;
- amino acid sequences that cross-block (as defined herein) the binding of at least one of the p19+ sequences, p19- sequences, p40+ sequences and/or p40- sequences listed in Table A-2 above to IL-23 and/or that compete with at least one of the p19+ sequences, p19- sequences, p40+ sequences and/or p40- sequences listed in Table A-2 above for binding to IL-23.
- amino acid sequences that are directed against (as defined herein) IL-27 and that have at least 80%, preferably at least 85%, such as 90% or 95% or more sequence identity with at least one of the IL-27 sequences listed in Table A-2 above;
- amino acid sequences that cross-block (as defined herein) the binding of at least one of the IL-27 sequences listed in Table A-2 above to IL-27 and/or that compete with at least one of the IL-27 sequences listed in Table A-2 above for binding to IL-27.
- amino acid sequences that are directed against (as defined herein) IL-12Rb1 and that have at least 80%, preferably at least 85%, such as 90% or 95% or more sequence identity with at least one of the IL-12Rb1 sequences listed in Table A-2 above;
- amino acid sequences that cross-block (as defined herein) the binding of at least one of the IL-12Rb1 sequences listed in Table A-2 aboveto IL-12Rb1 and/or that compete with at least one of the IL-12Rb1 sequences listed in Table A-2 above for binding to IL-12Rb1.
- amino acid sequences that are directed against (as defined herein) the (cognate) receptor for IL-12 and/or the (cognate) receptor for IL-23and that have at least 80%, preferably at least 85%, such as 90% or 95% or more sequence identity with at least one of the IL-12Rb1 sequences listed in Table A-2 above;

- amino acid sequences that cross-block (as defined herein) the binding of at least one of the IL-12Rb1 sequences listed in Table A-2 above to the (cognate) receptor for IL-12 and/or the (cognate) receptor for IL-23 and/or that compete with at least one of the IL-12Rb1 sequences listed in Table A-2 above for binding to the (cognate) receptor for IL-12 and/or the (cognate) receptor for IL-23.
- amino acid sequences that are directed against (as defined herein) IL-12Rb2 and that have at least 80%, preferably at least 85%, such as 90% or 95% or more sequence identity with at least one of the IL-12Rb2 sequences listed in Table A-2 above;
- amino acid sequences that cross-block (as defined herein) the binding of at least one of the IL-12Rb2 sequences listed in Table A-2 above and/or that compete with at least one of the IL-12Rb2 sequences listed in Table A-2 above for binding to IL-12Rb2;
- amino acid sequences that are directed against (as defined herein) the (cognate) receptor for IL-12 and that have at least 80%, preferably at least 85%, such as 90% or 95% or more sequence identity with at least one of the IL-12Rb2 sequences listed in Table A-2 above;
- amino acid sequences that cross-block (as defined herein) the binding of at least one of the IL-12Rb2 sequences listed in Table A-2 above to the (cognate) receptor for IL-12 and/or that compete with at least one of the IL-12Rb2 sequences listed in Table A-2 above for binding to the (cognate) receptor for IL-12.
- amino acid sequences that are directed against (as defined herein) IL-23R and that have at least 80%, preferably at least 85%, such as 90% or 95% or more sequence identity with at least one of the IL-23R sequences listed in Table A-2;
- amino acid sequences that cross-block (as defined herein) the binding of at least one of the IL-23R sequences listed in Table A-2 to IL-23R and/or that compete with at least one of the IL-23R sequences listed in Table A-2;
- amino acid sequences that are directed against (as defined herein) the (cognate) receptor for IL-23 and that have at least 80%, preferably at least 85%, such as 90% or 95% or more sequence identity with at least one of the IL-23R sequences listed in Table A-2 above;
- amino acid sequences that cross-block (as defined herein) the binding of at least one of the IL-23R sequences listed in Table A-2 above to the (cognate) receptor for IL-23

and/or that compete with at least one of the IL-23R sequences listed in Table A-2 above for binding to the (cognate) receptor for IL-23.

which amino acid sequences may be as further described herein (and may for example be Nanobodies); as well as polypeptides of the invention that comprise one or more of such amino acid sequences (which may be as further described herein, and may for example be bispecific and/or biparatopic polypeptides as described herein), and nucleic acid sequences that encode such amino acid sequences and polypeptides.

Accordingly, some particularly preferred Nanobodies of the invention are Nanobodies which can bind (as further defined herein) to and/or are directed against to heterodimeric cytokines and/or their receptors and which:

i) have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1890 to 2141, 2485 to 2529 and/or 2559 to 2614, in which for the purposes of determining the degree of amino acid identity, the amino acid residues that form the CDR sequences are disregarded. In this respect, reference is also made to the various groups of Framework 1 sequences, Framework 2 sequences, Framework 3 sequences and Framework 4 sequences mentioned Table A-1 (see also Figure 11 to 19) (with respect to the amino acid residues at positions 1 to 4 and 27 to 30 of the framework 1 sequences, reference is also made to the comments made below. Thus, for determining the degree of amino acid identity, these residues are preferably disregarded);

and in which:

ii) preferably one or more of the amino acid residues at positions 11, 37, 44, 45, 47, 83, 84, 103, 104 and 108 according to the Kabat numbering are chosen from the Hallmark residues mentioned in Table A-4 below.

In these Nanobodies, the CDR sequences are generally as further defined herein.

Again, such Nanobodies may be derived in any suitable manner and from any suitable source, and may for example be naturally occurring V_{HH} sequences (i.e. from a suitable species of Camelid) or synthetic or semi-synthetic amino acid sequences, including but not limited to "humanized" (as defined herein) Nanobodies, "camelized" (as defined herein) immunoglobulin sequences (and in particular camelized heavy chain variable domain sequences), as well as Nanobodies that have been obtained by techniques such as affinity maturation (for example, starting from synthetic, random or naturally occurring

immunoglobulin sequences), CDR grafting, veneering, combining fragments derived from different immunoglobulin sequences, PCR assembly using overlapping primers, and similar techniques for engineering immunoglobulin sequences well known to the skilled person; or any suitable combination of any of the foregoing as further described herein. Also, when a Nanobody comprises a V_{HH} sequence, said Nanobody may be suitably humanized, as further described herein, so as to provide one or more further (partially or fully) humanized Nanobodies of the invention. Similarly, when a Nanobody comprises a synthetic or semi-synthetic sequence (such as a partially humanized sequence), said Nanobody may optionally be further suitably humanized, again as described herein, again so as to provide one or more further (partially or fully) humanized Nanobodies of the invention.

In particular, humanized Nanobodies may be amino acid sequences that are as generally defined for Nanobodies in the previous paragraphs, but in which at least one amino acid residue is present (and in particular, in at least one of the framework residues) that is and/or that corresponds to a humanizing substitution (as defined herein). Some preferred, but non-limiting humanizing substitutions (and suitable combinations thereof) will become clear to the skilled person based on the disclosure herein. In addition, or alternatively, other potentially useful humanizing substitutions can be ascertained by comparing the sequence of the framework regions of a naturally occurring V_{HH} sequence with the corresponding framework sequence of one or more closely related human V_H sequences, after which one or more of the potentially useful humanizing substitutions (or combinations thereof) thus determined can be introduced into said V_{HH} sequence (in any manner known per se, as further described herein) and the resulting humanized V_{HH} sequences can be tested for affinity for the target, for stability, for ease and level of expression, and/or for other desired properties. In this way, by means of a limited degree of trial and error, other suitable humanizing substitutions (or suitable combinations thereof) can be determined by the skilled person based on the disclosure herein. Also, based on the foregoing, (the framework regions of) a Nanobody may be partially humanized or fully humanized.

Some particularly preferred humanized Nanobodies of the invention are humanized variants of the Nanobodies of SEQ ID NO's: 1890 to 2141, 2485 to 2490 and/or 2502 to 2529, which may for example, be humanized variants of Nanobodies that are directed against p19 (for example, humanized variants of Nanobodies that are p19+ sequences or p19- sequences, for example a humanized variant of one of the Nanobodies shown in Figures 20

and 21, respectively), against p40 (for example humanized variants of Nanobodies that are p40- sequences or p40+ sequences, for example a humanized variant of one of the Nanobodies shown in Figures 22 and 23, respectively), against p35 (for example a humanized variant of one of the Nanobodies shown in Figure 24), against IL-27 (for example of one of the Nanobodies shown in Figure 26), against IL-12Rb1 (for example a humanized variant of one of the Nanobodies shown in Figure 27), against IL-12Rb2 (for example a humanized variant of one of the Nanobodies shown in Figure 28), or against IL-23R (for example a humanized variant of one of the Nanobodies shown in Figure 29). Examples of such humanized Nanobodies are given in SEQ ID NO's: 2559 to 2614 (see also Figure 31), and the skilled person will be able to find other suitable humanized variants based on the disclosure herein, optionally after some limited trial-and-error.

Thus, some other preferred Nanobodies of the invention are Nanobodies which can bind (as further defined herein) to heterodimeric cytokines and/or their receptors and which:

i) are a humanized variant of one of the amino acid sequences of SEQ ID NO's: 1890 to 2141, 2485 to 2490 and/or 2502 to 2529; and/or

ii) have at least 80% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1890 to 2141, 2485 to 2490 and/or 2502 to 2529, in which for the purposes of determining the degree of amino acid identity, the amino acid residues that form the CDR sequences are disregarded;

and in which:

i) preferably one or more of the amino acid residues at positions 11, 37, 44, 45, 47, 83, 84, 103, 104 and 108 according to the Kabat numbering are chosen from the Hallmark residues mentioned in Table A-4 below.

Another aspect of the invention relates to nanobodies that are directed against p19 from mouse. Some non-limiting examples of such nanobodies are given in SEQ ID NO's: 2491-2501.

According to another specific aspect of the invention, the invention provides a number of stretches of amino acid residues (i.e. small peptides) that are particularly suited for binding to heterodimeric cytokines and/or their receptors (i.e. to p19, p40, p35, IL-12, IL-23, IL-27, IL-12Rb1, IL-12Rb2, IL-23R, the cognate receptor for IL-12 or the cognate receptor for IL-23, respectively, as further described herein). These stretches of amino acid residues may be present in, and/or may be corporated into, an amino acid sequence of the invention, in

particular in such a way that they form (part of) the antigen binding site of an amino acid sequence of the invention. As these stretches of amino acid residues were first generated as CDR sequences of heavy chain antibodies or V_{HH} sequences that were raised against heterodimeric cytokines and/or their receptors (or may be based on and/or derived from such CDR sequences, as further described herein), they will also generally be referred to herein as "*CDR sequences*" (i.e. as CDR1 sequences, CDR2 sequences and CDR3 sequences, respectively). It should however be noted that the invention in its broadest sense is not limited to a specific structural role or function that these stretches of amino acid residues may have in an amino acid sequence of the invention, as long as these stretches of amino acid residues allow the amino acid sequence of the invention to bind to heterodimeric cytokines and/or their receptors. Thus, generally, the invention in its broadest sense comprises any amino acid sequence that is capable of binding to heterodimeric cytokines and/or their receptors and that comprises one or more CDR sequences as described herein, and in particular a suitable combination of two or more such CDR sequences, that are suitably linked to each other via one or more further amino acid sequences, such that the entire amino acid sequence forms a binding domain and/or binding unit that is capable of binding to heterodimeric cytokines and/or their receptors. It should however also be noted that the presence of only one such CDR sequence in an amino acid sequence of the invention may by itself already be sufficient to provide an amino acid sequence of the invention that is capable of binding to heterodimeric cytokines and/or their receptors; reference is for example again made to the so-called "Expedite fragments" described in WO 03/050531.

Thus, in another specific, but non-limiting aspect, the amino acid sequence of the invention may be an amino acid sequence that comprises at least one amino acid sequence that is chosen from the group consisting of the CDR1 sequences, CDR2 sequences and CDR3 sequences that are described herein from or any suitable combination thereof. Particularly suitable combinations wll become clear to the skilled person based on the disclosure herein. In particular, an amino acid sequence of the invention may be an amino acid sequence that comprises at least one antigen binding site, wherein said antigen binding site comprises at least one amino acid sequence that is chosen from the group consisting of the CDR1 sequences, CDR2 sequences and CDR3 sequences that are described herein or any suitable combination thereof, such as the combinations that are described herein.

Generally, in this aspect of the invention, the amino acid sequence of the invention may be any amino acid sequence that comprises at least one stretch of amino acid residues, in which said stretch of amino acid residues has an amino acid sequence that corresponds to the sequence of at least one of the CDR sequences described herein. Such an amino acid sequence may or may not comprise an immunoglobulin fold. For example, and without limitation, such an amino acid sequence may be a suitable fragment of an immunoglobulin sequence that comprises at least one such CDR sequence, but that is not large enough to form a (complete) immunoglobulin fold (reference is for example again made to the "Expedite fragments" described in WO 03/050531). Alternatively, such an amino acid sequence may be a suitable "protein scaffold" that comprises least one stretch of amino acid residues that corresponds to such a CDR sequence (i.e. as part of its antigen binding site). Suitable scaffolds for presenting amino acid sequences will be clear to the skilled person, and for example comprise, without limitation, to binding scaffolds based on or derived from immunoglobulins (i.e. other than the immunoglobulin sequences already described herein), protein scaffolds derived from protein A domains (such as Affibodies™), tendamistat, fibronectin, lipocalin, CTLA-4, T-cell receptors, designed ankyrin repeats, avimers and PDZ domains (Binz et al., Nat. Biotech 2005, Vol 23:1257), and binding moieties based on DNA or RNA including but not limited to DNA or RNA aptamers (Ulrich et al., Comb Chem High Throughput Screen 2006 9(8):619-32).

Again, any amino acid sequence of the invention that comprises one or more of these CDR sequences is preferably such that it can specifically bind (as defined herein) to heterodimeric cytokines and/or their receptors, and more in particular such that it can bind to heterodimeric cytokines and/or their receptors with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value, as further described herein), that is as defined herein.

In particular, the amino acid sequences of the invention may be amino acid sequences that are directed against p19 (which may be "p19+ sequences" or "p19- sequences", both as defined herein); amino acid sequences that are directed against p40 (which may be "p40+ sequences" or "p40- sequences", both as defined herein); amino acid sequences that are directed against p35; amino acid sequences that are directed against IL-23 (which may be amino acid sequences that are directed against p19 or against p40); amino acid sequences that

are directed against IL-12(which may be amino acid sequences that are directed against p35 or against p40); amino acid sequences that are directed against IL-23 (which may be amino acid sequences that are directed against p19 or against p40); amino acid sequences that are directed against IL-27; amino acid sequences that are directed against IL-12Rb1;amino acid sequences that are directed against IL-12Rb2; amino acid sequences that are directed against IL-23R; amino acid sequences that are directed against the cognate receptor of IL-12 (which may be amino acid sequences that are directed against IL-12Rb1 or IL-12Rb2); and/or amino acid sequences that are directed against the cognate receptor of IL-23 (which may be amino acid sequences that are directed against IL-12Rb1 or IL-23R). These amino acid sequences may be as further described herein and form further aspects of the invention (as do nucleotide sequences/nucleic acids encoding the same, polypeptides comprising the same and the use of these amino acid sequences in such constructs, methods for preparing the same and uses of the same, all as further described herein).

A) "p19+ sequences".

One specific, but non-limiting aspect relates to "p19+ sequences", which generally are defined herein as amino acid sequences of the invention that are directed against (as defined herein) the p19 subunit (as present in for example IL-23), and that are capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p19 subunit to its receptor, and in particular capable of are capable of modulating, neutralizing, blocking and/or inhibiting the binding of IL-23 to IL-23R (for example in the alpha-screen assay of Example 19 or 22).

P19+ sequences may generally be as further described herein (for example, in terms of affinity, specificity etc. for p19) for amino acid sequences of the invention in general. Also, as described herein for the amino acid sequences of the invention, the p19+ sequences are preferably such that they form or are capable of forming (optionally after suitable folding) a single antigen binding domain or antigen binding unit, and may for example be amino acid sequences that comprise an immunoglobulin fold, amino acid sequences that are comprised of four framework regions and three CDR's, and may in particular be domain antibodies, single domain antibodies, VHH's, "dAb's" or Nanobodies (all as further described herein), or suitable fragments thereof.

In one particular aspect, a p19+ sequence may comprise one or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 2" (as defined and listed in Table A-1; see also Figure 11);

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 2";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 2";

d) the amino acid sequences from the "CDR2 Sequences Group 4" (as defined and listed in Table A-1; see also Figure 11);

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 4";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 4";

g) the amino acid sequences from the "CDR3 Sequences Group 6" (as defined and listed in Table A-1; see also Figure 11);

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 6";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 6";

or any suitable combination thereof.

Optionally, when an amino acid sequence of the invention contains one or more amino acid sequences according to b) and/or c), Optional Condition I, Optional Condition II and/or Optional Condition III (all as defined herein) may apply to said amino acid sequence (i.e. compared to the original amino acid sequence according to a)). Also, optionally, when an amino acid sequence of the invention contains one or more amino acid sequences according to e) and/or f), Optional Condition I, Optional Condition II and/or Optional Condition III (all as defined herein) may apply to said amino acid sequence (i.e. compared to the original amino acid sequence according to d)). Also, optionally, when an amino acid sequence of the invention contains one or more amino acid sequences according to h) and/or i), Optional Condition I, Optional Condition II and/or Optional Condition III (all as defined herein) may

apply to said amino acid sequence (i.e. compared to the original amino acid sequence according to g)).

In this specific aspect, the amino acid sequence preferably comprises one or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 2";

b) the amino acid sequences from the "CDR2 Sequences Group 4"; and

c) the amino acid sequences from the "CDR3 Sequences Group 6";

or any suitable combination thereof.

Also, preferably, in such an amino acid sequence, at least one of said stretches of amino acid residues forms part of the antigen binding site for binding against p19.

In a more specific, but again non-limiting aspect, a p19+ sequence may comprise two or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 2";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 2";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 2";

d) the amino acid sequences from the "CDR2 Sequences Group 4";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 4";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 4";

g) the amino acid sequences from the "CDR3 Sequences Group 6";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 6";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 6";

such that (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b) or c), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e), f), g), h) or i); (ii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e) or f), the second stretch of amino acid residues corresponds to one of the

amino acid sequences according to a), b), c), g), h) or i); or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to g), h) or i), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), d), e) or f).

In this specific aspect, the amino acid sequence preferably comprises two or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 2";

b) the amino acid sequences from the "CDR2 Sequences Group 4"; and

c) the amino acid sequences from the "CDR3 Sequences Group 6";

such that, (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR1 Sequences Group 2", the second stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR2 Sequences Group 4" or from the "CDR3 Sequences Group 6"; (ii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR2 Sequences Group 4", the second stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR1 Sequences Group 2" or from the "CDR3 Sequences Group 6"; or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR3 Sequences Group 6", the second stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR1 Sequences Group 2" or from the "CDR2 Sequences Group 4".

Also, in such an amino acid sequence, the at least two stretches of amino acid residues again preferably form part of the antigen binding site for binding against p19.

In an even more specific, but non-limiting aspect, a p19+ sequence may comprise three or more stretches of amino acid residues, in which the first stretch of amino acid residues is chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 2";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 2";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 2";

the second stretch of amino acid residues is chosen from the group consisting of:

d) the amino acid sequences from the "CDR2 Sequences Group 4";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 4";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 4";

and the third stretch of amino acid residues is chosen from the group consisting of:

g) the amino acid sequences from the "CDR3 Sequences Group 6";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 6";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 6".

Preferably, in this specifc aspect, the first stretch of amino acid residues is chosen from the group consisting of the amino acid sequences from the "CDR1 Sequences Group 2"; the second stretch of amino acid residues is chosen from the group consisting of the amino acid sequences from the "CDR2 Sequences Group 4"; and the third stretch of amino acid residues is chosen from the group consisting of the amino acid sequences from the "CDR3 Sequences Group 6".

Again, preferably, in such an amino acid sequence, the at least three stretches of amino acid residues forms part of the antigen binding site for binding against p19.

Preferred combinations of such stretches of amino acid sequences will become clear from the further disclosure herein.

Preferably, in such amino acid sequences the CDR sequences have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the p19+ sequences listed in Table A-2 and Figure 20. This degree of amino acid identity can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said amino acid sequence and one or more of the sequences of SEQ ID NO's: 1890; 1891; 1892; 1893; 1894; 1895; 1896; 1897; 1898; 1899; 1900; 2485; 2486; 2487; 2488; 2489 and/or 2490 (see Table A-2 and Figure 20), in which the amino acid residues that form the framework regions are disregarded. Also, such amino acid sequences of the invention can be as further described herein.

Also, such amino acid sequences are preferably such that they can specifically bind (as defined herein) to the p19 subunit; and more in particular bind to the p19 subunit with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value (all as further) described herein) that is as defined herein.

When the amino acid sequence of the invention essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), the amino acid sequence of the invention is preferably such that:

- CDR1 is chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 2";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 2";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 2";

and/or

- CDR2 is chosen from the group consisting of:

d) the amino acid sequences from the "CDR2 Sequences Group 4";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 4";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 4";

and/or

- CDR3 is chosen from the group consisting of:

g) the amino acid sequences from the "CDR3 Sequences Group 6";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 6";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 6".

In particular, such an amino acid sequence of the invention may be such that CDR1 is chosen from the group consisting of the amino acid sequences from the "CDR1 Sequences Group 2"; and/or CDR2 is chosen from the group consisting of the amino acid sequences

from the "CDR2 Sequences Group 4"; and/or CDR3 is chosen from the group consisting of the amino acid sequences from the "CDR3 Sequences Group 6".

In particular, when the amino acid sequence of the invention essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), the amino acid sequence of the invention is preferably such that:

- CDR1 is chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 2";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 2";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 2";

and

- CDR2 is chosen from the group consisting of:

d) the amino acid sequences from the "CDR2 Sequences Group 4";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 4";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 4";

and

- CDR3 is chosen from the group consisting of:

g) the amino acid sequences from the "CDR3 Sequences Group 6";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 6";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 6"; or any suitable fragment of such an amino acid sequence

In particular, such an amino acid sequence of the invention may be such that CDR1 is chosen from the group consisting of the amino acid sequences from the "CDR1 Sequences Group 2"; and CDR2 is chosen from the group consisting of the amino acid sequences from the "CDR2 Sequences Group 4"; and CDR3 is chosen from the group consisting of the amino acid sequences from the "CDR3 Sequences Group 6".

Again, preferred combinations of CDR sequences will become clear from the further description herein.

Also, such amino acid sequences are preferably such that they can specifically bind (as defined herein) to the p19 subunit; and more in particular bind to the p19 subunit with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value (all as further) described herein) that is as defined herein.

In one preferred, but non-limiting aspect, the invention relates to an amino acid sequence that essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), in which the CDR sequences of said amino acid sequence have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 1890; 1891; 1892; 1893; 1894; 1895; 1896; 1897; 1898; 1899; 1900; 2485; 2486; 2487; 2488; 2489 and/or 2490 (see Table A-2 and Figure 20). This degree of amino acid identity can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said amino acid sequence and one or more of the sequences of SEQ ID NO's: 1890; 1891; 1892; 1893; 1894; 1895; 1896; 1897; 1898; 1899; 1900; 2485; 2486; 2487; 2488; 2489 and/or 2490 (see Table A-2 and Figure 20), in which the amino acid residues that form the framework regions are disregarded. Such amino acid sequences of the invention can be as further described herein.

Some preferred, but non-limiting examples of p19+ sequences are the amino acid sequences of SEQ ID NO's: 1890; 1891; 1892; 1893; 1894; 1895; 1896; 1897; 1898; 1899; 1900; 2485; 2486; 2487; 2488; 2489 and/or 2490 (see Table A-2 and Figure 20). Thus, according to another preferred, but non-limiting aspect of the invention, a p19+ sequence is an amino acid sequence that is directed against (as defined herein) the p19 subunit (as present in for example IL-23) and that are capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p19 subunit to its receptor, and in particular capable of are capable of modulating, neutralizing, blocking and/or inhibiting the binding of IL-23 to IL-23R (for example in the alpha-screen assay of Example 19 or 22), and that either

a) has at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1890; 1891; 1892; 1893; 1894; 1895; 1896; 1897; 1898; 1899; 1900; 2485; 2486; 2487; 2488; 2489 and/or 2490 (see Table A-2 and Figure 20);

and/or that

b) has no more than 20, preferably no more than 10, such as 9, 8, 7, 6, 5, 4, 3, 2 or only one amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1890; 1891; 1892; 1893; 1894; 1895; 1896; 1897; 1898; 1899; 1900; 2485; 2486; 2487; 2488; 2489 and/or 2490 (see Table A-2 and Figure 20). Preferably, such an amino acid sequence has no more than a total of 5 (such as 4, 3. 2 or only one) such amino acid differences in the CDR's and/or no more than a total of 5 (such as 4, 3. 2 or only 1) such amino acid differences in the framework sequences;

and/or that

c) is either (i) capable of cross-blocking (as defined herein) the interaction of at least one of the amino acid sequences of SEQ ID NO's: 1890; 1891; 1892; 1893; 1894; 1895; 1896; 1897; 1898; 1899; 1900; 2485; 2486; 2487; 2488; 2489 and/or 2490 with the p19 subunit and/or (ii) being able to compete with (i.e. is a competitor for) the binding of at least one of the amino acid sequences of SEQ ID NO's: 1890; 1891; 1892; 1893; 1894; 1895; 1896; 1897; 1898; 1899; 1900; 2485; 2486; 2487; 2488; 2489 and/or 2490 (see Table A-2 and Figure 20) to the p19 subunit.

In another preferred, but non-limiting aspect, a p19+ sequence is chosen from one of the amino acid sequences of SEQ ID NO's: 1890; 1891; 1892; 1893; 1894; 1895; 1896; 1897; 1898; 1899; 1900; 2485; 2486; 2487; 2488; 2489 and/or 2490 (see Table A-2 and Figure 20).

<u>B) "p19- sequences".</u>

One specific, but non-limiting aspect relates to "p19- sequences", which generally are defined herein as amino acid sequences of the invention that are directed against (as defined herein) the p19 subunit (as present in for example IL-23), but that (essentially) are not capable of neutralizing or inhibiting the binding of a heterodimeric cytokine comprising a p19 subunit to its receptor (for example, in a suitable alpha-screen assay as exemplified in

Examples 19 and 22 for IL-23 and its cognate receptor and for IL-12 and its cognate receptor).

P19- sequences may generally be as further described herein (for example, in terms of affinity, specificity etc. for p19) for amino acid sequences of the invention in general. Also, as described herein for the amino acid sequences of the invention, the p19- sequences are preferably such that they form or are capable of forming (optionally after suitable folding) a single antigen binding domain or antigen binding unit, and may for example be amino acid sequences that comprise an immunoglobulin fold, amino acid sequences that are comprised of four framework regions and three CDR's, and may in particular be domain antibodies, single domain antibodies, VHH's, "dAb's" or Nanobodies (all as further described herein), or suitable fragments thereof.

In one particular aspect, a p19- sequence may comprise one or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 9" (as defined and listed in Table A-1; see also Figure 12);

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 9";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 9";

d) the amino acid sequences from the "CDR2 Sequences Group 11" (as defined and listed in Table A-1; see also Figure 12);

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 11";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 11";

g) the amino acid sequences from the "CDR3 Sequences Group 13" (as defined and listed in Table A-1; see also Figure 12);

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 13";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 13";

or any suitable combination thereof.

Optionally, when an amino acid sequence of the invention contains one or more amino acid sequences according to b) and/or c), Optional Condition I, Optional Condition II and/or Optional Condition III (all as defined herein) may apply to said amino acid sequence (i.e. compared to the original amino acid sequence according to a)). Also, optionally, when an amino acid sequence of the invention contains one or more amino acid sequences according to e) and/or f), Optional Condition I, Optional Condition II and/or Optional Condition III (all as defined herein) may apply to said amino acid sequence (i.e. compared to the original amino acid sequence according to d)). Also, optionally, when an amino acid sequence of the invention contains one or more amino acid sequences according to h) and/or i), Optional Condition I, Optional Condition II and/or Optional Condition III (all as defined herein) may apply to said amino acid sequence (i.e. compared to the original amino acid sequence according to g)).

In this specific aspect, the amino acid sequence preferably comprises one or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 9";

b) the amino acid sequences from the "CDR2 Sequences Group 11"; and

c) the amino acid sequences from the "CDR3 Sequences Group 13";

or any suitable combination thereof.

Also, preferably, in such an amino acid sequence, at least one of said stretches of amino acid residues forms part of the antigen binding site for binding against p19.

In a more specific, but again non-limiting aspect, a p19- sequence may comprise two or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 9";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 9";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 9";

d) the amino acid sequences from the "CDR2 Sequences Group 11";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 11";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 11";

g) the amino acid sequences from the "CDR3 Sequences Group 13";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 13";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 13";

such that (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b) or c), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e), f), g), h) or i); (ii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e) or f), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), g), h) or i); or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to g), h) or i), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), d), e) or f).

In this specific aspect, the amino acid sequence preferably comprises two or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 9";

b) the amino acid sequences from the "CDR2 Sequences Group 11"; and

c) the amino acid sequences from the "CDR3 Sequences Group 13";

such that, (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR1 Sequences Group 9", the second stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR2 Sequences Group 11" or from the "CDR3 Sequences Group 13"; (ii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR2 Sequences Group 11", the second stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR1 Sequences Group 9" or from the "CDR3 Sequences Group 13"; or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR3 Sequences Group 13", the second stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR1 Sequences Group 9" or from the "CDR2 Sequences Group 11".

Also, in such an amino acid sequence, the at least two stretches of amino acid residues again preferably form part of the antigen binding site for binding against p19.

In an even more specific, but non-limiting aspect, a p19- sequence may comprise three or more stretches of amino acid residues, in which the first stretch of amino acid residues is chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 9";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 9";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 9";

the second stretch of amino acid residues is chosen from the group consisting of:

d) the amino acid sequences from the "CDR2 Sequences Group 11";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 11";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 11";

and the third stretch of amino acid residues is chosen from the group consisting of:

g) the amino acid sequences from the "CDR3 Sequences Group 13";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 13";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 13".

Preferably, in this specifc aspect, the first stretch of amino acid residues is chosen from the group consisting of the amino acid sequences from the "CDR1 Sequences Group 9"; the second stretch of amino acid residues is chosen from the group consisting of the amino acid sequences from the "CDR2 Sequences Group 11"; and the third stretch of amino acid residues is chosen from the group consisting of the amino acid sequences from the "CDR3 Sequences Group 13".

Again, preferably, in such an amino acid sequence, the at least three stretches of amino acid residues forms part of the antigen binding site for binding against p19.

Preferred combinations of such stretches of amino acid sequences will become clear from the further disclosure herein.

Preferably, in such amino acid sequences the CDR sequences have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino

acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the p19- sequences listed in Table A-2 and Figure 21. This degree of amino acid identity can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said amino acid sequence and one or more of the sequences of SEQ ID NO's: 1901; 1902; 1903; 1904; 1905; 1906; 1907; 1908; 1909; 1910; 1911; 1912; 1913; 1914; 1915; 1916; 1917; 1918; 1919; 1920; 1921; 1922; 1923; 1924; 1925; 1926; 1927; 1928; 1929; 1930; 1931; 1932; 1933; 1934; 1935; 1936; 1937; 1938; 1939; 2502 and/or 2503 (see Table A-2 and Figure 21), in which the amino acid residues that form the framework regions are disregarded. Also, such amino acid sequences of the invention can be as further described herein.

Also, such amino acid sequences are preferably such that they can specifically bind (as defined herein) to the p19 subunit; and more in particular bind to the p19 subunit with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value (all as further) described herein) that is as defined herein.

When the amino acid sequence of the invention essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), the amino acid sequence of the invention is preferably such that:

- CDR1 is chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 9";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 9";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 9";

and/or

- CDR2 is chosen from the group consisting of:

d) the amino acid sequences from the "CDR2 Sequences Group 11";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 11";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 11";

and/or

- CDR3 is chosen from the group consisting of:

g) the amino acid sequences from the "CDR3 Sequences Group 13";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 13";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 13".

In particular, such an amino acid sequence of the invention may be such that CDR1 is chosen from the group consisting of the amino acid sequences from the "CDR1 Sequences Group 9"; and/or CDR2 is chosen from the group consisting of the amino acid sequences from the "CDR2 Sequences Group 11"; and/or CDR3 is chosen from the group consisting of the amino acid sequences from the "CDR3 Sequences Group 13".

In particular, when the amino acid sequence of the invention essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), the amino acid sequence of the invention is preferably such that:

- CDR1 is chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 9";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 9";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 9";

and

- CDR2 is chosen from the group consisting of:

d) the amino acid sequences from the "CDR2 Sequences Group 11";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 11";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 11";

and

- CDR3 is chosen from the group consisting of:

g) the amino acid sequences from the "CDR3 Sequences Group 13";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 13";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 13"; or any suitable fragment of such an amino acid sequence

In particular, such an amino acid sequence of the invention may be such that CDR1 is chosen from the group consisting of the amino acid sequences from the "CDR1 Sequences Group 9"; and CDR2 is chosen from the group consisting of the amino acid sequences from the "CDR2 Sequences Group 11"; and CDR3 is chosen from the group consisting of the amino acid sequences from the "CDR3 Sequences Group 13".

Again, preferred combinations of CDR sequences will become clear from the further description herein.

Also, such amino acid sequences are preferably such that they can specifically bind (as defined herein) to the p19 subunit; and more in particular bind to the p19 subunit with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value (all as further) described herein) that is as defined herein.

In one preferred, but non-limiting aspect, the invention relates to an amino acid sequence that essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), in which the CDR sequences of said amino acid sequence have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 1901; 1902; 1903; 1904; 1905; 1906; 1907; 1908; 1909; 1910; 1911; 1912; 1913; 1914; 1915; 1916; 1917; 1918; 1919; 1920; 1921; 1922; 1923; 1924; 1925; 1926; 1927; 1928; 1929; 1930; 1931; 1932; 1933; 1934; 1935; 1936; 1937; 1938; 1939; 2502 and/or 2503 (see Table A-2 and Figure 21). This degree of amino acid identity can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said amino acid sequence and one or more of the sequences of SEQ ID NO's: 1901; 1902; 1903; 1904; 1905; 1906; 1907; 1908; 1909; 1910; 1911; 1912; 1913; 1914; 1915; 1916; 1917; 1918; 1919; 1920; 1921; 1922; 1923; 1924; 1925; 1926; 1927; 1928; 1929; 1930; 1931; 1932; 1933;

1934; 1935; 1936; 1937; 1938; 1939; 2502 and/or 2503 (see Table A-2 and Figure 21), in which the amino acid residues that form the framework regions are disregarded. Such amino acid sequences of the invention can be as further described herein.

Some preferred, but non-limiting examples of p19- sequence are the amino acid sequences of SEQ ID NO's: 1901; 1902; 1903; 1904; 1905; 1906; 1907; 1908; 1909; 1910; 1911; 1912; 1913; 1914; 1915; 1916; 1917; 1918; 1919; 1920; 1921; 1922; 1923; 1924; 1925; 1926; 1927; 1928; 1929; 1930; 1931; 1932; 1933; 1934; 1935; 1936; 1937; 1938; 1939; 2502 and/or 2503 (see Table A-2 and Figure 21). Thus, according to another preferred, but non-limiting aspect of the invention, a p19- sequence is an amino acid sequence that is directed against (as defined herein) the p19 subunit (as present in for example IL-23) but that (essentially) are not capable of neutralizing or inhibiting the binding of a heterodimeric cytokine comprising a p19 subunit to its receptor (for example, in a suitable alpha-screen assay as exemplified in Examples 19 and 22 for IL-23 and its cognate receptor and for IL-12 and its cognate receptor), and that either:

a) has at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1901; 1902; 1903; 1904; 1905; 1906; 1907; 1908; 1909; 1910; 1911; 1912; 1913; 1914; 1915; 1916; 1917; 1918; 1919; 1920; 1921; 1922; 1923; 1924; 1925; 1926; 1927; 1928; 1929; 1930; 1931; 1932; 1933; 1934; 1935; 1936; 1937; 1938; 1939; 2502 and/or 2503 (see Table A-2 and Figure 21);

and/or that

b) has no more than 20, preferably no more than 10, such as 9, 8, 7, 6, 5, 4, 3, 2 or only one amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1901; 1902; 1903; 1904; 1905; 1906; 1907; 1908; 1909; 1910; 1911; 1912; 1913; 1914; 1915; 1916; 1917; 1918; 1919; 1920; 1921; 1922; 1923; 1924; 1925; 1926; 1927; 1928; 1929; 1930; 1931; 1932; 1933; 1934; 1935; 1936; 1937; 1938; 1939; 2502 and/or 2503 (see Table A-2 and Figure 21). Preferably, such an amino acid sequence has no more than a total of 5 (such as 4, 3. 2 or only one) such amino acid differences in the CDR's and/or no more than a total of 5 (such as 4, 3. 2 or only 1) such amino acid differences in the framework sequences;

and/or that

c) is either (i) capable of cross-blocking (as defined herein) the interaction of at least one of the amino acid sequences of SEQ ID NO's: 1901; 1902; 1903; 1904; 1905; 1906; 1907; 1908; 1909; 1910; 1911; 1912; 1913; 1914; 1915; 1916; 1917; 1918; 1919; 1920; 1921; 1922; 1923; 1924; 1925; 1926; 1927; 1928; 1929; 1930; 1931; 1932; 1933; 1934; 1935; 1936; 1937; 1938; 1939; 2502 and/or 2503 (see Table A-2 and Figure 20) with the p19 subunit and/or (ii) being able to compete with (i.e. is a competitor for) the binding of at least one of the amino acid sequences of SEQ ID NO's: 1901; 1902; 1903; 1904; 1905; 1906; 1907; 1908; 1909; 1910; 1911; 1912; 1913; 1914; 1915; 1916; 1917; 1918; 1919; 1920; 1921; 1922; 1923; 1924; 1925; 1926; 1927; 1928; 1929; 1930; 1931; 1932; 1933; 1934; 1935; 1936; 1937; 1938; 1939; 2502 and/or 2503 (see Table A-2 and Figure 21) to the p19 subunit.

In another preferred, but non-limiting aspect, a p19 sequence is chosen from one of the amino acid sequences of SEQ ID NO's: 1901; 1902; 1903; 1904; 1905; 1906; 1907; 1908; 1909; 1910; 1911; 1912; 1913; 1914; 1915; 1916; 1917; 1918; 1919; 1920; 1921; 1922; 1923; 1924; 1925; 1926; 1927; 1928; 1929; 1930; 1931; 1932; 1933; 1934; 1935; 1936; 1937; 1938; 1939; 2502 and/or 2503 (see Table A-2 and Figure 21).

C) P40- sequences.

One specific, but non-limiting aspect relates to "p40- sequences", which generally are defined herein as amino acid sequences of the invention that are directed against (as defined herein) the p40 subunit (as present in for example IL-23 and IL-12), but that (essentially) are not capable of neutralizing or inhibiting the binding of a heterodimeric cytokine comprising a p40 subunit to its receptor (for example, in a suitable alpha-screen assay as exemplified in Examples 19 and 22 for IL-23 and its cognate receptor and for IL-12 and its cognate receptor).

P40- sequences may generally be as further described herein (for example, in terms of affinity, specificity etc. for p40) for amino acid sequences of the invention in general. Also, as described herein for the amino acid sequences of the invention, the p40- sequences are preferably such that they form or are capable of forming (optionally after suitable folding) a single antigen binding domain or antigen binding unit, and may for example be amino acid sequences that comprise an immunoglobulin fold, amino acid sequences that are comprised of four framework regions and three CDR's, and may in particular be domain antibodies,

single domain antibodies, VHH's, "dAb's" or Nanobodies (all as further described herein), or suitable fragments thereof.

In one particular aspect, a p40- sequence may comprise one or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 16" (as defined and listed in Table A-1; see also Figure 13);

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 16";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 16";

d) the amino acid sequences from the "CDR2 Sequences Group 18" (as defined and listed in Table A-1; see also Figure 13);

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 18";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 18";

g) the amino acid sequences from the "CDR3 Sequences Group 20" (as defined and listed in Table A-1; see also Figure 13);

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 20";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 20";

or any suitable combination thereof.

Optionally, when an amino acid sequence of the invention contains one or more amino acid sequences according to b) and/or c), Optional Condition I, Optional Condition II and/or Optional Condition III (all as defined herein) may apply to said amino acid sequence (i.e. compared to the original amino acid sequence according to a)). Also, optionally, when an amino acid sequence of the invention contains one or more amino acid sequences according to e) and/or f), Optional Condition I, Optional Condition II and/or Optional Condition III (all as defined herein) may apply to said amino acid sequence (i.e. compared to the original amino acid sequence according to d)). Also, optionally, when an amino acid sequence of the invention contains one or more amino acid sequences according to h) and/or i), Optional

Condition I, Optional Condition II and/or Optional Condition III (all as defined herein) may apply to said amino acid sequence (i.e. compared to the original amino acid sequence according to g)).

In this specific aspect, the amino acid sequence preferably comprises one or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 16";

b) the amino acid sequences from the "CDR2 Sequences Group 18"; and

c) the amino acid sequences from the "CDR3 Sequences Group 20";

or any suitable combination thereof.

Also, preferably, in such an amino acid sequence, at least one of said stretches of amino acid residues forms part of the antigen binding site for binding against p40.

In a more specific, but again non-limiting aspect, a p40- sequence may comprise two or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 16";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 16";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 16";

d) the amino acid sequences from the "CDR2 Sequences Group 18";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 18";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 18";

g) the amino acid sequences from the "CDR3 Sequences Group 20";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 20";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 20";

such that (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b) or c), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e), f), g), h) or i); (ii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences

according to d), e) or f), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), g), h) or i); or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to g), h) or i), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), d), e) or f).

In this specific aspect, the amino acid sequence preferably comprises two or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 16";

b) the amino acid sequences from the "CDR2 Sequences Group 18"; and

c) the amino acid sequences from the "CDR3 Sequences Group 20";

such that, (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR1 Sequences Group 16", the second stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR2 Sequences Group 18" or from the "CDR3 Sequences Group 20"; (ii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR2 Sequences Group 18", the second stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR1 Sequences Group 16" or from the "CDR3 Sequences Group 20"; or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR3 Sequences Group 20", the second stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR1 Sequences Group 16" or from the "CDR2 Sequences Group 18".

Also, in such an amino acid sequence, the at least two stretches of amino acid residues again preferably form part of the antigen binding site for binding against p40.

In an even more specific, but non-limiting aspect, a p40- sequence may comprise three or more stretches of amino acid residues, in which the first stretch of amino acid residues is chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 16";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 16";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 16";

the second stretch of amino acid residues is chosen from the group consisting of:

d) the amino acid sequences from the "CDR2 Sequences Group 18";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 18";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 18";

and the third stretch of amino acid residues is chosen from the group consisting of:

g) the amino acid sequences from the "CDR3 Sequences Group 20";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 20";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 20".

Preferably, in this specifc aspect, the first stretch of amino acid residues is chosen from the group consisting of the amino acid sequences from the "CDR1 Sequences Group 16"; the second stretch of amino acid residues is chosen from the group consisting of the amino acid sequences from the "CDR2 Sequences Group 18"; and the third stretch of amino acid residues is chosen from the group consisting of the amino acid sequences from the "CDR3 Sequences Group 20".

Again, preferably, in such an amino acid sequence, the at least three stretches of amino acid residues forms part of the antigen binding site for binding against p40.

Preferred combinations of such stretches of amino acid sequences will become clear from the further disclosure herein.

Preferably, in such amino acid sequences the CDR sequences have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the p40- sequences listed in Table A-2 and Figure 22. This degree of amino acid identity can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said amino acid sequence and one or more of the sequences of SEQ ID NO's: 1940; 1941; 1942; 1943; 1944; 1945; 1955; 1958; 1968; 1971; 1972; 1974; 1975; 1976; 1977; 1978; 1979; 1980; 1983; 1986; 1989; 1991; 1992; 1996; 2002; 2004; 2006; 2007; 2023; 2024; 2028; 2033; 2504; 2505; 2506; 2507; 2508 and/or 2509 (see Table A-2 and Figure 22), in which the amino acid

residues that form the framework regions are disregarded. Also, such amino acid sequences of the invention can be as further described herein.

Also, such amino acid sequences are preferably such that they can specifically bind (as defined herein) to the p40 subunit; and more in particular bind to the p40 subunit with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value (all as further) described herein) that is as defined herein.

When the amino acid sequence of the invention essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), the amino acid sequence of the invention is preferably such that:

- CDR1 is chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 16";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 16";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 16";

and/or

- CDR2 is chosen from the group consisting of:

d) the amino acid sequences from the "CDR2 Sequences Group 18";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 18";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 18";

and/or

- CDR3 is chosen from the group consisting of:

g) the amino acid sequences from the "CDR3 Sequences Group 20";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 20";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 20".

In particular, such an amino acid sequence of the invention may be such that CDR1 is chosen from the group consisting of the amino acid sequences from the "CDR1 Sequences

Group 16"; and/or CDR2 is chosen from the group consisting of the amino acid sequences from the "CDR2 Sequences Group 18"; and/or CDR3 is chosen from the group consisting of the amino acid sequences from the "CDR3 Sequences Group 20".

In particular, when the amino acid sequence of the invention essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), the amino acid sequence of the invention is preferably such that:

- CDR1 is chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 16";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 16";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 16";

and

- CDR2 is chosen from the group consisting of:

d) the amino acid sequences from the "CDR2 Sequences Group 18";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 18";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 18";

and

- CDR3 is chosen from the group consisting of:

g) the amino acid sequences from the "CDR3 Sequences Group 20";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 20";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 20"; or any suitable fragment of such an amino acid sequence

In particular, such an amino acid sequence of the invention may be such that CDR1 is chosen from the group consisting of the amino acid sequences from the "CDR1 Sequences Group 16"; and CDR2 is chosen from the group consisting of the amino acid sequences from

the "CDR2 Sequences Group 18"; and CDR3 is chosen from the group consisting of the amino acid sequences from the "CDR3 Sequences Group 20".

Again, preferred combinations of CDR sequences will become clear from the further description herein.

Also, such amino acid sequences are preferably such that they can specifically bind (as defined herein) to the p40 subunit; and more in particular bind to the p40 subunit with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value (all as further) described herein) that is as defined herein.

In one preferred, but non-limiting aspect, the invention relates to an amino acid sequence that essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), in which the CDR sequences of said amino acid sequence have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 1940; 1941; 1942; 1943; 1944; 1945; 1955; 1958; 1968; 1971; 1972; 1974; 1975; 1976; 1977; 1978; 1979; 1980; 1983; 1986; 1989; 1991; 1992; 1996; 2002; 2004; 2006; 2007; 2023; 2024; 2028; 2033; 2504; 2505; 2506; 2507; 2508 and/or 2509 (see Table A-2 and Figure 22). This degree of amino acid identity can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said amino acid sequence and one or more of the sequences of SEQ ID NO's: 1940; 1941; 1942; 1943; 1944; 1945; 1955; 1958; 1968; 1971; 1972; 1974; 1975; 1976; 1977; 1978; 1979; 1980; 1983; 1986; 1989; 1991; 1992; 1996; 2002; 2004; 2006; 2007; 2023; 2024; 2028; 2033; 2504; 2505; 2506; 2507; 2508 and/or 2509 (see Table A-2 and Figure 22), in which the amino acid residues that form the framework regions are disregarded. Such amino acid sequences of the invention can be as further described herein.

Some preferred, but non-limiting examples of p40- sequence are the amino acid sequences of SEQ ID NO's: 1940; 1941; 1942; 1943; 1944; 1945; 1955; 1958; 1968; 1971; 1972; 1974; 1975; 1976; 1977; 1978; 1979; 1980; 1983; 1986; 1989; 1991; 1992; 1996; 2002; 2004; 2006; 2007; 2023; 2024; 2028; 2033; 2504; 2505; 2506; 2507; 2508 and/or 2509 (see Table A-2 and Figure 22). Thus, according to another preferred, but non-limiting aspect

of the invention, a p40- sequence is an amino acid sequence that is directed against (as defined herein) the p40 subunit (as present in for example IL-23 and IL-12) but that (essentially) are not capable of neutralizing or inhibiting the binding of a heterodimeric cytokine comprising a p40 subunit to its receptor (for example, in a suitable alpha-screen assay as exemplified in Examples 19 and 22 for IL-23 and its cognate receptor and for IL-12 and its cognate receptor), and that either:

a) has at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1940; 1941; 1942; 1943; 1944; 1945; 1955; 1958; 1968; 1971; 1972; 1974; 1975; 1976; 1977; 1978; 1979; 1980; 1983; 1986; 1989; 1991; 1992; 1996; 2002; 2004; 2006; 2007; 2023; 2024; 2028; 2033; 2504; 2505; 2506; 2507; 2508 and/or 2509 (see Table A-2 and Figure 22);

and/or that

b) has no more than 20, preferably no more than 10, such as 9, 8, 7, 6, 5, 4, 3, 2 or only one amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1940; 1941; 1942; 1943; 1944; 1945; 1955; 1958; 1968; 1971; 1972; 1974; 1975; 1976; 1977; 1978; 1979; 1980; 1983; 1986; 1989; 1991; 1992; 1996; 2002; 2004; 2006; 2007; 2023; 2024; 2028; 2033; 2504; 2505; 2506; 2507; 2508 and/or 2509 (see Table A-2 and Figure 22). Preferably, such an amino acid sequence has no more than a total of 5 (such as 4, 3. 2 or only one) such amino acid differences in the CDR's and/or no more than a total of 5 (such as 4, 3. 2 or only 1) such amino acid differences in the framework sequences;

and/or that

c) is either (i) capable of cross-blocking (as defined herein) the interaction of at least one of the amino acid sequences of SEQ ID NO's: 1940; 1941; 1942; 1943; 1944; 1945; 1955; 1958; 1968; 1971; 1972; 1974; 1975; 1976; 1977; 1978; 1979; 1980; 1983; 1986; 1989; 1991; 1992; 1996; 2002; 2004; 2006; 2007; 2023; 2024; 2028; 2033; 2504; 2505; 2506; 2507; 2508 and/or 2509 (see Table A-2 and Figure 20) with the p40 subunit and/or (ii) being able to compete with (i.e. is a competitor for) the binding of at least one of the amino acid sequences of SEQ ID NO's: 1940; 1941; 1942; 1943; 1944; 1945; 1955; 1958; 1968; 1971; 1972; 1974; 1975; 1976; 1977; 1978; 1979; 1980; 1983;

1986; 1989; 1991; 1992; 1996; 2002; 2004; 2006; 2007; 2023; 2024; 2028; 2033; 2504; 2505; 2506; 2507; 2508 and/or 2509 (see Table A-2 and Figure 22) to the p40 subunit.

In another preferred, but non-limiting aspect, a p40 sequence is chosen from one of the amino acid sequences of SEQ ID NO's: 1940; 1941; 1942; 1943; 1944; 1945; 1955; 1958; 1968; 1971; 1972; 1974; 1975; 1976; 1977; 1978; 1979; 1980; 1983; 1986; 1989; 1991; 1992; 1996; 2002; 2004; 2006; 2007; 2023; 2024; 2028; 2033; 2504; 2505; 2506; 2507; 2508 and/or 2509 (see Table A-2 and Figure 22).

D) P40+ sequences.

One specific, but non-limiting aspect relates to "p40+ sequences", which generally are defined herein as amino acid sequences of the invention that are directed against (as defined herein) the p40 subunit (as present in for example IL-23 and IL-12), and that are capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p40 subunit to its receptor, and in particular capable of modulating, neutralizing, blocking and/or inhibiting the binding of IL-23 to its (cognate) receptor (in particular, in the alpha-screen assay of described in Example 19 or 22); and/or the binding of IL-12 to its (cognate) receptor (in particular, in the alpha-screen assay of described in Example 19).

P40+ sequences may generally be as further described herein (for example, in terms of affinity, specificity etc. for p40) for amino acid sequences of the invention in general. Also, as described herein for the amino acid sequences of the invention, the p40+ sequences are preferably such that they form or are capable of forming (optionally after suitable folding) a single antigen binding domain or antigen binding unit, and may for example be amino acid sequences that comprise an immunoglobulin fold, amino acid sequences that are comprised of four framework regions and three CDR's, and may in particular be domain antibodies, single domain antibodies, VHH's, "dAb's" or Nanobodies (all as further described herein), or suitable fragments thereof.

In one particular aspect, a p40+ sequence may comprise one or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 23" (as defined and listed in Table A-1; see also Figure 14);

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 23";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 23";

d) the amino acid sequences from the "CDR2 Sequences Group 25" (as defined and listed in Table A-1; see also Figure 14);

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 25";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 25";

g) the amino acid sequences from the "CDR3 Sequences Group 27" (as defined and listed in Table A-1; see also Figure 14);

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 27";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 27";

or any suitable combination thereof.

Optionally, when an amino acid sequence of the invention contains one or more amino acid sequences according to b) and/or c), Optional Condition I, Optional Condition II and/or Optional Condition III (all as defined herein) may apply to said amino acid sequence (i.e. compared to the original amino acid sequence according to a)). Also, optionally, when an amino acid sequence of the invention contains one or more amino acid sequences according to e) and/or f), Optional Condition I, Optional Condition II and/or Optional Condition III (all as defined herein) may apply to said amino acid sequence (i.e. compared to the original amino acid sequence according to d)). Also, optionally, when an amino acid sequence of the invention contains one or more amino acid sequences according to h) and/or i), Optional Condition I, Optional Condition II and/or Optional Condition III (all as defined herein) may apply to said amino acid sequence (i.e. compared to the original amino acid sequence according to g)).

In this specific aspect, the amino acid sequence preferably comprises one or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 23";

b) the amino acid sequences from the "CDR2 Sequences Group 25"; and

c) the amino acid sequences from the "CDR3 Sequences Group 27";

or any suitable combination thereof.

Also, preferably, in such an amino acid sequence, at least one of said stretches of amino acid residues forms part of the antigen binding site for binding against p40.

In a more specific, but again non-limiting aspect, a p40+ sequence may comprise two or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 23";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 23";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 23";

d) the amino acid sequences from the "CDR2 Sequences Group 25";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 25";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 25";

g) the amino acid sequences from the "CDR3 Sequences Group 27";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 27";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 27";

such that (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b) or c), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e), f), g), h) or i); (ii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e) or f), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), g), h) or i); or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to g), h) or i), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), d), e) or f).

In this specific aspect, the amino acid sequence preferably comprises two or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 23";

b) the amino acid sequences from the "CDR2 Sequences Group 25"; and

c) the amino acid sequences from the "CDR3 Sequences Group 27";

such that, (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR1 Sequences Group 23", the second stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR2 Sequences Group 25" or from the "CDR3 Sequences Group 27"; (ii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR2 Sequences Group 25", the second stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR1 Sequences Group 23" or from the "CDR3 Sequences Group 27"; or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR3 Sequences Group 27", the second stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR1 Sequences Group 23" or from the "CDR2 Sequences Group 25".

Also, in such an amino acid sequence, the at least two stretches of amino acid residues again preferably form part of the antigen binding site for binding against p40.

In an even more specific, but non-limiting aspect, a p40+ sequence may comprise three or more stretches of amino acid residues, in which the first stretch of amino acid residues is chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 23";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 23";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 23";

the second stretch of amino acid residues is chosen from the group consisting of:

d) the amino acid sequences from the "CDR2 Sequences Group 25";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 25";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 25";

and the third stretch of amino acid residues is chosen from the group consisting of:

g) the amino acid sequences from the "CDR3 Sequences Group 27";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 27";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 27".

Preferably, in this specifc aspect, the first stretch of amino acid residues is chosen from the group consisting of the amino acid sequences from the "CDR1 Sequences Group 23"; the second stretch of amino acid residues is chosen from the group consisting of the amino acid sequences from the "CDR2 Sequences Group 25"; and the third stretch of amino acid residues is chosen from the group consisting of the amino acid sequences from the "CDR3 Sequences Group 27".

Again, preferably, in such an amino acid sequence, the at least three stretches of amino acid residues forms part of the antigen binding site for binding against p40.

Preferred combinations of such stretches of amino acid sequences will become clear from the further disclosure herein.

Preferably, in such amino acid sequences the CDR sequences have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the p40+ sequences listed in Table A-2 and Figure 23. This degree of amino acid identity can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said amino acid sequence and one or more of the sequences of SEQ ID NO's: 1942; 1946; 1948; 1950; 1952; 1953; 1954; 1956; 1957; 1959; 1962; 1963; 1964; 1965; 1967; 1969; 1970; 1973; 1981; 1982; 1984; 1985; 1987; 1988; 1990; 1993; 1994; 1995; 1997; 1998; 1999; 2000; 2001; 2003; 2005; 2030; 2510; 2511; 2512; 2513; 2514; 2515; 2516; 2517; 2518; 2519; 2520; 2521; 2522; 2523; 2524; 2525; 2526; 2527 and/or 2528 (see Table A-2 and Figure 23), in which the amino acid residues that form the framework regions are disregarded. Also, such amino acid sequences of the invention can be as further described herein.

Also, such amino acid sequences are preferably such that they can specifically bind (as defined herein) to the p40 subunit; and more in particular bind to the p40 subunit with an

affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value (all as further) described herein) that is as defined herein.

When the amino acid sequence of the invention essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), the amino acid sequence of the invention is preferably such that:

- CDR1 is chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 23";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 23";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 23";

and/or

- CDR2 is chosen from the group consisting of:

d) the amino acid sequences from the "CDR2 Sequences Group 25";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 25";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 25";

and/or

- CDR3 is chosen from the group consisting of:

g) the amino acid sequences from the "CDR3 Sequences Group 27";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 27";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 27".

In particular, such an amino acid sequence of the invention may be such that CDR1 is chosen from the group consisting of the amino acid sequences from the "CDR1 Sequences Group 23"; and/or CDR2 is chosen from the group consisting of the amino acid sequences from the "CDR2 Sequences Group 25"; and/or CDR3 is chosen from the group consisting of the amino acid sequences from the "CDR3 Sequences Group 27".

In particular, when the amino acid sequence of the invention essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), the amino acid sequence of the invention is preferably such that:

- CDR1 is chosen from the group consisting of:
  - a) the amino acid sequences from the "CDR1 Sequences Group 23";
  - b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 23";
  - c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 23";

  and
- CDR2 is chosen from the group consisting of:
  - d) the amino acid sequences from the "CDR2 Sequences Group 25";
  - e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 25";
  - f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 25";

  and
- CDR3 is chosen from the group consisting of:
  - g) the amino acid sequences from the "CDR3 Sequences Group 27";
  - h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 27";
  - i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 27"; or any suitable fragment of such an amino acid sequence

In particular, such an amino acid sequence of the invention may be such that CDR1 is chosen from the group consisting of the amino acid sequences from the "CDR1 Sequences Group 23"; and CDR2 is chosen from the group consisting of the amino acid sequences from the "CDR2 Sequences Group 25"; and CDR3 is chosen from the group consisting of the amino acid sequences from the "CDR3 Sequences Group 27".

Again, preferred combinations of CDR sequences will become clear from the further description herein.

Also, such amino acid sequences are preferably such that they can specifically bind (as defined herein) to the p40 subunit; and more in particular bind to the p40 subunit with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value (all as further) described herein) that is as defined herein.

In one preferred, but non-limiting aspect, the invention relates to an amino acid sequence that essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), in which the CDR sequences of said amino acid sequence have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 1942; 1946; 1948; 1950; 1952; 1953; 1954; 1956; 1957; 1959; 1962; 1963; 1964; 1965; 1967; 1969; 1970; 1973; 1981; 1982; 1984; 1985; 1987; 1988; 1990; 1993; 1994; 1995; 1997; 1998; 1999; 2000; 2001; 2003; 2005; 2030; 2510; 2511; 2512; 2513; 2514; 2515; 2516; 2517; 2518; 2519; 2520; 2521; 2522; 2523; 2524; 2525; 2526; 2527 and/or 2528 (see Table A-2 and Figure 23). This degree of amino acid identity can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said amino acid sequence and one or more of the sequences of SEQ ID NO's: 1942; 1946; 1948; 1950; 1952; 1953; 1954; 1956; 1957; 1959; 1962; 1963; 1964; 1965; 1967; 1969; 1970; 1973; 1981; 1982; 1984; 1985; 1987; 1988; 1990; 1993; 1994; 1995; 1997; 1998; 1999; 2000; 2001; 2003; 2005; 2030; 2510; 2511; 2512; 2513; 2514; 2515; 2516; 2517; 2518; 2519; 2520; 2521; 2522; 2523; 2524; 2525; 2526; 2527 and/or 2528 (see Table A-2 and Figure 23), in which the amino acid residues that form the framework regions are disregarded. Such amino acid sequences of the invention can be as further described herein.

Some preferred, but non-limiting examples of p40+ sequences are the amino acid sequences of SEQ ID NO's: 1942; 1946; 1948; 1950; 1952; 1953; 1954; 1956; 1957; 1959; 1962; 1963; 1964; 1965; 1967; 1969; 1970; 1973; 1981; 1982; 1984; 1985; 1987; 1988; 1990; 1993; 1994; 1995; 1997; 1998; 1999; 2000; 2001; 2003; 2005; 2030; 2510; 2511; 2512; 2513; 2514; 2515; 2516; 2517; 2518; 2519; 2520; 2521; 2522; 2523; 2524; 2525; 2526; 2527 and/or 2528 (see Table A-2 and Figure 23). Thus, according to another preferred, but non-limiting aspect of the invention, a p40+ sequence is an amino acid sequence that is

directed against (as defined herein) the p40 subunit (as present in for example IL-23 and Il-12) and that are capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p40 subunit to its receptor, and in particular capable of modulating, neutralizing, blocking and/or inhibiting the binding of IL-23 to its (cognate) receptor (in particular, in the alpha-screen assay of described in Example 19 or 22); and/or the binding of IL-12 to its (cognate) receptor (in particular, in the alpha-screen assay of described in Example 19), and that either

a) has at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1942; 1946; 1948; 1950; 1952; 1953; 1954; 1956; 1957; 1959; 1962; 1963; 1964; 1965; 1967; 1969; 1970; 1973; 1981; 1982; 1984; 1985; 1987; 1988; 1990; 1993; 1994; 1995; 1997; 1998; 1999; 2000; 2001; 2003; 2005; 2030; 2510; 2511; 2512; 2513; 2514; 2515; 2516; 2517; 2518; 2519; 2520; 2521; 2522; 2523; 2524; 2525; 2526; 2527 and/or 2528 (see Table A-2 and Figure 23);

and/or that

b) has no more than 20, preferably no more than 10, such as 9, 8, 7, 6, 5, 4, 3, 2 or only one amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1942; 1946; 1948; 1950; 1952; 1953; 1954; 1956; 1957; 1959; 1962; 1963; 1964; 1965; 1967; 1969; 1970; 1973; 1981; 1982; 1984; 1985; 1987; 1988; 1990; 1993; 1994; 1995; 1997; 1998; 1999; 2000; 2001; 2003; 2005; 2030; 2510; 2511; 2512; 2513; 2514; 2515; 2516; 2517; 2518; 2519; 2520; 2521; 2522; 2523; 2524; 2525; 2526; 2527 and/or 2528 (see Table A-2 and Figure 23). Preferably, such an amino acid sequence has no more than a total of 5 (such as 4, 3. 2 or only one) such amino acid differences in the CDR's and/or no more than a total of 5 (such as 4, 3. 2 or only 1) such amino acid differences in the framework sequences;

and/or that

c) is either (i) capable of cross-blocking (as defined herein) the interaction of at least one of the amino acid sequences of SEQ ID NO's: 1942; 1946; 1948; 1950; 1952; 1953; 1954; 1956; 1957; 1959; 1962; 1963; 1964; 1965; 1967; 1969; 1970; 1973; 1981; 1982; 1984; 1985; 1987; 1988; 1990; 1993; 1994; 1995; 1997; 1998; 1999; 2000; 2001; 2003; 2005; 2030; 2510; 2511; 2512; 2513; 2514; 2515; 2516; 2517; 2518; 2519; 2520; 2521;

2522; 2523; 2524; 2525; 2526; 2527 and/or 2528 with the p40 subunit and/or (ii) being able to compete with (i.e. is a competitor for) the binding of at least one of the amino acid sequences of SEQ ID NO's: 1942; 1946; 1948; 1950; 1952; 1953; 1954; 1956; 1957; 1959; 1962; 1963; 1964; 1965; 1967; 1969; 1970; 1973; 1981; 1982; 1984; 1985; 1987; 1988; 1990; 1993; 1994; 1995; 1997; 1998; 1999; 2000; 2001; 2003; 2005; 2030; 2510; 2511; 2512; 2513; 2514; 2515; 2516; 2517; 2518; 2519; 2520; 2521; 2522; 2523; 2524; 2525; 2526; 2527 and/or 2528 (see Table A-2 and Figure 23) to the p40 subunit.

In another preferred, but non-limiting aspect, a p40+ sequence is chosen from one of the amino acid sequences of SEQ ID NO's: 1942; 1946; 1948; 1950; 1952; 1953; 1954; 1956; 1957; 1959; 1962; 1963; 1964; 1965; 1967; 1969; 1970; 1973; 1981; 1982; 1984; 1985; 1987; 1988; 1990; 1993; 1994; 1995; 1997; 1998; 1999; 2000; 2001; 2003; 2005; 2030; 2510; 2511; 2512; 2513; 2514; 2515; 2516; 2517; 2518; 2519; 2520; 2521; 2522; 2523; 2524; 2525; 2526; 2527 and/or 2528 (see Table A-2 and Figure 23).

<u>E) P35 sequences.</u>

One specific, but non-limiting aspect relates to "p35 sequences", which generally are defined herein as amino acid sequences of the invention that are directed against (as defined herein) the p35 subunit (as present in for example IL-12).

P35 sequences may generally be as further described herein for amino acid sequences of the invention, i.e. in terms of affinity, specificity etc. for p35. Also, as described herein for the amino acid sequences of the invention, the p35 sequences are preferably such that they form or are capable of forming (optionally after suitable folding) a single antigen binding domain or antigen binding unit, and may for example be amino acid sequences that comprise an immunoglobulin fold, amino acid sequences that are comprised of four framework regions and three CDR's, and may in particular be domain antibodies, single domain antibodies, VHH's, "dAb's" or Nanobodies (all as further described herein), or suitable fragments thereof.

In one particular aspect, a p35 sequence may comprise one or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 30" (as defined and listed in Table A-1; see also Figure 15);

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 30";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 30";

d) the amino acid sequences from the "CDR2 Sequences Group 32" (as defined and listed in Table A-1; see also Figure 15);

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 32";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 32";

g) the amino acid sequences from the "CDR3 Sequences Group 34" (as defined and listed in Table A-1; see also Figure 15);

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 34";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 34";

or any suitable combination thereof.

Optionally, when an amino acid sequence of the invention contains one or more amino acid sequences according to b) and/or c), Optional Condition I, Optional Condition II and/or Optional Condition III (all as defined herein) may apply to said amino acid sequence (i.e. compared to the original amino acid sequence according to a)). Also, optionally, when an amino acid sequence of the invention contains one or more amino acid sequences according to e) and/or f), Optional Condition I, Optional Condition II and/or Optional Condition III (all as defined herein) may apply to said amino acid sequence (i.e. compared to the original amino acid sequence according to d)). Also, optionally, when an amino acid sequence of the invention contains one or more amino acid sequences according to h) and/or i), Optional Condition I, Optional Condition II and/or Optional Condition III (all as defined herein) may apply to said amino acid sequence (i.e. compared to the original amino acid sequence according to g)).

In this specific aspect, the amino acid sequence preferably comprises one or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 30";

b) the amino acid sequences from the "CDR2 Sequences Group 32"; and

c) the amino acid sequences from the "CDR3 Sequences Group 34";

or any suitable combination thereof.

Also, preferably, in such an amino acid sequence, at least one of said stretches of amino acid residues forms part of the antigen binding site for binding against p35.

In a more specific, but again non-limiting aspect, a p35 sequence may comprise two or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 30";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 30";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 30";

d) the amino acid sequences from the "CDR2 Sequences Group 32";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 32";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 32";

g) the amino acid sequences from the "CDR3 Sequences Group 34";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 34";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 34";

such that (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b) or c), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e), f), g), h) or i); (ii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e) or f), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), g), h) or i); or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to g), h) or i), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), d), e) or f).

In this specific aspect, the amino acid sequence preferably comprises two or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 30";

b) the amino acid sequences from the "CDR2 Sequences Group 32"; and

c) the amino acid sequences from the "CDR3 Sequences Group 34";

such that, (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR1 Sequences Group 30", the second stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR2 Sequences Group 32" or from the "CDR3 Sequences Group 34"; (ii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR2 Sequences Group 32", the second stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR1 Sequences Group 30" or from the "CDR3 Sequences Group 34"; or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR3 Sequences Group 34", the second stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR1 Sequences Group 30" or from the "CDR2 Sequences Group 32".

Also, in such an amino acid sequence, the at least two stretches of amino acid residues again preferably form part of the antigen binding site for binding against p35.

In an even more specific, but non-limiting aspect, a p35 sequence may comprise three or more stretches of amino acid residues, in which the first stretch of amino acid residues is chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 30";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 30";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 30";

the second stretch of amino acid residues is chosen from the group consisting of:

d) the amino acid sequences from the "CDR2 Sequences Group 32";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 32";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 32";

and the third stretch of amino acid residues is chosen from the group consisting of:

g) the amino acid sequences from the "CDR3 Sequences Group 34";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 34";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 34".

Preferably, in this specifc aspect, the first stretch of amino acid residues is chosen from the group consisting of the amino acid sequences from the "CDR1 Sequences Group 30"; the second stretch of amino acid residues is chosen from the group consisting of the amino acid sequences from the "CDR2 Sequences Group 32"; and the third stretch of amino acid residues is chosen from the group consisting of the amino acid sequences from the "CDR3 Sequences Group 34".

Again, preferably, in such an amino acid sequence, the at least three stretches of amino acid residues forms part of the antigen binding site for binding against p35.

Preferred combinations of such stretches of amino acid sequences will become clear from the further disclosure herein.

Preferably, in such amino acid sequences the CDR sequences have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the p35 sequences listed in Table A-2 and Figure 24. This degree of amino acid identity can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said amino acid sequence and one or more of the sequences of SEQ ID NO's: 1947; 1949; 1951; 1960; 1961; 1966; 2008; 2009; 2010; 2011; 2012; 2013; 2014; 2015; 2016; 2017; 2018; 2019; 2020; 2021; 2022; 2025; 2026; 2027; 2029; 2031; 2032; 2034; 2035; 2036; 2037 and/or 2529 (see Table A-2 and Figure 24), in which the amino acid residues that form the framework regions are disregarded. Also, such amino acid sequences of the invention can be as further described herein.

Also, such amino acid sequences are preferably such that they can specifically bind (as defined herein) to the p35 subunit; and more in particular bind to the p35 subunit with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value

(actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value (all as further) described herein) that is as defined herein.

When the amino acid sequence of the invention essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), the amino acid sequence of the invention is preferably such that:

- CDR1 is chosen from the group consisting of:
  a) the amino acid sequences from the "CDR1 Sequences Group 30";
  b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 30";
  c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 30";

  and/or
- CDR2 is chosen from the group consisting of:
  d) the amino acid sequences from the "CDR2 Sequences Group 32";
  e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 32";
  f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 32";

  and/or
- CDR3 is chosen from the group consisting of:
  g) the amino acid sequences from the "CDR3 Sequences Group 34";
  h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 34";
  i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 34".

In particular, such an amino acid sequence of the invention may be such that CDR1 is chosen from the group consisting of the amino acid sequences from the "CDR1 Sequences Group 30"; and/or CDR2 is chosen from the group consisting of the amino acid sequences from the "CDR2 Sequences Group 32"; and/or CDR3 is chosen from the group consisting of the amino acid sequences from the "CDR3 Sequences Group 34".

In particular, when the amino acid sequence of the invention essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions

(CDR1 to CDR3, respectively), the amino acid sequence of the invention is preferably such that:

- CDR1 is chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 30";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 30";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 30";

and

- CDR2 is chosen from the group consisting of:

d) the amino acid sequences from the "CDR2 Sequences Group 32";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 32";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 32";

and

- CDR3 is chosen from the group consisting of:

g) the amino acid sequences from the "CDR3 Sequences Group 34";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 34";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 34"; or any suitable fragment of such an amino acid sequence

In particular, such an amino acid sequence of the invention may be such that CDR1 is chosen from the group consisting of the amino acid sequences from the "CDR1 Sequences Group 30"; and CDR2 is chosen from the group consisting of the amino acid sequences from the "CDR2 Sequences Group 32"; and CDR3 is chosen from the group consisting of the amino acid sequences from the "CDR3 Sequences Group 34".

Again, preferred combinations of CDR sequences will become clear from the further description herein.

Also, such amino acid sequences are preferably such that they can specifically bind (as defined herein) to the p35 subunit; and more in particular bind to the p35 subunit with an

affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value (all as further) described herein) that is as defined herein.

In one preferred, but non-limiting aspect, the invention relates to an amino acid sequence that essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), in which the CDR sequences of said amino acid sequence have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 1947; 1949; 1951; 1960; 1961; 1966; 2008; 2009; 2010; 2011; 2012; 2013; 2014; 2015; 2016; 2017; 2018; 2019; 2020; 2021; 2022; 2025; 2026; 2027; 2029; 2031; 2032; 2034; 2035; 2036; 2037 and/or 2529 (see Table A-2 and Figure 24). This degree of amino acid identity can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said amino acid sequence and one or more of the sequences of SEQ ID NO's: 1947; 1949; 1951; 1960; 1961; 1966; 2008; 2009; 2010; 2011; 2012; 2013; 2014; 2015; 2016; 2017; 2018; 2019; 2020; 2021; 2022; 2025; 2026; 2027; 2029; 2031; 2032; 2034; 2035; 2036; 2037 and/or 2529 (see Table A-2 and Figure 24), in which the amino acid residues that form the framework regions are disregarded. Such amino acid sequences of the invention can be as further described herein.

Some preferred, but non-limiting examples of p35 sequences are the amino acid sequences of SEQ ID NO's: 1947; 1949; 1951; 1960; 1961; 1966; 2008; 2009; 2010; 2011; 2012; 2013; 2014; 2015; 2016; 2017; 2018; 2019; 2020; 2021; 2022; 2025; 2026; 2027; 2029; 2031; 2032; 2034; 2035; 2036; 2037 and/or 2529 (see Table A-2 and Figure 24). Thus, according to another preferred, but non-limiting aspect of the invention, a p35 sequence is an amino acid sequence that is directed against (as defined herein) the p35 subunit (as present in for example IL-12) and that either:

a) has at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 1947; 1949; 1951; 1960; 1961; 1966; 2008; 2009; 2010; 2011; 2012;

2013; 2014; 2015; 2016; 2017; 2018; 2019; 2020; 2021; 2022; 2025; 2026; 2027; 2029; 2031; 2032; 2034; 2035; 2036; 2037 and/or 2529 (see Table A-2 and Figure 24);

and/or that

b) has no more than 20, preferably no more than 10, such as 9, 8, 7, 6, 5, 4, 3, 2 or only one amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 1947; 1949; 1951; 1960; 1961; 1966; 2008; 2009; 2010; 2011; 2012; 2013; 2014; 2015; 2016; 2017; 2018; 2019; 2020; 2021; 2022; 2025; 2026; 2027; 2029; 2031; 2032; 2034; 2035; 2036; 2037 and/or 2529 (see Table A-2 and Figure 24). Preferably, such an amino acid sequence has no more than a total of 5 (such as 4, 3. 2 or only one) such amino acid differences in the CDR's and/or no more than a total of 5 (such as 4, 3. 2 or only 1) such amino acid differences in the framework sequences;

and/or that

c) is either (i) capable of cross-blocking (as defined herein) the interaction of at least one of the amino acid sequences of SEQ ID NO's: 1947; 1949; 1951; 1960; 1961; 1966; 2008; 2009; 2010; 2011; 2012; 2013; 2014; 2015; 2016; 2017; 2018; 2019; 2020; 2021; 2022; 2025; 2026; 2027; 2029; 2031; 2032; 2034; 2035; 2036; 2037 and/or 2529 with the p35 subunit and/or (ii) being able to compete with (i.e. is a competitor for) the binding of at least one of the amino acid sequences of SEQ ID NO's: 1947; 1949; 1951; 1960; 1961; 1966; 2008; 2009; 2010; 2011; 2012; 2013; 2014; 2015; 2016; 2017; 2018; 2019; 2020; 2021; 2022; 2025; 2026; 2027; 2029; 2031; 2032; 2034; 2035; 2036; 2037 and/or 2529 (see Table A-2 and Figure 24) to the p35 subunit.

In another preferred, but non-limiting aspect, a p35 sequence is chosen from one of the amino acid sequences of SEQ ID NO's: 1947; 1949; 1951; 1960; 1961; 1966; 2008; 2009; 2010; 2011; 2012; 2013; 2014; 2015; 2016; 2017; 2018; 2019; 2020; 2021; 2022; 2025; 2026; 2027; 2029; 2031; 2032; 2034; 2035; 2036; 2037 and/or 2529 (see Table A-2 and Figure 24).

F) IL-27 sequences.

One specific, but non-limiting aspect relates to "IL-27 sequences", which generally are defined herein as amino acid sequences of the invention that are directed against (as defined herein) IL-27 (either against the EBI3 subunit or the p28 subunit).

IL-27 sequences may generally be as further described herein (for example, in terms of affinity, specificity etc. for IL-27 or one of its subunits) for amino acid sequences of the invention in general. Also, as described herein for the amino acid sequences of the invention, the IL-27 sequences are preferably such that they form or are capable of forming (optionally after suitable folding) a single antigen binding domain or antigen binding unit, and may for example be amino acid sequences that comprise an immunoglobulin fold, amino acid sequences that are comprised of four framework regions and three CDR's, and may in particular be domain antibodies, single domain antibodies, VHH's, "dAb's" or Nanobodies (all as further described herein), or suitable fragments thereof.

In one particular aspect, an IL-27 sequence may comprise one or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 37" (as defined and listed in Table A-1; see also Figure 16);

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 37";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 37";

d) the amino acid sequences from the "CDR2 Sequences Group 39" (as defined and listed in Table A-1; see also Figure 16);

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 39";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 39";

g) the amino acid sequences from the "CDR3 Sequences Group 41" (as defined and listed in Table A-1; see also Figure 16);

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 41";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 41";

or any suitable combination thereof.

Optionally, when an amino acid sequence of the invention contains one or more amino acid sequences according to b) and/or c), Optional Condition I, Optional Condition II

and/or Optional Condition III (all as defined herein) may apply to said amino acid sequence (i.e. compared to the original amino acid sequence according to a)). Also, optionally, when an amino acid sequence of the invention contains one or more amino acid sequences according to e) and/or f), Optional Condition I, Optional Condition II and/or Optional Condition III (all as defined herein) may apply to said amino acid sequence (i.e. compared to the original amino acid sequence according to d)). Also, optionally, when an amino acid sequence of the invention contains one or more amino acid sequences according to h) and/or i), Optional Condition I, Optional Condition II and/or Optional Condition III (all as defined herein) may apply to said amino acid sequence (i.e. compared to the original amino acid sequence according to g)).

In this specific aspect, the amino acid sequence preferably comprises one or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 37";

b) the amino acid sequences from the "CDR2 Sequences Group 39"; and

c) the amino acid sequences from the "CDR3 Sequences Group 41";

or any suitable combination thereof.

Also, preferably, in such an amino acid sequence, at least one of said stretches of amino acid residues forms part of the antigen binding site for binding against IL-27.

In a more specific, but again non-limiting aspect, an IL-27 sequence may comprise two or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 37";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 37";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 37";

d) the amino acid sequences from the "CDR2 Sequences Group 39";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 39";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 39";

g) the amino acid sequences from the "CDR3 Sequences Group 41";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 41";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 41";

such that (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b) or c), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e), f), g), h) or i); (ii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e) or f), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), g), h) or i); or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to g), h) or i), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), d), e) or f).

In this specific aspect, the amino acid sequence preferably comprises two or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 37";

b) the amino acid sequences from the "CDR2 Sequences Group 39"; and

c) the amino acid sequences from the "CDR3 Sequences Group 41";

such that, (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR1 Sequences Group 37", the second stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR2 Sequences Group 39" or from the "CDR3 Sequences Group 41"; (ii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR2 Sequences Group 39", the second stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR1 Sequences Group 37" or from the "CDR3 Sequences Group 41"; or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR3 Sequences Group 41", the second stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR1 Sequences Group 37" or from the "CDR2 Sequences Group 39".

Also, in such an amino acid sequence, the at least two stretches of amino acid residues again preferably form part of the antigen binding site for binding against IL-27.

In an even more specific, but non-limiting aspect, an IL-27 sequence may comprise three or more stretches of amino acid residues, in which the first stretch of amino acid residues is chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 37";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 37";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 37";

the second stretch of amino acid residues is chosen from the group consisting of:

d) the amino acid sequences from the "CDR2 Sequences Group 39";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 39";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 39";

and the third stretch of amino acid residues is chosen from the group consisting of:

g) the amino acid sequences from the "CDR3 Sequences Group 41";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 41";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 41".

Preferably, in this specifc aspect, the first stretch of amino acid residues is chosen from the group consisting of the amino acid sequences from the "CDR1 Sequences Group 37"; the second stretch of amino acid residues is chosen from the group consisting of the amino acid sequences from the "CDR2 Sequences Group 39"; and the third stretch of amino acid residues is chosen from the group consisting of the amino acid sequences from the "CDR3 Sequences Group 41".

Again, preferably, in such an amino acid sequence, the at least three stretches of amino acid residues forms part of the antigen binding site for binding against IL-27.

Preferred combinations of such stretches of amino acid sequences will become clear from the further disclosure herein.

Preferably, in such amino acid sequences the CDR sequences have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino

acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the IL-27 sequences listed in Table A-2 and Figure 26. This degree of amino acid identity can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said amino acid sequence and one or more of the sequences of SEQ ID NO's: 2038; 2039; 2040; 2041; 2042; 2043; 2044; 2045; 2046; 2047; 2048; 2049; 2050; 2051; 2052; 2053; 2054; 2055; 2056; 2057; 2058; 2059; 2060; 2061; 2062; 2063; 2064; 2065; 2066; 2067; 2068; 2069; 2070; 2071; 2072; 2073; 2074; 2075 and/or 2076 (see Table A-2 and Figure 26), in which the amino acid residues that form the framework regions are disregarded. Also, such amino acid sequences of the invention can be as further described herein.

Also, such amino acid sequences are preferably such that they can specifically bind (as defined herein) to IL-27 (i.e. to the EBI3 subunit or the p28 subunit); and more in particular bind to IL-27 with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value (all as further) described herein) that is as defined herein.

When the amino acid sequence of the invention essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), the amino acid sequence of the invention is preferably such that:

- CDR1 is chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 37";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 37";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 37";

and/or

- CDR2 is chosen from the group consisting of:

d) the amino acid sequences from the "CDR2 Sequences Group 39";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 39";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 39";

and/or

- CDR3 is chosen from the group consisting of:

g) the amino acid sequences from the "CDR3 Sequences Group 41";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 41";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 41".

In particular, such an amino acid sequence of the invention may be such that CDR1 is chosen from the group consisting of the amino acid sequences from the "CDR1 Sequences Group 37"; and/or CDR2 is chosen from the group consisting of the amino acid sequences from the "CDR2 Sequences Group 39"; and/or CDR3 is chosen from the group consisting of the amino acid sequences from the "CDR3 Sequences Group 41".

In particular, when the amino acid sequence of the invention essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), the amino acid sequence of the invention is preferably such that:

- CDR1 is chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 37";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 37";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 37";

and

- CDR2 is chosen from the group consisting of:

d) the amino acid sequences from the "CDR2 Sequences Group 39";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 39";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 39";

and

- CDR3 is chosen from the group consisting of:

g) the amino acid sequences from the "CDR3 Sequences Group 41";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 41";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 41"; or any suitable fragment of such an amino acid sequence

In particular, such an amino acid sequence of the invention may be such that CDR1 is chosen from the group consisting of the amino acid sequences from the "CDR1 Sequences Group 37"; and CDR2 is chosen from the group consisting of the amino acid sequences from the "CDR2 Sequences Group 39"; and CDR3 is chosen from the group consisting of the amino acid sequences from the "CDR3 Sequences Group 41".

Again, preferred combinations of CDR sequences will become clear from the further description herein.

Also, such amino acid sequences are preferably such that they can specifically bind (as defined herein) to IL-27; and more in particular bind to IL-27 with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value (all as further) described herein) that is as defined herein.

In one preferred, but non-limiting aspect, the invention relates to an amino acid sequence that essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), in which the CDR sequences of said amino acid sequence have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 2038; 2039; 2040; 2041; 2042; 2043; 2044; 2045; 2046; 2047; 2048; 2049; 2050; 2051; 2052; 2053; 2054; 2055; 2056; 2057; 2058; 2059; 2060; 2061; 2062; 2063; 2064; 2065; 2066; 2067; 2068; 2069; 2070; 2071; 2072; 2073; 2074; 2075 and/or 2076 (see Table A-2 and Figure 26). This degree of amino acid identity can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said amino acid sequence and one or more of the sequences of SEQ ID NO's: 2038; 2039; 2040; 2041; 2042; 2043; 2044; 2045; 2046; 2047; 2048; 2049; 2050; 2051; 2052; 2053; 2054; 2055; 2056; 2057; 2058; 2059; 2060; 2061; 2062; 2063; 2064; 2065; 2066; 2067; 2068; 2069; 2070; 2071; 2072; 2073;

2074; 2075 and/or 2076 (see Table A-2 and Figure 26), in which the amino acid residues that form the framework regions are disregarded. Such amino acid sequences of the invention can be as further described herein.

Some preferred, but non-limiting examples of IL-27 sequences are the amino acid sequences of SEQ ID NO's: 2038; 2039; 2040; 2041; 2042; 2043; 2044; 2045; 2046; 2047; 2048; 2049; 2050; 2051; 2052; 2053; 2054; 2055; 2056; 2057; 2058; 2059; 2060; 2061; 2062; 2063; 2064; 2065; 2066; 2067; 2068; 2069; 2070; 2071; 2072; 2073; 2074; 2075 and/or 2076 (see Table A-2 and Figure 26). Thus, according to another preferred, but non-limiting aspect of the invention, an IL-27 sequence is an amino acid sequence that is directed against (as defined herein) IL-27 and that either:

a) has at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 2038; 2039; 2040; 2041; 2042; 2043; 2044; 2045; 2046; 2047; 2048; 2049; 2050; 2051; 2052; 2053; 2054; 2055; 2056; 2057; 2058; 2059; 2060; 2061; 2062; 2063; 2064; 2065; 2066; 2067; 2068; 2069; 2070; 2071; 2072; 2073; 2074; 2075 and/or 2076 (see Table A-2 and Figure 26);

and/or that

b) has no more than 20, preferably no more than 10, such as 9, 8, 7, 6, 5, 4, 3, 2 or only one amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 2038; 2039; 2040; 2041; 2042; 2043; 2044; 2045; 2046; 2047; 2048; 2049; 2050; 2051; 2052; 2053; 2054; 2055; 2056; 2057; 2058; 2059; 2060; 2061; 2062; 2063; 2064; 2065; 2066; 2067; 2068; 2069; 2070; 2071; 2072; 2073; 2074; 2075 and/or 2076 (see Table A-2 and Figure 26). Preferably, such an amino acid sequence has no more than a total of 5 (such as 4, 3. 2 or only one) such amino acid differences in the CDR's and/or no more than a total of 5 (such as 4, 3. 2 or only 1) such amino acid differences in the framework sequences;

and/or that

c) is either (i) capable of cross-blocking (as defined herein) the interaction of at least one of the amino acid sequences of SEQ ID NO's: 2038; 2039; 2040; 2041; 2042; 2043; 2044; 2045; 2046; 2047; 2048; 2049; 2050; 2051; 2052; 2053; 2054; 2055; 2056; 2057; 2058; 2059; 2060; 2061; 2062; 2063; 2064; 2065; 2066; 2067; 2068; 2069; 2070; 2071;

2072; 2073; 2074; 2075 and/or 2076 with IL-27 and/or (ii) being able to compete with (i.e. is a competitor for) the binding of at least one of the amino acid sequences of SEQ ID NO's: 2038; 2039; 2040; 2041; 2042; 2043; 2044; 2045; 2046; 2047; 2048; 2049; 2050; 2051; 2052; 2053; 2054; 2055; 2056; 2057; 2058; 2059; 2060; 2061; 2062; 2063; 2064; 2065; 2066; 2067; 2068; 2069; 2070; 2071; 2072; 2073; 2074; 2075 and/or 2076 (see Table A-2 and Figure 26) to IL-27.

In another preferred, but non-limiting aspect, an IL-27 sequence is chosen from one of the amino acid sequences of SEQ ID NO's: 2038; 2039; 2040; 2041; 2042; 2043; 2044; 2045; 2046; 2047; 2048; 2049; 2050; 2051; 2052; 2053; 2054; 2055; 2056; 2057; 2058; 2059; 2060; 2061; 2062; 2063; 2064; 2065; 2066; 2067; 2068; 2069; 2070; 2071; 2072; 2073; 2074; 2075 and/or 2076 (see Table A-2 and Figure 26).

G) IL-12Rb1 sequences.

One specific, but non-limiting aspect relates to "IL-12Rb1 sequences", which generally are defined herein as amino acid sequences of the invention that are directed against (as defined herein) the IL-12Rb1 subunit, as present in both the receptor for IL-12 as well as the receptor for IL-23 (and thereby, against both the receptor for IL-12 as well as IL-23).

IL-12Rb1 sequences may generally be as further described herein (for example, in terms of affinity, specificity etc. for IL-12Rb1) for amino acid sequences of the invention in general. Also, as described herein for the amino acid sequences of the invention, the IL-12Rb1 sequences are preferably such that they form or are capable of forming (optionally after suitable folding) a single antigen binding domain or antigen binding unit, and may for example be amino acid sequences that comprise an immunoglobulin fold, amino acid sequences that are comprised of four framework regions and three CDR's, and may in particular be domain antibodies, single domain antibodies, VHH's, "dAb's" or Nanobodies (all as further described herein), or suitable fragments thereof.

In one particular aspect, an IL-12Rb1 sequence may comprise one or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 44" (as defined and listed in Table A-1; see also Figure 17);

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 44";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 44";

d) the amino acid sequences from the "CDR2 Sequences Group 46" (as defined and listed in Table A-1; see also Figure 17);

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 46";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 46";

g) the amino acid sequences from the "CDR3 Sequences Group 48" (as defined and listed in Table A-1; see also Figure 17);

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 48";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 48";

or any suitable combination thereof.

Optionally, when an amino acid sequence of the invention contains one or more amino acid sequences according to b) and/or c), Optional Condition I, Optional Condition II and/or Optional Condition III (all as defined herein) may apply to said amino acid sequence (i.e. compared to the original amino acid sequence according to a)). Also, optionally, when an amino acid sequence of the invention contains one or more amino acid sequences according to e) and/or f), Optional Condition I, Optional Condition II and/or Optional Condition III (all as defined herein) may apply to said amino acid sequence (i.e. compared to the original amino acid sequence according to d)). Also, optionally, when an amino acid sequence of the invention contains one or more amino acid sequences according to h) and/or i), Optional Condition I, Optional Condition II and/or Optional Condition III (all as defined herein) may apply to said amino acid sequence (i.e. compared to the original amino acid sequence according to g)).

In this specific aspect, the amino acid sequence preferably comprises one or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 44";

b) the amino acid sequences from the "CDR2 Sequences Group 46"; and

c) the amino acid sequences from the "CDR3 Sequences Group 48";

or any suitable combination thereof.

Also, preferably, in such an amino acid sequence, at least one of said stretches of amino acid residues forms part of the antigen binding site for binding against IL-12Rb1.

In a more specific, but again non-limiting aspect, an IL-12Rb1 sequence may comprise two or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 44";
b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 44";
c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 44";
d) the amino acid sequences from the "CDR2 Sequences Group 46";
e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 46";
f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 46";
g) the amino acid sequences from the "CDR3 Sequences Group 48";
h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 48";
i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 48";

such that (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b) or c), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e), f), g), h) or i); (ii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e) or f), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), g), h) or i); or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to g), h) or i), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), d), e) or f).

In this specific aspect, the amino acid sequence preferably comprises two or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 44";

b) the amino acid sequences from the "CDR2 Sequences Group 46"; and

c) the amino acid sequences from the "CDR3 Sequences Group 48";

such that, (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR1 Sequences Group 44", the second stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR2 Sequences Group 46" or from the "CDR3 Sequences Group 48"; (ii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR2 Sequences Group 46", the second stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR1 Sequences Group 44" or from the "CDR3 Sequences Group 48"; or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR3 Sequences Group 48", the second stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR1 Sequences Group 44" or from the "CDR2 Sequences Group 46".

Also, in such an amino acid sequence, the at least two stretches of amino acid residues again preferably form part of the antigen binding site for binding against IL-12Rb1.

In an even more specific, but non-limiting aspect, an IL-12Rb1 sequence may comprise three or more stretches of amino acid residues, in which the first stretch of amino acid residues is chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 44";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 44";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 44";

the second stretch of amino acid residues is chosen from the group consisting of:

d) the amino acid sequences from the "CDR2 Sequences Group 46";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 46";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 46";

and the third stretch of amino acid residues is chosen from the group consisting of:

g) the amino acid sequences from the "CDR3 Sequences Group 48";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 48";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 48".

Preferably, in this specifc aspect, the first stretch of amino acid residues is chosen from the group consisting of the amino acid sequences from the "CDR1 Sequences Group 44"; the second stretch of amino acid residues is chosen from the group consisting of the amino acid sequences from the "CDR2 Sequences Group 46"; and the third stretch of amino acid residues is chosen from the group consisting of the amino acid sequences from the "CDR3 Sequences Group 48".

Again, preferably, in such an amino acid sequence, the at least three stretches of amino acid residues forms part of the antigen binding site for binding against IL-12Rb1.

Preferred combinations of such stretches of amino acid sequences will become clear from the further disclosure herein.

Preferably, in such amino acid sequences the CDR sequences have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the IL-12Rb1 sequences listed in Table A-2 and Figure 27. This degree of amino acid identity can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said amino acid sequence and one or more of the sequences of SEQ ID NO's: 2077; 2078; 2079; 2080; 2081; 2082; 2083; 2084; 2085; 2086; 2087; 2088; 2089; 2090; 2091; 2092; 2093; 2094; 2095; 2096; 2097; 2098; 2099; 2100; 2101; 2102 and/or 2103 (see Table A-2 and Figure 27), in which the amino acid residues that form the framework regions are disregarded. Also, such amino acid sequences of the invention can be as further described herein.

Also, such amino acid sequences are preferably such that they can specifically bind (as defined herein) to the IL-12Rb1 subunit (i.e. as present in the receptor for IL-12 and/or in the receptor for IL-23); and more in particular bind to the IL-12Rb1 subunit with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value (all as further) described herein) that is as defined herein.

When the amino acid sequence of the invention essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), the amino acid sequence of the invention is preferably such that:

- CDR1 is chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 44";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 44";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 44";

and/or

- CDR2 is chosen from the group consisting of:

d) the amino acid sequences from the "CDR2 Sequences Group 46";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 46";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 46";

and/or

- CDR3 is chosen from the group consisting of:

g) the amino acid sequences from the "CDR3 Sequences Group 48";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 48";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 48".

In particular, such an amino acid sequence of the invention may be such that CDR1 is chosen from the group consisting of the amino acid sequences from the "CDR1 Sequences Group 44"; and/or CDR2 is chosen from the group consisting of the amino acid sequences from the "CDR2 Sequences Group 46"; and/or CDR3 is chosen from the group consisting of the amino acid sequences from the "CDR3 Sequences Group 48".

In particular, when the amino acid sequence of the invention essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), the amino acid sequence of the invention is preferably such that:

- CDR1 is chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 44";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 44";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 44";

and

- CDR2 is chosen from the group consisting of:

d) the amino acid sequences from the "CDR2 Sequences Group 46";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 46";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 46";

and

- CDR3 is chosen from the group consisting of:

g) the amino acid sequences from the "CDR3 Sequences Group 48";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 48";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 48"; or any suitable fragment of such an amino acid sequence

In particular, such an amino acid sequence of the invention may be such that CDR1 is chosen from the group consisting of the amino acid sequences from the "CDR1 Sequences Group 44"; and CDR2 is chosen from the group consisting of the amino acid sequences from the "CDR2 Sequences Group 46"; and CDR3 is chosen from the group consisting of the amino acid sequences from the "CDR3 Sequences Group 48".

Again, preferred combinations of CDR sequences will become clear from the further description herein.

Also, such amino acid sequences are preferably such that they can specifically bind (as defined herein) to IL-12Rb1; and more in particular bind to IL-12Rb1 with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or

apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value (all as further) described herein) that is as defined herein.

In one preferred, but non-limiting aspect, the invention relates to an amino acid sequence that essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), in which the CDR sequences of said amino acid sequence have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 2077; 2078; 2079; 2080; 2081; 2082; 2083; 2084; 2085; 2086; 2087; 2088; 2089; 2090; 2091; 2092; 2093; 2094; 2095; 2096; 2097; 2098; 2099; 2100; 2101; 2102 and/or 2103 (see Table A-2 and Figure 27). This degree of amino acid identity can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said amino acid sequence and one or more of the sequences of SEQ ID NO's: 2077; 2078; 2079; 2080; 2081; 2082; 2083; 2084; 2085; 2086; 2087; 2088; 2089; 2090; 2091; 2092; 2093; 2094; 2095; 2096; 2097; 2098; 2099; 2100; 2101; 2102 and/or 2103 (see Table A-2 and Figure 27), in which the amino acid residues that form the framework regions are disregarded. Such amino acid sequences of the invention can be as further described herein.

Some preferred, but non-limiting examples of IL-12Rb1 sequences are the amino acid sequences of SEQ ID NO's: 2077; 2078; 2079; 2080; 2081; 2082; 2083; 2084; 2085; 2086; 2087; 2088; 2089; 2090; 2091; 2092; 2093; 2094; 2095; 2096; 2097; 2098; 2099; 2100; 2101; 2102 and/or 2103 (see Table A-2 and Figure 27). Thus, according to another preferred, but non-limiting aspect of the invention, an IL-12Rb1 sequence is an amino acid sequence that is directed against (as defined herein) IL-12Rb1 and that either:

a) has at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 2077; 2078; 2079; 2080; 2081; 2082; 2083; 2084; 2085; 2086; 2087; 2088; 2089; 2090; 2091; 2092; 2093; 2094; 2095; 2096; 2097; 2098; 2099; 2100; 2101; 2102 and/or 2103 (see Table A-2 and Figure 27);

and/or that

b) has no more than 20, preferably no more than 10, such as 9, 8, 7, 6, 5, 4, 3, 2 or only one amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 2077; 2078; 2079; 2080; 2081; 2082; 2083; 2084; 2085; 2086; 2087; 2088; 2089; 2090; 2091; 2092; 2093; 2094; 2095; 2096; 2097; 2098; 2099; 2100; 2101; 2102 and/or 2103 (see Table A-2 and Figure 27). Preferably, such an amino acid sequence has no more than a total of 5 (such as 4, 3. 2 or only one) such amino acid differences in the CDR's and/or no more than a total of 5 (such as 4, 3. 2 or only 1) such amino acid differences in the framework sequences;

and/or that

c) is either (i) capable of cross-blocking (as defined herein) the interaction of at least one of the amino acid sequences of SEQ ID NO's: 2077; 2078; 2079; 2080; 2081; 2082; 2083; 2084; 2085; 2086; 2087; 2088; 2089; 2090; 2091; 2092; 2093; 2094; 2095; 2096; 2097; 2098; 2099; 2100; 2101; 2102 and/or 2103 with the IL-12Rb1 subunit and/or (ii) being able to compete with (i.e. is a competitor for) the binding of at least one of the amino acid sequences of SEQ ID NO's: 2077; 2078; 2079; 2080; 2081; 2082; 2083; 2084; 2085; 2086; 2087; 2088; 2089; 2090; 2091; 2092; 2093; 2094; 2095; 2096; 2097; 2098; 2099; 2100; 2101; 2102 and/or 2103 (see Table A-2 and Figure 27) to IL-12Rb1.

In another preferred, but non-limiting aspect, an IL-12Rb1 sequence is chosen from one of the amino acid sequences of SEQ ID NO's: 2077; 2078; 2079; 2080; 2081; 2082; 2083; 2084; 2085; 2086; 2087; 2088; 2089; 2090; 2091; 2092; 2093; 2094; 2095; 2096; 2097; 2098; 2099; 2100; 2101; 2102 and/or 2103 (see Table A-2 and Figure 27).

H) IL-12Rb2 sequences.

One specific, but non-limiting aspect relates to "IL-12Rb2 sequences", which generally are defined herein as amino acid sequences of the invention that are directed against (as defined herein) the IL-12Rb2 subunit, for example as present in the receptor for IL-12 (and thereby against the receptor for IL-12).

IL-12Rb2 sequences may generally be as further described herein (for example, in terms of affinity, specificity etc. for IL-12Rb2) for amino acid sequences of the invention in general. Also, as described herein for the amino acid sequences of the invention, the IL-12Rb2 sequences are preferably such that they form or are capable of forming (optionally after suitable folding) a single antigen binding domain or antigen binding unit, and may for

example be amino acid sequences that comprise an immunoglobulin fold, amino acid sequences that are comprised of four framework regions and three CDR's, and may in particular be domain antibodies, single domain antibodies, VHH's, "dAb's" or Nanobodies (all as further described herein), or suitable fragments thereof.

In one particular aspect, an IL-12Rb2 sequence may comprise one or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 51" (as defined and listed in Table A-1; see also Figure 18);

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 51";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 51";

d) the amino acid sequences from the "CDR2 Sequences Group 53" (as defined and listed in Table A-1; see also Figure 18);

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 53";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 53";

g) the amino acid sequences from the "CDR3 Sequences Group 55" (as defined and listed in Table A-1; see also Figure 18);

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 55";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 55";

or any suitable combination thereof.

Optionally, when an amino acid sequence of the invention contains one or more amino acid sequences according to b) and/or c), Optional Condition I, Optional Condition II and/or Optional Condition III (all as defined herein) may apply to said amino acid sequence (i.e. compared to the original amino acid sequence according to a)). Also, optionally, when an amino acid sequence of the invention contains one or more amino acid sequences according to e) and/or f), Optional Condition I, Optional Condition II and/or Optional Condition III (all as defined herein) may apply to said amino acid sequence (i.e. compared to the original

amino acid sequence according to d)). Also, optionally, when an amino acid sequence of the invention contains one or more amino acid sequences according to h) and/or i), Optional Condition I, Optional Condition II and/or Optional Condition III (all as defined herein) may apply to said amino acid sequence (i.e. compared to the original amino acid sequence according to g)).

In this specific aspect, the amino acid sequence preferably comprises one or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 51";

b) the amino acid sequences from the "CDR2 Sequences Group 53"; and

c) the amino acid sequences from the "CDR3 Sequences Group 55";

or any suitable combination thereof.

Also, preferably, in such an amino acid sequence, at least one of said stretches of amino acid residues forms part of the antigen binding site for binding against IL-12Rb2.

In a more specific, but again non-limiting aspect, an IL-12Rb2 sequence may comprise two or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 51";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 51";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 51";

d) the amino acid sequences from the "CDR2 Sequences Group 53";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 53";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 53";

g) the amino acid sequences from the "CDR3 Sequences Group 55";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 55";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 55";

such that (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b) or c), the second stretch of amino acid residues

corresponds to one of the amino acid sequences according to d), e), f), g), h) or i); (ii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e) or f), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), g), h) or i); or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to g), h) or i), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), d), e) or f).

In this specific aspect, the amino acid sequence preferably comprises two or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 51";

b) the amino acid sequences from the "CDR2 Sequences Group 53"; and

c) the amino acid sequences from the "CDR3 Sequences Group 55";

such that, (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR1 Sequences Group 51", the second stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR2 Sequences Group 53" or from the "CDR3 Sequences Group 55"; (ii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR2 Sequences Group 53", the second stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR1 Sequences Group 51" or from the "CDR3 Sequences Group 55"; or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR3 Sequences Group 55", the second stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR1 Sequences Group 51" or from the "CDR2 Sequences Group 53".

Also, in such an amino acid sequence, the at least two stretches of amino acid residues again preferably form part of the antigen binding site for binding against IL-12Rb2.

In an even more specific, but non-limiting aspect, an IL-12Rb2 sequence may comprise three or more stretches of amino acid residues, in which the first stretch of amino acid residues is chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 51";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 51";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 51";

the second stretch of amino acid residues is chosen from the group consisting of:

d) the amino acid sequences from the "CDR2 Sequences Group 53";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 53";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 53";

and the third stretch of amino acid residues is chosen from the group consisting of:

g) the amino acid sequences from the "CDR3 Sequences Group 55";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 55";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 55".

Preferably, in this specifc aspect, the first stretch of amino acid residues is chosen from the group consisting of the amino acid sequences from the "CDR1 Sequences Group 51"; the second stretch of amino acid residues is chosen from the group consisting of the amino acid sequences from the "CDR2 Sequences Group 53"; and the third stretch of amino acid residues is chosen from the group consisting of the amino acid sequences from the "CDR3 Sequences Group 55".

Again, preferably, in such an amino acid sequence, the at least three stretches of amino acid residues forms part of the antigen binding site for binding against IL-12Rb2.

Preferred combinations of such stretches of amino acid sequences will become clear from the further disclosure herein.

Preferably, in such amino acid sequences the CDR sequences have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the IL-12Rb2 sequences listed in Table A-2 and Figure 28. This degree of amino acid identity can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said amino acid sequence and one or more of the sequences of SEQ ID NO's: 2104; 2105; 2106; 2107; 2108; 2109; 2110; 2111; 2112; 2113; 2114; 2115; 2116; 2117; 2118; 2119; 2120;

2121; 2122; 2123 and/or 2124 (see Table A-2 and Figure 28), in which the amino acid residues that form the framework regions are disregarded. Also, such amino acid sequences of the invention can be as further described herein.

Also, such amino acid sequences are preferably such that they can specifically bind (as defined herein) to the IL-12Rb2 subunit (i.e. as present in the receptor for IL-12); and more in particular bind to the IL-12Rb2 subunit with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value (all as further) described herein) that is as defined herein.

When the amino acid sequence of the invention essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), the amino acid sequence of the invention is preferably such that:

- CDR1 is chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 51";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 51";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 51";

and/or

- CDR2 is chosen from the group consisting of:

d) the amino acid sequences from the "CDR2 Sequences Group 53";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 53";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 53";

and/or

- CDR3 is chosen from the group consisting of:

g) the amino acid sequences from the "CDR3 Sequences Group 55";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 55";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 55".

In particular, such an amino acid sequence of the invention may be such that CDR1 is chosen from the group consisting of the amino acid sequences from the "CDR1 Sequences Group 51"; and/or CDR2 is chosen from the group consisting of the amino acid sequences from the "CDR2 Sequences Group 53"; and/or CDR3 is chosen from the group consisting of the amino acid sequences from the "CDR3 Sequences Group 55".

In particular, when the amino acid sequence of the invention essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), the amino acid sequence of the invention is preferably such that:

- CDR1 is chosen from the group consisting of:
  a) the amino acid sequences from the "CDR1 Sequences Group 51";
  b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 51";
  c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 51";

  and
- CDR2 is chosen from the group consisting of:
  d) the amino acid sequences from the "CDR2 Sequences Group 53";
  e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 53";
  f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 53";

  and
- CDR3 is chosen from the group consisting of:
  g) the amino acid sequences from the "CDR3 Sequences Group 55";
  h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 55";
  i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 55"; or any suitable fragment of such an amino acid sequence

In particular, such an amino acid sequence of the invention may be such that CDR1 is chosen from the group consisting of the amino acid sequences from the "CDR1 Sequences

Group 51"; and CDR2 is chosen from the group consisting of the amino acid sequences from the "CDR2 Sequences Group 53"; and CDR3 is chosen from the group consisting of the amino acid sequences from the "CDR3 Sequences Group 55".

Again, preferred combinations of CDR sequences will become clear from the further description herein.

Also, such amino acid sequences are preferably such that they can specifically bind (as defined herein) to IL-12Rb2; and more in particular bind to IL-12Rb2 with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value (all as further) described herein) that is as defined herein.

In one preferred, but non-limiting aspect, the invention relates to an amino acid sequence that essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), in which the CDR sequences of said amino acid sequence have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 2104; 2105; 2106; 2107; 2108; 2109; 2110; 2111; 2112; 2113; 2114; 2115; 2116; 2117; 2118; 2119; 2120; 2121; 2122; 2123 and/or 2124 (see Table A-2 and Figure 28). This degree of amino acid identity can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said amino acid sequence and one or more of the sequences of SEQ ID NO's: 2104; 2105; 2106; 2107; 2108; 2109; 2110; 2111; 2112; 2113; 2114; 2115; 2116; 2117; 2118; 2119; 2120; 2121; 2122; 2123 and/or 2124 (see Table A-2 and Figure 28), in which the amino acid residues that form the framework regions are disregarded. Such amino acid sequences of the invention can be as further described herein.

Some preferred, but non-limiting examples of IL-12Rb2 sequences are the amino acid sequences of SEQ ID NO's: 2104; 2105; 2106; 2107; 2108; 2109; 2110; 2111; 2112; 2113; 2114; 2115; 2116; 2117; 2118; 2119; 2120; 2121; 2122; 2123 and/or 2124 (see Table A-2 and Figure 28). Thus, according to another preferred, but non-limiting aspect of the invention, an IL-12Rb2 sequence is an amino acid sequence that is directed against (as defined herein) IL-12Rb2 and that either:

a) has at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 2104; 2105; 2106; 2107; 2108; 2109; 2110; 2111; 2112; 2113; 2114; 2115; 2116; 2117; 2118; 2119; 2120; 2121; 2122; 2123 and/or 2124 (see Table A-2 and Figure 28);

and/or that

b) has no more than 20, preferably no more than 10, such as 9, 8, 7, 6, 5, 4, 3, 2 or only one amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 2104; 2105; 2106; 2107; 2108; 2109; 2110; 2111; 2112; 2113; 2114; 2115; 2116; 2117; 2118; 2119; 2120; 2121; 2122; 2123 and/or 2124 (see Table A-2 and Figure 28). Preferably, such an amino acid sequence has no more than a total of 5 (such as 4, 3, 2 or only one) such amino acid differences in the CDR's and/or no more than a total of 5 (such as 4, 3. 2 or only 1) such amino acid differences in the framework sequences;

and/or that

c) is either (i) capable of cross-blocking (as defined herein) the interaction of at least one of the amino acid sequences of SEQ ID NO's: 2104; 2105; 2106; 2107; 2108; 2109; 2110; 2111; 2112; 2113; 2114; 2115; 2116; 2117; 2118; 2119; 2120; 2121; 2122; 2123 and/or 2124 with the IL-12Rb2 subunit and/or (ii) being able to compete with (i.e. is a competitor for) the binding of at least one of the amino acid sequences of SEQ ID NO's: 2104; 2105; 2106; 2107; 2108; 2109; 2110; 2111; 2112; 2113; 2114; 2115; 2116; 2117; 2118; 2119; 2120; 2121; 2122; 2123 and/or 2124 (see Table A-2 and Figure 28) to IL-12Rb2.

In another preferred, but non-limiting aspect, an IL-12Rb2 sequence is chosen from one of the amino acid sequences of SEQ ID NO's: 2104; 2105; 2106; 2107; 2108; 2109; 2110; 2111; 2112; 2113; 2114; 2115; 2116; 2117; 2118; 2119; 2120; 2121; 2122; 2123 and/or 2124 (see Table A-2 and Figure 28).

<u>I) IL-23R sequences.</u>

One specific, but non-limiting aspect relates to "IL-23R sequences", which generally are defined herein as amino acid sequences of the invention that are directed against (as

defined herein) the IL-23R subunit, for example as present in the (cognate) receptor for IL-23 (and thereby against the receptor for IL-23).

IL-23R sequences may generally be as further described herein (for example, in terms of affinity, specificity etc. for IL-23R) for amino acid sequences of the invention in general. Also, as described herein for the amino acid sequences of the invention, the IL-23R sequences are preferably such that they form or are capable of forming (optionally after suitable folding) a single antigen binding domain or antigen binding unit, and may for example be amino acid sequences that comprise an immunoglobulin fold, amino acid sequences that are comprised of four framework regions and three CDR's, and may in particular be domain antibodies, single domain antibodies, VHH's, "dAb's" or Nanobodies (all as further described herein), or suitable fragments thereof.

In one particular aspect, an IL-23R sequence may comprise one or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 58" (as defined and listed in Table A-1; see also Figure 19);

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 58";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 58";

d) the amino acid sequences from the "CDR2 Sequences Group 60" (as defined and listed in Table A-1; see also Figure 19);

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 60";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 60";

g) the amino acid sequences from the "CDR3 Sequences Group 62" (as defined and listed in Table A-1; see also Figure 19);

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 62";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 62";

or any suitable combination thereof.

Optionally, when an amino acid sequence of the invention contains one or more amino acid sequences according to b) and/or c), Optional Condition I, Optional Condition II and/or Optional Condition III (all as defined herein) may apply to said amino acid sequence (i.e. compared to the original amino acid sequence according to a)). Also, optionally, when an amino acid sequence of the invention contains one or more amino acid sequences according to e) and/or f), Optional Condition I, Optional Condition II and/or Optional Condition III (all as defined herein) may apply to said amino acid sequence (i.e. compared to the original amino acid sequence according to d)). Also, optionally, when an amino acid sequence of the invention contains one or more amino acid sequences according to h) and/or i), Optional Condition I, Optional Condition II and/or Optional Condition III (all as defined herein) may apply to said amino acid sequence (i.e. compared to the original amino acid sequence according to g)).

In this specific aspect, the amino acid sequence preferably comprises one or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 58";

b) the amino acid sequences from the "CDR2 Sequences Group 60"; and

c) the amino acid sequences from the "CDR3 Sequences Group 62";

or any suitable combination thereof.

Also, preferably, in such an amino acid sequence, at least one of said stretches of amino acid residues forms part of the antigen binding site for binding against IL-23R.

In a more specific, but again non-limiting aspect, an IL-23R sequence may comprise two or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 58";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 58";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 58";

d) the amino acid sequences from the "CDR2 Sequences Group 60";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 60";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 60";

g) the amino acid sequences from the "CDR3 Sequences Group 62";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 62";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 62";

such that (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b) or c), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e), f), g), h) or i); (ii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to d), e) or f), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), g), h) or i); or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences according to g), h) or i), the second stretch of amino acid residues corresponds to one of the amino acid sequences according to a), b), c), d), e) or f).

In this specific aspect, the amino acid sequence preferably comprises two or more stretches of amino acid residues chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 58";

b) the amino acid sequences from the "CDR2 Sequences Group 60"; and

c) the amino acid sequences from the "CDR3 Sequences Group 62";

such that, (i) when the first stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR1 Sequences Group 58", the second stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR2 Sequences Group 60" or from the "CDR3 Sequences Group 62"; (ii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR2 Sequences Group 60", the second stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR1 Sequences Group 58" or from the "CDR3 Sequences Group 62"; or (iii) when the first stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR3 Sequences Group 62", the second stretch of amino acid residues corresponds to one of the amino acid sequences from the "CDR1 Sequences Group 58" or from the "CDR2 Sequences Group 60".

Also, in such an amino acid sequence, the at least two stretches of amino acid residues again preferably form part of the antigen binding site for binding against IL-23R.

In an even more specific, but non-limiting aspect, an IL-23R sequence may comprise three or more stretches of amino acid residues, in which the first stretch of amino acid residues is chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 58";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 58";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 58";

the second stretch of amino acid residues is chosen from the group consisting of:

d) the amino acid sequences from the "CDR2 Sequences Group 60";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 60";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 60";

and the third stretch of amino acid residues is chosen from the group consisting of:

g) the amino acid sequences from the "CDR3 Sequences Group 62";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 62";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 62".

Preferably, in this specifc aspect, the first stretch of amino acid residues is chosen from the group consisting of the amino acid sequences from the "CDR1 Sequences Group 58"; the second stretch of amino acid residues is chosen from the group consisting of the amino acid sequences from the "CDR2 Sequences Group 60"; and the third stretch of amino acid residues is chosen from the group consisting of the amino acid sequences from the "CDR3 Sequences Group 62".

Again, preferably, in such an amino acid sequence, the at least three stretches of amino acid residues forms part of the antigen binding site for binding against IL-23R.

Preferred combinations of such stretches of amino acid sequences will become clear from the further disclosure herein.

Preferably, in such amino acid sequences the CDR sequences have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino

acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the IL-23R sequences listed in Table A-2 and Figure 29. This degree of amino acid identity can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said amino acid sequence and one or more of the sequences of SEQ ID NO's: 2125; 2126; 2127; 2128; 2129; 2130; 2131; 2132; 2133; 2134; 2135; 2136; 2137; 2138; 2139; 2140 and/or 2141 (see Table A-2 and Figure 29), in which the amino acid residues that form the framework regions are disregarded. Also, such amino acid sequences of the invention can be as further described herein.

Also, such amino acid sequences are preferably such that they can specifically bind (as defined herein) to the IL-23R subunit (i.e. as present in the receptor for IL-23); and more in particular bind to the IL-23R subunit with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value (all as further) described herein) that is as defined herein.

When the amino acid sequence of the invention essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), the amino acid sequence of the invention is preferably such that:

- CDR1 is chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 58";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 58";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 58";

and/or

- CDR2 is chosen from the group consisting of:

d) the amino acid sequences from the "CDR2 Sequences Group 60";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 60";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 60";

and/or

- CDR3 is chosen from the group consisting of:

g) the amino acid sequences from the "CDR3 Sequences Group 62";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 62";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 62".

In particular, such an amino acid sequence of the invention may be such that CDR1 is chosen from the group consisting of the amino acid sequences from the "CDR1 Sequences Group 58"; and/or CDR2 is chosen from the group consisting of the amino acid sequences from the "CDR2 Sequences Group 60"; and/or CDR3 is chosen from the group consisting of the amino acid sequences from the "CDR3 Sequences Group 62".

In particular, when the amino acid sequence of the invention essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), the amino acid sequence of the invention is preferably such that:

- CDR1 is chosen from the group consisting of:

a) the amino acid sequences from the "CDR1 Sequences Group 58";

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR1 Sequences Group 58";

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR1 Sequences Group 58";

and

- CDR2 is chosen from the group consisting of:

d) the amino acid sequences from the "CDR2 Sequences Group 60";

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR2 Sequences Group 60";

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR2 Sequences Group 60";

and

- CDR3 is chosen from the group consisting of:

g) the amino acid sequences from the "CDR3 Sequences Group 62";

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the "CDR3 Sequences Group 62";

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the "CDR3 Sequences Group 62"; or any suitable fragment of such an amino acid sequence

In particular, such an amino acid sequence of the invention may be such that CDR1 is chosen from the group consisting of the amino acid sequences from the "CDR1 Sequences Group 58"; and CDR2 is chosen from the group consisting of the amino acid sequences from the "CDR2 Sequences Group 60"; and CDR3 is chosen from the group consisting of the amino acid sequences from the "CDR3 Sequences Group 62".

Again, preferred combinations of CDR sequences will become clear from the further description herein.

Also, such amino acid sequences are preferably such that they can specifically bind (as defined herein) to IL-23R; and more in particular bind to IL-23R with an affinity (suitably measured and/or expressed as a K_D-value (actual or apparent), a K_A-value (actual or apparent), a k_{on}-rate and/or a k_{off}-rate, or alternatively as an IC_{50} value (all as further) described herein) that is as defined herein.

In one preferred, but non-limiting aspect, the invention relates to an amino acid sequence that essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), in which the CDR sequences of said amino acid sequence have at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with the CDR sequences of at least one of the amino acid sequences of SEQ ID NO's: 2125; 2126; 2127; 2128; 2129; 2130; 2131; 2132; 2133; 2134; 2135; 2136; 2137; 2138; 2139; 2140 and/or 2141 (see Table A-2 and Figure 29). This degree of amino acid identity can for example be determined by determining the degree of amino acid identity (in a manner described herein) between said amino acid sequence and one or more of the sequences of SEQ ID NO's: 2125; 2126; 2127; 2128; 2129; 2130; 2131; 2132; 2133; 2134; 2135; 2136; 2137; 2138; 2139; 2140 and/or 2141 (see Table A-2 and Figure 29), in which the amino acid residues that form the framework regions are disregarded. Such amino acid sequences of the invention can be as further described herein.

Some preferred, but non-limiting examples of IL-23R sequences are the amino acid sequences of SEQ ID NO's: 2125; 2126; 2127; 2128; 2129; 2130; 2131; 2132; 2133; 2134; 2135; 2136; 2137; 2138; 2139; 2140 and/or 2141 (see Table A-2 and Figure 29). Thus, according to another preferred, but non-limiting aspect of the invention, an IL-23R sequence is an amino acid sequence that is directed against (as defined herein) IL-23R, and that either:

a) has at least 70% amino acid identity, preferably at least 80% amino acid identity, more preferably at least 90% amino acid identity, such as 95% amino acid identity or more or even essentially 100% amino acid identity with at least one of the amino acid sequences of SEQ ID NO's: 2125; 2126; 2127; 2128; 2129; 2130; 2131; 2132; 2133; 2134; 2135; 2136; 2137; 2138; 2139; 2140 and/or 2141 (see Table A-2 and Figure 29);

and/or that

b) has no more than 20, preferably no more than 10, such as 9, 8, 7, 6, 5, 4, 3, 2 or only one amino acid difference with at least one of the amino acid sequences of SEQ ID NO's: 2125; 2126; 2127; 2128; 2129; 2130; 2131; 2132; 2133; 2134; 2135; 2136; 2137; 2138; 2139; 2140 and/or 2141 (see Table A-2 and Figure 29). Preferably, such an amino acid sequence has no more than a total of 5 (such as 4, 3, 2 or only one) such amino acid differences in the CDR's and/or no more than a total of 5 (such as 4, 3. 2 or only 1) such amino acid differences in the framework sequences;

and/or that

c) is either (i) capable of cross-blocking (as defined herein) the interaction of at least one of the amino acid sequences of SEQ ID NO's: 2125; 2126; 2127; 2128; 2129; 2130; 2131; 2132; 2133; 2134; 2135; 2136; 2137; 2138; 2139; 2140 and/or 2141 with the IL-23R subunit and/or (ii) being able to compete with (i.e. is a competitor for) the binding of at least one of the amino acid sequences of SEQ ID NO's: 2125; 2126; 2127; 2128; 2129; 2130; 2131; 2132; 2133; 2134; 2135; 2136; 2137; 2138; 2139; 2140 and/or 2141 (see Table A-2 and Figure 29) to IL-23R.

In another preferred, but non-limiting aspect, an IL-23R sequence is chosen from one of the amino acid sequences of SEQ ID NO's: 2125; 2126; 2127; 2128; 2129; 2130; 2131; 2132; 2133; 2134; 2135; 2136; 2137; 2138; 2139; 2140 and/or 2141 (see Table A-2 and Figure 29).

In some other non-limiting aspects, the invention relates to:

- an amino acid sequence, protein or polypeptide that is directed against a heterodimeric cytokine that comprises at least one p19 subunit, which amino acid sequence, protein or polypeptide comprises or essentially consists of at least one p19+ sequence (as defined herein);
- an amino acid sequence, protein or polypeptide that is directed against a heterodimeric cytokine that comprises at least one p19 subunit, which amino acid sequence, protein or polypeptide comprises or essentially consists of at least one p19- sequence (as defined herein);
- an amino acid sequence, protein or polypeptide that is directed against a heterodimeric cytokine that comprises at least one p40 subunit, which amino acid sequence, protein or polypeptide comprises or essentially consists of at least one p40- sequence (as defined herein);
- an amino acid sequence, protein or polypeptide that is directed against a heterodimeric cytokine that comprises at least one p40 subunit, which amino acid sequence, protein or polypeptide comprises or essentially consists of at least one p40+ sequence (as defined herein);
- an amino acid sequence, protein or polypeptide that is directed against a heterodimeric cytokine that comprises at least one p35 subunit, which amino acid sequence, protein or polypeptide comprises or essentially consists of at least one p35 sequence (as defined herein);
- an amino acid sequence, protein or polypeptide that is directed against IL-23, which amino acid sequence, protein or polypeptide comprises or essentially consists of at least one p19+ sequence (as defined herein);
- an amino acid sequence, protein or polypeptide that is directed against IL-23, which amino acid sequence, protein or polypeptide comprises or essentially consists of at least one p19- sequence (as defined herein);
- an amino acid sequence, protein or polypeptide that is directed against IL-23, which amino acid sequence, protein or polypeptide comprises or essentially consists of at least one p40- sequence (as defined herein);
- an amino acid sequence, protein or polypeptide that is directed against IL-23, which amino acid sequence, protein or polypeptide comprises or essentially consists of at least one p40+ sequence (as defined herein);

- an amino acid sequence, protein or polypeptide that is directed against IL-12, which amino acid sequence, protein or polypeptide comprises or essentially consists of at least one p35 sequence (as defined herein);
- an amino acid sequence, protein or polypeptide that is directed against IL-12, which amino acid sequence, protein or polypeptide comprises or essentially consists of at least one p40- sequence (as defined herein);
- an amino acid sequence, protein or polypeptide that is directed against IL-12, which amino acid sequence, protein or polypeptide comprises or essentially consists of at least one p40+ sequence (as defined herein);
- an amino acid sequence, protein or polypeptide that is directed against IL-12 and IL-23, and that is preferably specific for (as defined herein) IL-12 and/or IL-23 compared to IL-27 and/or IL-35 , which amino acid sequence, protein or polypeptide comprises or essentially consists of at least one p40- sequence (as defined herein);
- an amino acid sequence, protein or polypeptide that is directed against IL-12 and IL-23, and that is preferably specific for (as defined herein) IL-12 and/or IL-23 compared to IL-27 and/or IL-35 , which amino acid sequence, protein or polypeptide comprises or essentially consists of at least one p40+ sequence (as defined herein);
- an amino acid sequence, protein or polypeptide that is directed against IL-27, and that is preferably specific for (as defined herein) IL-27 compared to IL-12 and/or IL-23 , which amino acid sequence, protein or polypeptide comprises or essentially consists of at least one IL-27 sequence (as defined herein);
- an amino acid sequence, protein or polypeptide that is directed against a receptor for a heterodimeric cytokine that comprises at least one IL-12Rb1 subunit, which amino acid sequence, protein or polypeptide comprises or essentially consists of at least one IL-12Rb1 sequence (as defined herein);
- an amino acid sequence, protein or polypeptide that is directed against a receptor for a heterodimeric cytokine that comprises at least one IL-12Rb2 subunit, which amino acid sequence, protein or polypeptide comprises or essentially consists of at least one IL-12Rb2 sequence (as defined herein);
- an amino acid sequence, protein or polypeptide that is directed against a receptor for a heterodimeric cytokine that comprises at least one IL-23R subunit, which amino acid

sequence, protein or polypeptide comprises or essentially consists of at least one IL-23R sequence (as defined herein);

- an amino acid sequence, protein or polypeptide that is directed against the (cognate) receptor for IL-23, which amino acid sequence, protein or polypeptide comprises or essentially consists of at least one IL-12Rb1 sequence (as defined herein);
- an amino acid sequence, protein or polypeptide that is directed against the (cognate) receptor for IL-23, and that is preferably specific for (as defined herein) the (cognate) receptor for IL-23 compared to the (cognate) receptor for IL-12, which amino acid sequence, protein or polypeptide comprises or essentially consists of at least one IL-23R sequence (as defined herein);
- an amino acid sequence, protein or polypeptide that is directed against the (cognate) receptor for IL-12, which amino acid sequence, protein or polypeptide comprises or essentially consists of at least one IL-12Rb1 sequence (as defined herein);
- an amino acid sequence, protein or polypeptide that is directed against the (cognate) receptor for IL-12, and that is preferably specific for (as defined herein) the (cognate) receptor for IL-12 compared to the (cognate) receptor for IL-23, which amino acid sequence, protein or polypeptide comprises or essentially consists of at least one IL-12Rb2 sequence (as defined herein);
- an amino acid sequence, protein or polypeptide that is directed against the (cognate) receptor for IL-12 as well as the cognate receptor for IL-23, and that is preferably specific for (as defined herein) the (cognate) receptor for IL-12 and/or the cognate receptor for IL-27 and/or the (cognate) receptor for Il-35, which amino acid sequence, protein or polypeptide comprises or essentially consists of at least one IL-12Rb1 sequence (as defined herein).

Again, such amino acid sequences, proteins or polypeptides can be as further described herein. The invention also relates to nucleotide sequences/nucleic acids encoding the same, to preparations and formulations comprising the same, to methods for producing the same and to uses of the same, all as further described herein.

In the amino acid sequence of the invention (such as the p19+ sequences, p19- sequences, p40+ sequences, p40- sequences, p35 sequences, IL-27 sequences, IL-12Rb1 sequences, IL-12Rb2 sequences and IL-23 sequences described herein), the framework

sequences may be any suitable framework sequences, and examples of suitable framework sequences will be clear to the skilled person, for example on the basis the standard handbooks and the further disclosure and prior art mentioned herein.

The framework sequences are preferably (a suitable combination of) immunoglobulin framework sequences or framework sequences that have been derived from immunoglobulin framework sequences (for example, by humanization or camelization). For example, the framework sequences may be framework sequences derived from a light chain variable domain (e.g. a V_L-sequence) and/or from a heavy chain variable domain (e.g. a V_H-sequence). In one particularly preferred aspect, the framework sequences are either framework sequences that have been derived from a V_{HH}-sequence (in which said framework sequences may optionally have been partially or fully humanzed) or are conventional V_H sequences that have been camelized (as defined herein).

The framework sequences are preferably such that the amino acid sequence of the invention is a domain antibody (or an amino acid sequence that is suitable for use as a domain antibody); is a single domain antibody (or an amino acid sequence that is suitable for use as a single domain antibody); is a "dAb" (or an amino acid sequence that is suitable for use as a dAb); or is a Nanobody™ (including but not limited to V_{HH} sequence). Again, suitable framework sequences will be clear to the skilled person, for example on the basis the standard handbooks and the further disclosure and prior art mentioned herein.

In particular, the framework sequences present in the amino acid sequences of the invention may contain one or more of Hallmark residues (as defined herein), such that the amino acid sequence of the invention is a Nanobody™. Some preferred, but non-limiting examples of (suitable combinations of) such framework sequences will become clear from the further disclosure herein.

Again, as generally described herein for the amino acid sequences of the invention, it is also possible to use suitable fragments (or combinations of fragments) of any of the foregoing, such as fragments that contain one or more CDR sequences, suitably flanked by and/or linked via one or more framework sequences (for example, in the same order as these CDR's and framework sequences may occur in the full-sized immunoglobulin sequence from which the fragment has been derived). Such fragments may also again be such that they comprise or can form an immunoglobulin fold, or alternatively be such that they do not comprise or cannot form an immunoglobulin fold.

In one specific aspect, such a fragment comprises a single CDR sequence as described herein (and in particular a CDR3 sequence), that is flanked on each side by (part of) a framework sequence (and in particular, part of the framework sequence(s) that, in the immunoglobulin sequence from which the fragment is derived, are adjacent to said CDR sequence. For example, a CDR3 sequence may be preceded by (part of) a FR3 sequence and followed by (part of) a FR4 sequence). Such a fragment may also contain a disulphide bridge, and in particular a disulphide bridge that links the two framework regions that precede and follow the CDR sequence, respectively (for the purpose of forming such a disulphide bridge, cysteine residues that naturally occur in said framework regions may be used, or alternatively cysteine residues may be synthetically added to or introduced into said framework regions). For a further description of these "Expedite fragments", reference is again made to WO 03/050531, as well as to the US provisional application of Ablynx N.V. entitled *"Peptides capable of binding to serum proteins"* of Ablynx N.V. (inventors: Revets, Hilde Adi Pierrette; Kolkman, Joost Alexander; and Hoogenboom, Hendricus Renerus Jacobus Mattheus) filed on December 5, 2006 (see also PCT/EP2007/063348).

In another aspect, the invention relates to a compound or construct, and in particular a protein or polypeptide (also referred to herein as a "*compound of the invention*" or "*polypeptide of the invention*", respectively) that comprises or essentially consists of one or more amino acid sequences of the invention (or suitable fragments thereof), and optionally further comprises one or more other groups, residues, moieties or binding units. As will become clear to the skilled person from the further disclosure herein, such further groups, residues, moieties, binding units or amino acid sequences may or may not provide further functionality to the amino acid sequence of the invention (and/or to the compound or construct in which it is present) and may or may not modify the properties of the amino acid sequence of the invention.

For example, such further groups, residues, moieties or binding units may be one or more additional amino acid sequences, such that the compound or construct is a (fusion) protein or (fusion) polypeptide. In a preferred but non-limiting aspect, said one or more other groups, residues, moieties or binding units are immunoglobulin sequences. Even more preferably, said one or more other groups, residues, moieties or binding units are chosen from the group consisting of domain antibodies, amino acid sequences that are suitable for use as a domain antibody, single domain antibodies, amino acid sequences that are suitable for use as

a single domain antibody, "dAb"'s, amino acid sequences that are suitable for use as a dAb, or Nanobodies.

Alternatively, such groups, residues, moieties or binding units may for example be chemical groups, residues, moieties, which may or may not by themselves be biologically and/or pharmacologically active. For example, and without limitation, such groups may be linked to the one or more amino acid sequences of the invention so as to provide a "derivative" of an amino acid sequence or polypeptide of the invention, as further described herein.

Also within the scope of the present invention are compounds or constructs, that comprises or essentially consists of one or more derivatives as described herein, and optionally further comprises one or more other groups, residues, moieties or binding units, optionally linked via one or more linkers. Preferably, said one or more other groups, residues, moieties or binding units are amino acid sequences.

In the compounds or constructs described above, the one or more amino acid sequences of the invention and the one or more groups, residues, moieties or binding units may be linked directly to each other and/or via one or more suitable linkers or spacers. For example, when the one or more groups, residues, moieties or binding units are amino acid sequences, the linkers may also be amino acid sequences, so that the resulting compound or construct is a fusion (protein) or fusion (polypeptide).

The compounds or polypeptides of the invention can generally be prepared by a method which comprises at least one step of suitably linking the one or more amino acid sequences of the invention to the one or more further groups, residues, moieties or binding units, optionally via the one or more suitable linkers, so as to provide the compound or polypeptide of the invention. Polypeptides of the invention can also be prepared by a method which generally comprises at least the steps of providing a nucleic acid that encodes a polypeptide of the invention, expressing said nucleic acid in a suitable manner, and recovering the expressed polypeptide of the invention. Such methods can be performed in a manner known per se, which will be clear to the skilled person, for example on the basis of the methods and techniques further described herein.

The process of designing/selecting and/or preparing a compound or polypeptide of the invention, starting from an amino acid sequence of the invention, is also referred to herein as

"*formatting*" said amino acid sequence of the invention; and an amino acid of the invention that is made part of a compound or polypeptide of the invention is said to be "*formatted*" or to be "*in the format of*" said compound or polypeptide of the invention. Examples of ways in which an amino acid sequence of the invention can be formatted and examples of such formats will be clear to the skilled person based on the disclosure herein; and such formatted amino acid sequences form a further aspect of the invention.

In one specific aspect of the invention, a compound of the invention or a polypeptide of the invention may have an increased half-life, compared to the corresponding amino acid sequence of the invention. Some preferred, but non-limiting examples of such compounds and polypeptides will become clear to the skilled person based on the further disclosure herein, and for example comprise amino acid sequences or polypeptides of the invention that have been chemically modified to increase the half-life thereof (for example, by means of pegylation); amino acid sequences of the invention that comprise at least one additional binding site for binding to a serum protein (such as serum albumin; see for example EP 0 368 684 B1, page 4); or polypeptides of the invention that comprise at least one amino acid sequence of the invention that is linked to at least one moiety (and in particular at least one amino acid sequence) that increases the half-life of the amino acid sequence of the invention. Examples of polypeptides of the invention that comprise such half-life extending moieties or amino acid sequences will become clear to the skilled person based on the further disclosure herein; and for example include, without limitation, polypeptides in which the one or more amino acid sequences of the invention are suitable linked to one or more serum proteins or fragments thereof (such as (human) serum albumin or suitable fragments thereof) or to one or more binding units that can bind to serum proteins (such as, for example, domain antibodies, amino acid sequences that are suitable for use as a domain antibody, single domain antibodies, amino acid sequences that are suitable for use as a single domain antibody, "dAb"'s, amino acid sequences that are suitable for use as a dAb, or Nanobodies that can bind to serum proteins such as serum albumin (such as human serum albumin), serum immunoglobulins such as IgG, or transferrine; reference is made to the further description and references mentioned herein); polypeptides in which an amino acid sequence of the invention is linked to an Fc portion (such as a human Fc) or a suitable part or fragment thereof; or polypeptides in which the one or more amino acid sequences of the invention are suitable linked to one or more small proteins or peptides that can bind to serum proteins (such

as, without limitation, the proteins and peptides described in WO 91/01743, WO 01/45746, WO 02/076489 and to the US provisional application of Ablynx N.V. entitled *"Peptides capable of binding to serum proteins"* of Ablynx N.V. filed on December 5, 2006 (see also PCT/EP2007/063348 and WO 08/068280) as well as the US provisional applications 61/050,385 and 61/045,690 of Ablynx N.V. both entitled "Improved peptides capable of binding to serum proteins"

Generally, the compounds or polypeptides of the invention with increased half-life preferably have a half-life that is at least 1.5 times, preferably at least 2 times, such as at least 5 times, for example at least 10 times or more than 20 times, greater than the half-life of the corresponding amino acid sequence of the invention per se. For example, the compounds or polypeptides of the invention with increased half-life may have a half-life that is increased with more than 1 hours, preferably more than 2 hours, more preferably more than 6 hours, such as more than 12 hours, or even more than 24, 48 or 72 hours, compared to the corresponding amino acid sequence of the invention per se.

In a preferred, but non-limiting aspect of the invention, such compounds or polypeptides of the invention have a serum half-life that is increased with more than 1 hours, preferably more than 2 hours, more preferably more than 6 hours, such as more than 12 hours, or even more than 24, 48 or 72 hours, compared to the corresponding amino acid sequence of the invention per se.

In another preferred, but non-limiting aspect of the invention, such compounds or polypeptides of the invention exhibit a serum half-life in human of at least about 12 hours, preferably at least 24 hours, more preferably at least 48 hours, even more preferably at least 72 hours or more. For example, compounds or polypeptides of the invention may have a half-life of at least 5 days (such as about 5 to 10 days), preferably at least 9 days (such as about 9 to 14 days), more preferably at least about 10 days (such as about 10 to 15 days), or at least about 11 days (such as about 11 to 16 days), more preferably at least about 12 days (such as about 12 to 18 days or more), or more than 14 days (such as about 14 to 19 days).

Some preferred, but non-limiting examples of polypeptides of the inve ntion are:

- the polypeptides of SEQ ID NO: 2142; SEQ ID NO: 2143; SEQ ID NO: 2144; SEQ ID NO: 2145; SEQ ID NO: 2146; SEQ ID NO: 2147; SEQ ID NO: 2148; SEQ ID NO: 2149; SEQ ID NO: 2150; SEQ ID NO: 2151; SEQ ID NO: 2152; SEQ ID NO: 2153; SEQ ID NO: 2154; SEQ ID NO: 2155; SEQ ID NO: 2156; SEQ ID NO: 2157; SEQ ID

NO: 2158; SEQ ID NO: 2159; SEQ ID NO: 2160; SEQ ID NO: 2161; SEQ ID NO: 2162; SEQ ID NO: 2163; SEQ ID NO: 2164; SEQ ID NO: 2165; SEQ ID NO: 2166; SEQ ID NO: 2167; SEQ ID NO: 2168; SEQ ID NO: 2169; SEQ ID NO: 2530; SEQ ID NO: 2531; SEQ ID NO: 2532; SEQ ID NO: 2533; SEQ ID NO: 2534; SEQ ID NO: 2535; SEQ ID NO: 2536; SEQ ID NO: 2537; SEQ ID NO: 2538; SEQ ID NO: 2539; SEQ ID NO: 2540; SEQ ID NO: 2541; SEQ ID NO: 2542; SEQ ID NO: 2543; SEQ ID NO: 2544; SEQ ID NO: 2545; SEQ ID NO: 2546; SEQ ID NO: 2547; SEQ ID NO: 2548; SEQ ID NO: 2549; SEQ ID NO: 2550; SEQ ID NO: 2551; SEQ ID NO: 2552; SEQ ID NO: 2553; SEQ ID NO: 2554; SEQ ID NO: 2555; SEQ ID NO: 2556; SEQ ID NO: 2557 and/or SEQ ID NO: 2558 (see also Figure 30); which are some non-limiting examples of multivalent, multispecific and/or biparatopic polypeptides of the invention that are directed against p19 (i.e. comprising at least one p19+ sequence and/or at least one p19- sequence). These polypeptides are directed against (as defined herein) and (expected to be) specific for (as defined herein) a heterodimeric cytokine comprising a p19 subunit (compared to other heterodimeric cytokines that do not comprise a p19 subunit). For example, these polypeptides are expected to be specific for (as defined herein) IL-23 compared to IL-12 (and also IL-27 and/or IL-35);

- the polypeptides of SEQ ID NO: 2615; SEQ ID NO: 2616; SEQ ID NO: 2617; SEQ ID NO: 2618; SEQ ID NO: 2619; SEQ ID NO: 2620; SEQ ID NO: 2621 and/or SEQ ID NO: 2622 (see also Figure 32); which are some non-limiting examples of multivalent, multispecific and/or biparatopic polypeptides of the invention that are directed against p19 that comprise at least one humanized p19+ sequence and/or at least one humanized p19- sequence). These polypeptides are directed against (as defined herein) and (expected to be) specific for (as defined herein) a heterodimeric cytokine comprising a p19 subunit (compared to other heterodimeric cytokines that do not comprise a p19 subunit). For example, these polypeptides are expected to be specific for (as defined herein) IL-23 compared to IL-12 (and also IL-27 and/or IL-35);

- the polypeptides of SEQ ID NO: 2623; SEQ ID NO: 2624; SEQ ID NO: 2625; SEQ ID NO: 2626; SEQ ID NO: 2627; SEQ ID NO: 2628; SEQ ID NO: 2629; SEQ ID NO: 2643 and/or SEQ ID NO: 2644 (see also Figure 33); which are some non-limiting examples of multispecific "p19-p40" polypeptides of the invention that comprise at least one amino acid sequence of the invention that is directed against p19 (i.e. at least

one p19+ sequence and/or at least one p19- sequence) and at least one amino acid sequence of the invention that is directed against p40 (i.e. at least one p40+ sequence and/or at least one p40- sequence). These polypeptides are expected to be specific for (as defined herein) IL-23 compared to IL-12 (and also IL-27 and/or IL-35);

- the polypeptides of SEQ ID NO: 2630; SEQ ID NO: 2631; SEQ ID NO: 2632; SEQ ID NO: 2633; SEQ ID NO: 2634; SEQ ID NO: 2635; SEQ ID NO: 2636; SEQ ID NO: 2637; SEQ ID NO: 2638; SEQ ID NO: 2639; SEQ ID NO: 2640 and/or SEQ ID NO: 2641 (see also Figure 34); which are some non-limiting examples of multivalent, multispecific and/or biparatopic polypeptides of the invention that are directed against p40 (i.e. comprising at least one p40+ sequence and/or at least one p40- sequence). These polypeptides are directed against (as defined herein) and (expected to be) specific for (as defined herein) a heterodimeric cytokine comprising a p40 subunit (compared to other heterodimeric cytokines that do not comprise a p40 subunit). For example, these polypeptides are expected to be specific for (as defined herein) IL-23 and/or IL-12 compared to IL-27 and/or IL-35;

- the polypeptides of SEQ ID NO: 2645 and/or SEQ ID NO: 2646 (see also Figure 35), which are some non-limiting examples of multivalent, multispecific and/or biparatopic polypeptides of the invention that are directed against p35. These polypeptides are directed against (as defined herein) and (expected to be) specific for (as defined herein) a heterodimeric cytokine comprising a p35 subunit (compared to other heterodimeric cytokines that do not comprise a p35 subunit). For example, these polypeptides are expected to be specific for (as defined herein) IL-12 compared to IL-23 (and also IL-27 and/or IL-35);

- the polypeptides of SEQ ID NO: 2647 and/or SEQ ID NO: 2648 (see also Figure 36), which are some non-limiting examples of multispecific "p35-p40" polypeptides of tolypepe invention that comprise at least one amino acid sequence of the invention that is directed against p35 and at least one amino acid sequence of the invention that is directed against p40 (i.e. at least one p40+ sequence and/or at least one p40- sequence). These polypeptides are expected to be specific for (as defined herein) IL-12 compared to IL-23 (and also IL-27 and/or IL-35).

Other examples of polypeptides suitable for use in the invention, of amino acid sequences of the invention (or nucleotide sequences/nucleic acids comprising the same) that can be used in such polypeptides (such as the p19+ sequences, p19- sequences, p40+ sequences, p40- sequences, p35 sequences, IL-27 sequences, IL-12Rb1 sequences, IL-12Rb2 sequences and IL-23 sequences described herein), and how polypeptides of the invention can be constructed and produced using such amino acid sequences of the invention will be clear to the skilled person based on the disclosure herein.

Thus, some further aspects of the invention relate to:

- the polypeptide (construct) of SEQ ID NO: 2142; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2142;
- the polypeptide (construct) of SEQ ID NO: 2143; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2143;
- the polypeptide (construct) of SEQ ID NO: 2144; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2144;
- the polypeptide (construct) of SEQ ID NO: 2145; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2145;
- the polypeptide (construct) of SEQ ID NO: 2146; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2146;
- the polypeptide (construct) of SEQ ID NO: 2147; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2147;

- the polypeptide (construct) of SEQ ID NO: 2148; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2148;
- the polypeptide (construct) of SEQ ID NO: 2149; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2149;
- the polypeptide (construct) of SEQ ID NO: 2150; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2150;
- the polypeptide (construct) of SEQ ID NO: 2151; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2151;
- the polypeptide (construct) of SEQ ID NO: 2152; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2152;
- the polypeptide (construct) of SEQ ID NO: 2153; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2153;
- the polypeptide (construct) of SEQ ID NO: 2154; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2154;
- the polypeptide (construct) of SEQ ID NO: 2155; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2155;

- the polypeptide (construct) of SEQ ID NO: 2156; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2156;
- the polypeptide (construct) of SEQ ID NO: 2157; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2157;
- the polypeptide (construct) of SEQ ID NO: 2158; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2158;
- the polypeptide (construct) of SEQ ID NO: 2159; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2159;
- the polypeptide (construct) of SEQ ID NO: 2160; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2160;
- the polypeptide (construct) of SEQ ID NO: 2161; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2161;
- the polypeptide (construct) of SEQ ID NO: 2162; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2162;
- the polypeptide (construct) of SEQ ID NO: 2163; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2163;

- the polypeptide (construct) of SEQ ID NO: 2164; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2164;
- the polypeptide (construct) of SEQ ID NO: 2165; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2165;
- the polypeptide (construct) of SEQ ID NO: 2166; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2166;
- the polypeptide (construct) of SEQ ID NO: 2167; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2167;
- the polypeptide (construct) of SEQ ID NO: 2168; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2168;
- the polypeptide (construct) of SEQ ID NO: 2169; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2169;
- the polypeptide (construct) of SEQ ID NO: 2530; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2530;
- the polypeptide (construct) of SEQ ID NO: 2531; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2531;

- the polypeptide (construct) of SEQ ID NO: 2532; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2532;
- the polypeptide (construct) of SEQ ID NO: 2533; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2533;
- the polypeptide (construct) of SEQ ID NO: 2534; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2534;
- the polypeptide (construct) of SEQ ID NO: 2535; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2535;
- the polypeptide (construct) of SEQ ID NO: 2536; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2536;
- the polypeptide (construct) of SEQ ID NO: 2537; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2537;
- the polypeptide (construct) of SEQ ID NO: 2538; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2538;
- the polypeptide (construct) of SEQ ID NO: 2539; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2539;

- the polypeptide (construct) of SEQ ID NO: 2540; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2540;
- the polypeptide (construct) of SEQ ID NO: 2541; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2541;
- the polypeptide (construct) of SEQ ID NO: 2542; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2542;
- the polypeptide (construct) of SEQ ID NO: 2543; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2543;
- the polypeptide (construct) of SEQ ID NO: 2544; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2544;
- the polypeptide (construct) of SEQ ID NO: 2545; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2545;
- the polypeptide (construct) of SEQ ID NO: 2546; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2546;
- the polypeptide (construct) of SEQ ID NO: 2547; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2547;

- the polypeptide (construct) of SEQ ID NO: 2548; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2548;
- the polypeptide (construct) of SEQ ID NO: 2549; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2549;
- the polypeptide (construct) of SEQ ID NO: 2550; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2550;
- the polypeptide (construct) of SEQ ID NO: 2551; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2551;
- the polypeptide (construct) of SEQ ID NO: 2552; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2552;
- the polypeptide (construct) of SEQ ID NO: 2553; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2553;
- the polypeptide (construct) of SEQ ID NO: 2554; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2554;
- the polypeptide (construct) of SEQ ID NO: 2555; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2555;

- the polypeptide (construct) of SEQ ID NO: 2556; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2556;
- the polypeptide (construct) of SEQ ID NO: 2557; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2557;
- the polypeptide (construct) of SEQ ID NO: 2558; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2558;
- the polypeptide (construct) of SEQ ID NO: 2615; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2615;
- the polypeptide (construct) of SEQ ID NO: 2616; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2616;
- the polypeptide (construct) of SEQ ID NO: 2617; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2617;
- the polypeptide (construct) of SEQ ID NO: 2618; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2618;
- the polypeptide (construct) of SEQ ID NO: 2619; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2619;

- the polypeptide (construct) of SEQ ID NO: 2620; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2620;
- the polypeptide (construct) of SEQ ID NO: 2621; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2621;
- the polypeptide (construct) of SEQ ID NO: 2622; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2622;

as well as to nucleotide sequences or nucleotide sequences encoding the same. These polypeptide constructs are preferably further such that they are directed against p19 and/or IL-23 (and more preferably also specific for p19 and/or IL-23), and even more preferably capable of modulating, blocking, neutralizing or inhibiting the binding of IL-23 to its cognate receptor (for example, in the alpha-screen assay described in Example 19 or 22).

Yet further aspects of the invention relate to:

- the polypeptide (construct) of SEQ ID NO: 2623; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2623;
- the polypeptide (construct) of SEQ ID NO: 2624; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2624;
- the polypeptide (construct) of SEQ ID NO: 2625; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2625;

- the polypeptide (construct) of SEQ ID NO: 2626; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2626;
- the polypeptide (construct) of SEQ ID NO: 2627; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2627;
- the polypeptide (construct) of SEQ ID NO: 2628; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2628;
- the polypeptide (construct) of SEQ ID NO: 2629; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2629;
- the polypeptide (construct) of SEQ ID NO: 2643; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2643;
- the polypeptide (construct) of SEQ ID NO: 2644; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2644;

as well as to nucleotide sequences or nucleotide sequences encoding the same. These polypeptide constructs are preferably further such that they are directed against p19 and/or IL-23 (and more preferably also specific for p19 and/or IL-23), and even more preferably capable of modulating, blocking, neutralizing or inhibiting the binding of IL-23 to its cognate receptor (for example, in the alpha-screen assay described in Example 19 or 22).

Yet further aspects of the invention relate to:

- the polypeptide (construct) of SEQ ID NO: 2630; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2630;
- the polypeptide (construct) of SEQ ID NO: 2631; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2631;
- the polypeptide (construct) of SEQ ID NO: 2632; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2632;
- the polypeptide (construct) of SEQ ID NO: 2633; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2633;
- the polypeptide (construct) of SEQ ID NO: 2634; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2634;
- the polypeptide (construct) of SEQ ID NO: 2635; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2635;
- the polypeptide (construct) of SEQ ID NO: 2636; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2636;
- the polypeptide (construct) of SEQ ID NO: 2637; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2637;

- the polypeptide (construct) of SEQ ID NO: 2638; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2638;
- the polypeptide (construct) of SEQ ID NO: 2639; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2639;
- the polypeptide (construct) of SEQ ID NO: 2640; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2640;
- the polypeptide (construct) of SEQ ID NO: 2641; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2641;

as well as to nucleotide sequences or nucleotide sequences encoding the same. These polypeptide constructs are preferably further such that they are directed against p40, IL-12 and/or IL-23 (and more preferably also specific for p40, IL-12 and/or IL-23 compared to IL-27 and/or IL-35), and even more preferably capable of modulating, blocking, neutralizing or inhibiting the binding of IL-23 to its cognate receptor and/or of modulating, blocking, neutralizing or inhibiting the binding of IL-12 to its cognate receptor (for example, in the alpha-screen assay described in Example 19 or 22).

Yet further aspects of the invention relate to

- the polypeptide (construct) of SEQ ID NO: 2645; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2645;
- the polypeptide (construct) of SEQ ID NO: 2646; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least

90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2646;

as well as to nucleotide sequences or nucleotide sequences encoding the same. These polypeptide constructs are preferably further such that they are directed against p35 and/or IL-12 (and more preferably also specific for p35 and/or IL-12), and even more preferably capable of modulating, blocking, neutralizing or inhibiting the binding of IL-12 to its cognate receptor.

Yet other aspects of the invention relate to

- the polypeptide (construct) of SEQ ID NO: 2647; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2647;
- the polypeptide (construct) of SEQ ID NO: 2648; or a polypeptide (construct) that has at least 70%, preferably at least 80%, more preferably at least 85%, such as at least 90%, for example more than 95%, amino acid identity (as defined herein) with the polypeptide of SEQ ID NO: 2648;

as well as to nucleotide sequences or nucleotide sequences encoding the same. These polypeptide constructs are preferably further such that they are directed against p35 and/or IL-12 (and more preferably also specific for p35 and/or IL-12), and even more preferably capable of modulating, blocking, neutralizing or inhibiting the binding of IL-12 to its cognate receptor (for example, in the alpha-screen assay described in Example 19 or 22).

In another aspect, the invention relates to a nucleic acid that encodes an amino acid sequence of the invention (such as a (single) domain antibody and/or Nanobody of the invention) or a polypeptide of the invention (or a suitable fragment thereof). Such a nucleic acid will also be referred to herein as a "*nucleic acid of the invention*" and may for example be in the form of a genetic construct, as further described herein.

In another aspect, the invention relates to a host or host cell that expresses (or that under suitable circumstances is capable of expressing) an amino acid sequence of the invention (such as a (single) domain antibody and/or Nanobody of the invention) and/or a polypeptide of the invention; and/or that contains a nucleic acid of the invention. Some

preferred but non-limiting examples of such hosts or host cells will become clear from the further description herein.

The invention further relates to a product or composition containing or comprising at least one amino acid sequence of the invention, at least one polypeptide of the invention (or a suitable fragment thereof) and/or at least one nucleic acid of the invention, and optionally one or more further components of such compositions known per se, i.e. depending on the intended use of the composition. Such a product or composition may for example be a pharmaceutical composition (as described herein), a veterinary composition or a product or composition for diagnostic use (as also described herein). Some preferred but non-limiting examples of such products or compositions will become clear from the further description herein.

The invention also relates to the use of an amino acid sequence, Nanobody or polypeptide of the invention, or of a composition comprising the same, in (methods or compositions for) modulating (as defined herein) a heterodimeric cytokine, a receptor for a heterodimeric cytokine and/or heterodimeric cytokine-mediated signalling (as defined herein), either in vitro (e.g. in an in vitro or cellular assay) or in vivo (e.g. in an a single cell or multicellular organism, and in particular in a mammal, and more in particular in a human being, such as in a human being that is at risk of or suffers from a disease or disorder associated with heterodimeric cytokines and their receptors).

The invention also relates to methods for modulating (as defined herein) a heterodimeric cytokine, a receptor for a heterodimeric cytokine and/or heterodimeric cytokine-mediated signalling (as defined herein), either in vitro (e.g. in an in vitro or cellular assay) or in vivo (e.g. in an a single cell or multicellular organism, and in particular in a mammal, and more in particular in a human being, such as in a human being that is at risk of or suffers from a disease or disorder associated with heterodimeric cytokines and their receptors), which method comprises at least the step of contacting a heterodimeric cytokine and/or a receptor of a heterodimeric cytokine with at least one amino acid sequence, Nanobody or polypeptide of the invention, or with a composition comprising the same, in a manner and in an amount suitable to modulate the heterodimeric cytokine, the receptor and/or heterodimeric cytokine-mediated signalling.

The invention also relates to the use of an one amino acid sequence, Nanobody or polypeptide of the invention in the preparation of a composition (such as, without limitation,

a pharmaceutical composition or preparation as further described herein) for modulating (as defined herein) a heterodimeric cytokine, a receptor for a heterodimeric cytokine and/or heterodimeric cytokine-mediated signalling (as defined herein), either in vitro (e.g. in an in vitro or cellular assay) or in vivo (e.g. in an a single cell or multicellular organism, and in particular in a mammal, and more in particular in a human being, such as in a human being that is at risk of or suffers from a disease or disorder associated with heterodimeric cytokines and their receptors).

The invention further relates to methods for preparing or generating the amino acid sequences, compounds, constructs, polypeptides, nucleic acids, host cells, products and compositions described herein. Some preferred but non-limiting examples of such methods will become clear from the further description herein.

Generally, these methods may comprise the steps of:

a) providing a set, collection or library of amino acid sequences; and

b) screening said set, collection or library of amino acid sequences for amino acid sequences that can bind to and/or have affinity for heterodimeric cytokines and/or their receptors;

and

c) isolating the amino acid sequence(s) that can bind to and/or have affinity for heterodimeric cytokines and/or their receptors.

In such a method, the set, collection or library of amino acid sequences may be any suitable set, collection or library of amino acid sequences. For example, the set, collection or library of amino acid sequences may be a set, collection or library of immunoglobulin sequences (as described herein), such as a naïve set, collection or library of immunoglobulin sequences; a synthetic or semi-synthetic set, collection or library of immunoglobulin sequences; and/or a set, collection or library of immunoglobulin sequences that have been subjected to affinity maturation.

Also, in such a method, the set, collection or library of amino acid sequences may be a set, collection or library of heavy chain variable domains (such as V_H domains or V_{HH} domains) or of light chain variable domains. For example, the set, collection or library of amino acid sequences may be a set, collection or library of domain antibodies or single domain antibodies, or may be a set, collection or library of amino acid sequences that are capable of functioning as a domain antibody or single domain antibody.

In a preferred aspect of this method, the set, collection or library of amino acid sequences may be an immune set, collection or library of immunoglobulin sequences, for example derived from a mammal that has been suitably immunized with heterodimeric cytokines and/or their receptors or with a suitable antigenic determinant based thereon or derived therefrom, such as an antigenic part, fragment, region, domain, loop or other epitope thereof. In one particular aspect, said antigenic determinant may be an extracellular part, region, domain, loop or other extracellular epitope(s).

In the above methods, the set, collection or library of amino acid 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) amino acid sequences will be clear to the person skilled in the art, for example on the basis of the further disclosure herein. Reference is also made to the review by Hoogenboom in Nature Biotechnology, 23, 9, 1105-1116 (2005).

In another aspect, the method for generating amino acid sequences comprises at least the steps of:

a) providing a collection or sample of cells expressing amino acid sequences;

b) screening said collection or sample of cells for cells that express an amino acid sequence that can bind to and/or have affinity for heterodimeric cytokines and/or their receptors;

and

c) either (i) isolating said amino acid sequence; or (ii) isolating from said cell a nucleic acid sequence that encodes said amino acid sequence, followed by expressing said amino acid sequence.

For example, when the desired amino acid sequence is an immunoglobulin sequence, the collection or sample of cells may for example be a collection or sample of B-cells. Also, in this method, the sample of cells may be derived from a mammal that has been suitably immunized with heterodimeric cytokines and/or their receptors or with a suitable antigenic determinant based thereon or derived therefrom, such as an antigenic part, fragment, region, domain, loop or other epitope thereof. In one particular aspect, said antigenic determinant may be an extracellular part, region, domain, loop or other extracellular epitope(s).

The above method may be performed in any suitable manner, as will be clear to the skilled person. Reference is for example made to EP 0 542 810, WO 05/19824, WO

04/051268 and WO 04/106377. The screening of step b) is preferably performed using a flow cytometry technique such as FACS. For this, reference is for example made to Lieby et al., Blood, Vol. 97, No. 12, 3820 (2001).

In another aspect, the method for generating an amino acid sequence directed against heterodimeric cytokines and/or their receptors may comprise at least the steps of:

a) providing a set, collection or library of nucleic acid sequences encoding amino acid sequences;

b) screening said set, collection or library of nucleic acid sequences for nucleic acid sequences that encode an amino acid sequence that can bind to and/or has affinity for heterodimeric cytokines and/or their receptors;

and

c) isolating said nucleic acid sequence, followed by expressing said amino acid sequence.

In such a method, the set, collection or library of nucleic acid sequences encoding amino acid sequences may for example be a set, collection or library of nucleic acid sequences encoding a naïve set, collection or library of immunoglobulin sequences; a set, collection or library of nucleic acid sequences encoding a synthetic or semi-synthetic set, collection or library of immunoglobulin sequences; and/or a set, collection or library of nucleic acid sequences encoding a set, collection or library of immunoglobulin sequences that have been subjected to affinity maturation.

Also, in such a method, the set, collection or library of nucleic acid sequences may encode a set, collection or library of heavy chain variable domains (such as V_H domains or V_{HH} domains) or of light chain variable domains. For example, the set, collection or library of nucleic acid sequences may encode a set, collection or library of domain antibodies or single domain antibodies, or a set, collection or library of amino acid sequences that are capable of functioning as a domain antibody or single domain antibody.

In a preferred aspect of this method, the set, collection or library of amino acid sequences may be an immune set, collection or library of nucleic acid sequences, for example derived from a mammal that has been suitably immunized with heterodimeric cytokines and/or their receptors or with a suitable antigenic determinant based thereon or derived therefrom, such as an antigenic part, fragment, region, domain, loop or other epitope thereof. In one particular aspect, said antigenic determinant may be an extracellular part, region, domain, loop or other extracellular epitope(s).

The set, collection or library of nucleic acid sequences may for example encode an immune set, collection or library of heavy chain variable domains or of light chain variable domains. In one specific aspect, the set, collection or library of nucleotide sequences may encode a set, collection or library of V_{HH} sequences.

In the above methods, the set, collection or library of nucleotide 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) nucleotide sequences encoding amino acid sequences will be clear to the person skilled in the art, for example on the basis of the further disclosure herein. Reference is also made to the review by Hoogenboom in Nature Biotechnology, 23, 9, 1105-1116 (2005).

The invention also relates to amino acid sequences that are obtained by the above methods, or alternatively by a method that comprises the one of the above methods and in addition at least the steps of determining the nucleotide sequence or amino acid sequence of said immunoglobulin sequence; and of expressing or synthesizing said amino acid sequence in a manner known per se, such as by expression in a suitable host cell or host organism or by chemical synthesis.

Also, following the steps above, one or more amino acid sequences of the invention may be suitably humanized (or alternatively camelized); and/or the amino acid sequence(s) thus obtained may be linked to each other or to one or more other suitable amino acid sequences (optionally via one or more suitable linkers) so as to provide a polypeptide of the invention. Also, a nucleic acid sequence encoding an amino acid sequence of the invention may be suitably humanized (or alternatively camelized) and suitably expressed; and/or one or more nucleic acid sequences encoding an amino acid sequence of the invention may be linked to each other or to one or more nucleic acid sequences that encode other suitable amino acid sequences (optionally via nucleotide sequences that encode one or more suitable linkers), after which the nucleotide sequence thus obtained may be suitably expressed so as to provide a polypeptide of the invention.

The invention further relates to applications and uses of the amino acid sequences, polypeptides, nucleic acids, host cells, products and compositions described herein, as well as to methods for the prevention and/or treatment for diseases and disorders associated with

heterodimeric cytokines and/or their receptors. Some preferred but non-limiting applications and uses will become clear from the further description herein.

Some specific, preferred, but non-limiting aspects of the invention relate to:

1. A protein or polypeptide, comprising at least one amino acid sequence that is directed against the p19 subunit and at least one amino acid sequence that is directed against the p40 subunit, optionally linked via a suitable linker, and optionally comprising one or more further amino acid sequences, binding domains and/or binding units.

2. A protein or polypeptide according to aspect 1, in which the amino acid sequence that is directed against the p19 subunit is a p19+ sequence (i.e. an amino acid sequence that is capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p19 subunit to its receptor), and in which the amino acid sequence that is directed against the p40 subunit is a p40+ sequence (i.e. an amino acid sequence that is capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p40 subunit to its receptor).

3. A protein or polypeptide according to aspect 1, in which the amino acid sequence that is directed against the p19 subunit is a p19+ sequence (i.e. an amino acid sequence that is capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p19 subunit to its receptor), and in which the amino acid sequence that is directed against the p40 subunit is a p40- sequence (i.e. an amino acid sequence that is essentially not capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p40 subunit to its receptor).

4. A protein or polypeptide according to aspect 1, in which the amino acid sequence that is directed against the p19 subunit is a p19+ sequence (i.e. an amino acid sequence that is essentially not capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p19 subunit to its receptor), and in which the amino acid sequence that is directed against the p40 subunit is a p40+ sequence (i.e. an amino acid sequence that is capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p40 subunit to its receptor).

5. A protein or polypeptide, comprising at least one amino acid sequence that is directed against the p35 subunit and at least one amino acid sequence that is directed against the p40 subunit, optionally linked via a suitable linker, and optionally comprising one or more further amino acid sequences, binding domains and/or binding units.

6. A protein or polypeptide, comprising at least one amino acid sequence that is directed against a first epitope or antigenic determinant on the p19 subunit and at least one further amino acid sequence that is directed against a second epitope or antigenic determinant on the p19 subunit different from the first, optionally linked via a suitable linker, and optionally comprising one or more further amino acid sequences, binding domains and/or binding units.

7. A protein or polypeptide according to aspect 6, in which the first amino acid sequence is a p19+ sequence (i.e. an amino acid sequence that is essentially not capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p19 subunit to its receptor), and in which the second amino acid sequence is a p19- sequence (i.e. an amino acid sequence that is essentially not capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p19 subunit to its receptor).

8. A protein or polypeptide, comprising at least one amino acid sequence that is directed against a first epitope or antigenic determinant on the p40 subunit and at least one further amino acid sequence that is directed against a second epitope or antigenic determinant on the p40 subunit different from the first, optionally linked via a suitable linker, and optionally comprising one or more further amino acid sequences, binding domains and/or binding units.

9. A protein or polypeptide, in which the first amino acid sequence is a p40+ sequence (i.e. an amino acid sequence that is essentially not capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p40 subunit to its receptor), and in which the second amino acid sequence is a p40- sequence (i.e. an amino acid sequence that is essentially not capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p40 subunit to its receptor).

10. A protein or polypeptide according to any of aspects 1 to 9, in which each amino acid sequence that is comprised within said protein or polypeptide and that is directed

against a subunit forms and/or essentially consist of a single (antigen) binding domain or binding unit, and/or is capable of forming and/or of functioning as a single (antigen) binding domain or binding unit (optionally after suitable folding).

11. A protein or polypeptide according to any of aspects 1 to 10, in which each amino acid sequence that is comprised within said protein or polypeptide and that is directed against a subunit comprises an immunoglobulin fold or is capable of, under suitable conditions, forming an immunoglobulin fold.

12. A protein or polypeptide according to any of aspects 1 to 11, in which each amino acid sequence that is comprised within said protein or polypeptide and that is directed against a subunit essentially consist of 4 framework regions (FR1 to FR4 respectively) and 3 complementarity determining regions.

13. A protein or polypeptide according to any of aspects 1 to 12, in which each amino acid sequence that is comprised within said protein or polypeptide and that is directed against a subunit is a domain antibody (or an amino acid sequence that is suitable for use as a domain antibody), a single domain antibody (or an amino acid sequence that is suitable for use as a single domain antibody), a "dAb" (or an amino acid sequence that is suitable for use as a dAb) or a Nanobody™ (including but not limited to a VHH sequence) or another single variable domain, or any suitable fragment of any one thereof.

14. A protein or polypeptide that is directed against a heterodimeric protein, polypeptide, ligand or receptor that comprises:

- at least a first subunit;
- and
- at least a second subunit;

wherein said protein or polypeptide at least comprises a first binding domain or binding unit that is directed against said first subunit and a second binding domain or binding unit that is directed against said second subunit.

15. A protein or polypeptide that is directed against a first heterodimeric protein, polypeptide, ligand or receptor that comprises:

- at least a first subunit that is shared between said first heterodimeric protein, polypeptide, ligand or receptor and at least a second, different heterodimeric protein, polypeptide, ligand or receptor;

and

- at least a second subunit that is not shared between said first heterodimeric protein, polypeptide, ligand or receptor and said second, different heterodimeric protein, polypeptide, ligand or receptor;

wherein said protein or polypeptide at least comprises a first binding domain or binding unit that is directed against said first (i.e. shared) subunit and a second binding domain or binding unit that is directed against said second (i.e. not shared) subunit.

16. A protein or polypeptide that is directed against a first heterodimeric protein, polypeptide, ligand or receptor that comprises:

- at least a first subunit;

and

- at least a second subunit;

wherein said protein or polypeptide at least comprises a first binding domain or binding unit that is directed against said first subunit and a second binding domain or binding unit different from said first binding domain or binding unit that is also directed against said first subunit, but against a different epitope, antigenic determinant or binding site on said first subunit.

17. A protein or polypeptide according to aspect 15 or 16, which is directed against a ligand for a receptor, and which comprises at least one binding domain or binding unit that is capable of modulating, neutralizing, blocking and/or inhibiting the binding of the ligand to its (cognate) receptor and at least one binding domain or binding unit that is essentially not capable of modulating, neutralizing, blocking and/or inhibiting the binding of the ligand to its (cognate) receptor.

18. A protein or polypeptide according to aspect 15, which is directed against a ligand for a receptor, in which both the first binding domain or binding unit as well as the second binding domain or binding unit are capable of modulating, neutralizing, blocking and/or inhibiting the binding of the ligand to its (cognate) receptor.

19. A protein or polypeptide according to any of aspects 14 to 18, in which each binding domain or binding unit comprises an immunoglobulin fold or is capable of, under suitable conditions, forming an immunoglobulin fold.

20. A protein or polypeptide according to any of aspects 14 to 19, in which each binding domain or binding unit essentially consist of 4 framework regions (FR1 to FR4 respectively) and 3 complementarity determining regions.

21. A protein or polypeptide according to any of aspects 14 to 20, in which each binding domain or binding unit is a domain antibody (or an amino acid sequence that is suitable for use as a domain antibody), a single domain antibody (or an amino acid sequence that is suitable for use as a single domain antibody), a "dAb" (or an amino acid sequence that is suitable for use as a dAb) or a Nanobody™ (including but not limited to a VHH sequence) or another single variable domain, or any suitable fragment of any one thereof.

22. A nucleotide sequence or nucleic acid encoding a protein or polypeptide according to any of aspects 1 to 21.

23. A composition comprising at least one protein or polypeptide according to any of aspects 1 to 21 or a nucleotide sequence or nucleic acid according to aspect 22.

24. A pharmaceutical composition comprising at least one protein or polypeptide according to any of aspects 1 to 21 and at least one pharmaceutically acceptable carrier, diluent or excipient and/or adjuvant.

25. The use of (a nucleotide sequence and/or nucleic acid that encodes) a p19+ sequence in providing, constructing, and/or as part of (a nucleotide sequence and/or nucleic acid that encodes) a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that comprises said p19+ sequence (one or more) and one or more further binding domains or binding units.

26. The use of (a nucleotide sequence and/or nucleic acid that encodes) a p19- sequence in providing, constructing, and/or as part of (a nucleotide sequence and/or nucleic acid that encodes) a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that comprises said p19- sequence (one or more) and one or more further binding domains or binding units.

27. The use of (a nucleotide sequence and/or nucleic acid that encodes) a p40- sequence in providing, constructing, and/or as part of (a nucleotide sequence and/or nucleic acid that encodes) a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that comprises said p40- sequence (one or more) and one or more further binding domains or binding units.

28. The use of (a nucleotide sequence and/or nucleic acid that encodes) a p40+ sequence in providing, constructing, and/or as part of (a nucleotide sequence and/or nucleic acid that encodes) a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that comprises said p40+ sequence (one or more) and one or more further binding domains or binding units.

29. The use of (a nucleotide sequence and/or nucleic acid that encodes) a p35 sequence in providing, constructing, and/or as part of (a nucleotide sequence and/or nucleic acid that encodes) a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that comprises said p35 sequence (one or more) and one or more further binding domains or binding units.

30. The use according to any of aspects 25 to 29, in which the multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide is directed against a heterodimeric cytokine.

31. The use according to any of aspects 25 to 30, in which the construct, protein and/or polypeptide is a biparatopic construct, protein and/or polypeptide that is directed against one subunit of the heterodimeric cytokine.

32. The use according to any of aspects 30 and 31, in which the construct, protein and/or polypeptide is a multispecific construct, protein and/or polypeptide comprising at least one binding domain or binding unit that is directed against a first subunit of said heterodimeric cytokine and at least one binding domain or binding unit that is directed against a second subunit of said heterodimeric cytokine.

33. The use according to any of aspects 30 to 32, in which the construct, protein and/or polypeptide comprises at least one least one binding domain or binding unit that is capable of modulating, neutralizing, blocking and/or inhibiting the binding of the heterodimeric cytokine to its (cognate) receptor.

34. The use of (a nucleotide sequence and/or nucleic acid that encodes) an amino acid sequence that comprises or essentially consists of a single binding domain or binding unit in providing, constructing, and/or as part of (a nucleotide sequence and/or nucleic acid that encodes) a multispecific construct, protein and/or polypeptide that is directed against a heterodimeric protein, polypeptide, ligand or receptor, wherein said construct, protein and/or polypeptide comprises said amino acid sequence (one or more) and at least one further binding domain or binding unit, and wherein said one or

more amino acid sequences are directed against a first subunit of the heterodimeric protein, polypeptide, ligand or receptor and at least one of said further binding domains or binding units is directed against a second subunit of the heterodimeric protein, polypeptide, ligand or receptor different from the first subunit.

35. The use according to aspect 34, in which the construct, protein and/or polypeptide is a directed against a heterodimeric cytokine or against a heterodimeric receptor for a heterodimeric cytokine.

36. The use of (a nucleotide sequence and/or nucleic acid that encodes) an amino acid sequence that comprises or essentially consists of a single binding domain or binding unit in providing, constructing, and/or as part of (a nucleotide sequence and/or nucleic acid that encodes) a biparatopic construct, protein and/or polypeptide that is directed against a heterodimeric protein, polypeptide, ligand or receptor, wherein said construct, protein and/or polypeptide comprises said amino acid sequence (one or more) and at least one further binding domain or binding unit, and wherein said one or more amino acid sequences are directed against a first subunit of the heterodimeric protein, polypeptide, ligand or receptor and at least one of said further binding domains or binding units is also directed against said first subunit, but to a different epitope or antigenic determinant on sais subunit.

37. The use according to aspect 36, in which the construct, protein and/or polypeptide is directed against a ligand for a receptor and comprises at least one binding domain or binding unit that is capable of modulating, neutralizing, blocking and/or inhibiting the binding of the ligand to its (cognate) receptor and at least one binding domain or binding unit that is essentially not capable of modulating, neutralizing, blocking and/or inhibiting the binding of the ligand to its (cognate) receptor.

Also, all the amino acid sequences of the invention (such as (single) domain antibodies and/or Nanobodies), constructs, polypeptides and proteins described herein (in all their various and/or preferred aspects), preferably have IC50 values as follows:

- when the amino acid sequence of the invention, protein or polypeptide is a monovalent amino acid sequence (as described herein) that is directed against p19 and that is a p19+ sequence, an IC50 value in the assay described in Example 25 (using human IL-23 at

19pM) of less than 100 nM, more preferably less than 50nM, even more preferably less than 10nM, such as less than 1 nM (for example, in the picomolar range);

- when the amino acid sequence of the invention, protein or polypeptide is a monovalent amino acid sequence (as described herein) that is directed against p40 and that is a p40+ sequence, an IC50 value in the assay described in Example 25 (using human IL-23 at 19pM) and/or in the assay described in Example 27 (using human IL-12 at 1pM) of less than 100 nM, more preferably less than 50nM, even more preferably less than 10nM, such as less than 1 nM (for example, in the picomolar range);
- when the amino acid sequence of the invention, protein or polypeptide is a multivalent, multispecific and/or biparatopic construct that is directed against IL-23, and IC50 value in the assay described in Example 25 (using human IL-23 at 19pM) of less than 10 nM, more preferably less than 1nM, even more preferably less than 500pM, such as less than 100 pM (for example, in the 1-50 picomolar range);
- when the amino acid sequence of the invention, protein or polypeptide is a multivalent, multispecific and/or biparatopic construct that is directed against IL-12, and IC50 value in the assay described in Example 27 (using human IL-12 at 1pM) of less than 10 nM, more preferably less than 1nM, even more preferably less than 500pM, such as less than 100 pM (for example, in the 1-50 picomolar range).

Other aspects, embodiments, advantages and applications of the invention will also become clear from the further description herein, in which the invention will be described and discussed in more detail with reference to the Nanobodies of the invention and polypeptides of the invention comprising the same, which form some of the preferred aspects of the invention.

As will become clear from the further description herein, Nanobodies generally offer certain advantages (outlined herein) compared to "dAb's" or similar (single) domain antibodies or immunoglobulin sequences, which advantages are also provided by the Nanobodies of the invention. However, it will be clear to the skilled person that the more general aspects of the teaching below can also be applied (either directly or analogously) to other amino acid sequences of the invention.

Detailed desciption of the invention

In the present description, examples and claims:

a) Unless indicated or defined otherwise, all terms used have their usual meaning in the art, which will be clear to the skilled person. Reference is for example made to the standard handbooks, such as Sambrook et al, "Molecular Cloning: A Laboratory Manual" (2nd.Ed.), Vols. 1-3, Cold Spring Harbor Laboratory Press (1989); F. Ausubel et al, eds., "Current protocols in molecular biology", Green Publishing and Wiley Interscience, New York (1987); Lewin, "Genes II", John Wiley & Sons, New York, N.Y., (1985); Old et al., "Principles of Gene Manipulation: An Introduction to Genetic Engineering", 2nd edition, University of California Press, Berkeley, CA (1981); Roitt et al., "Immunology" (6th. Ed.), Mosby/Elsevier, Edinburgh (2001); Roitt et al., Roitt's Essential Immunology, 10th Ed. Blackwell Publishing, UK (2001); and Janeway et al., "Immunobiology" (6th Ed.), Garland Science Publishing/Churchill Livingstone, New York (2005), as well as to the general background art cited herein;

b) Unless indicated otherwise, the term "immunoglobulin sequence" - whether used herein to refer to a heavy chain antibody or to a conventional 4-chain antibody - is used as a general term to include both the full-size antibody, the individual chains thereof, as well as all parts, domains or fragments thereof (including but not limited to antigen-binding domains or fragments such as V_{HH} domains or V_H/V_L domains, respectively). In addition, the term "sequence" as used herein (for example in terms like "immunoglobulin sequence", "antibody sequence", "variable domain sequence", "V_{HH} sequence" or "protein sequence"), should generally be understood to include both the relevant amino acid sequence as well as nucleic acid sequences or nucleotide sequences encoding the same, unless the context requires a more limited interpretation;

c) Unless indicated otherwise, all methods, steps, techniques and manipulations that are not specifically described in detail can be performed and have been performed in a manner known per se, as will be clear to the skilled person. Reference is for example again made to the standard handbooks and the general background art mentioned herein and to the further references cited therein; as well as to for example the following reviews Presta, Adv. Drug Deliv. Rev. 2006, 58 (5-6): 640-56; Levin and Weiss, Mol. Biosyst. 2006, 2(1): 49-57; Irving et al., J. Immunol. Methods, 2001, 248(1-2), 31-45; Schmitz et al., Placenta, 2000, 21 Suppl. A, S106-12, Gonzales et al., Tumour Biol., 2005, 26(1), 31-43, which describe techniques for protein engineering, such as affinity

maturation and other techniques for improving the specificity and other desired properties of proteins such as immunoglobulins.

d) Amino acid residues will be indicated according to the standard three-letter or one-letter amino acid code, as mentioned in Table A-3;

Table A-3: one-letter and three-letter amino acid code

Nonpolar, uncharged (at pH 6.0 – 7.0)[3]	Alanine	Ala	A
	Valine	Val	V
	Leucine	Leu	L
	Isoleucine	Ile	I
	Phenylalanine	Phe	F
	Methionine[1]	Met	M
	Tryptophan	Trp	W
	Proline	Pro	P
Polar, uncharged (at pH 6.0-7.0)	Glycine[2]	Gly	G
	Serine	Ser	S
	Threonine	Thr	T
	Cysteine	Cys	C
	Asparagine	Asn	N
	Glutamine	Gln	Q
	Tyrosine	Tyr	Y
Polar, charged (at pH 6.0-7.0)	Lysine	Lys	K
	Arginine	Arg	R
	Histidine[4]	His	H
	Aspartate	Asp	D
	Glutamate	Glu	E

Notes:

(1) Sometimes also considered to be a polar uncharged amino acid.

(2) Sometimes also considered to be a nonpolar uncharged amino acid.

(3) As will be clear to the skilled person, the fact that an amino acid residue is referred to in this Table as being either charged or uncharged at pH 6.0 to 7.0 does not reflect in any way on the charge said amino acid residue may have at a pH lower than 6.0 and/or at a pH higher than 7.0; the amino acid residues mentioned in the Table can be either charged and/or uncharged at such a higher or lower pH, as will be clear to the skilled person.

(4) As is known in the art, the charge of a His residue is greatly dependant upon even small shifts in pH, but a His residu can generally be considered essentially uncharged at a pH of about 6.5.

e) For the purposes of comparing two or more nucleotide sequences, the percentage of "*sequence identity*" between a first nucleotide sequence and a second nucleotide sequence may be calculated by dividing [*the number of nucleotides in the first nucleotide sequence that are identical to the nucleotides at the corresponding positions in the second nucleotide sequence*] by [*the total number of nucleotides in the first nucleotide sequence*] and multiplying by [*100%*], in which each deletion, insertion, substitution or addition of a nucleotide in the second nucleotide sequence - compared to the first nucleotide sequence - is considered as a difference at a single nucleotide (position).

Alternatively, the degree of sequence identity between two or more nucleotide sequences may be calculated using a known computer algorithm for sequence alignment such as NCBI Blast v2.0, using standard settings.
Some other techniques, computer algorithms and settings for determining the degree of sequence identity are for example described in WO 04/037999, EP 0 967 284, EP 1 085 089, WO 00/55318, WO 00/78972, WO 98/49185 and GB 2 357 768-A.

Usually, for the purpose of determining the percentage of "sequence identity" between two nucleotide sequences in accordance with the calculation method outlined hereinabove, the nucleotide sequence with the greatest number of nucleotides will be taken as the "first" nucleotide sequence, and the other nucleotide sequence will be taken as the "second" nucleotide sequence;

f) For the purposes of comparing two or more amino acid sequences, the percentage of "*sequence identity*" between a first amino acid sequence and a second amino acid sequence (also referred to herein as *"amino acid identity"*) may be calculated by dividing [*the number of amino acid residues in the first amino acid sequence that are identical to the amino acid residues at the corresponding positions in the second amino acid sequence*] by [*the total number of amino acid residues in the first amino acid sequence*] and multiplying by [*100%*], in which each deletion, insertion, substitution or addition of an amino acid residue in the second amino acid sequence - compared to the first amino acid sequence - is considered as a difference at a single amino acid residue (position), i.e. as an "amino acid difference" as defined herein.

Alternatively, the degree of sequence identity between two amino acid sequences may be calculated using a known computer algorithm, such as those mentioned above

for determining the degree of sequence identity for nucleotide sequences, again using standard settings.

Usually, for the purpose of determining the percentage of "sequence identity" between two amino acid sequences in accordance with the calculation method outlined hereinabove, the amino acid sequence with the greatest number of amino acid residues will be taken as the "first" amino acid sequence, and the other amino acid sequence will be taken as the "second" amino acid sequence.

Also, in determining the degree of sequence identity between two amino acid sequences, the skilled person may take into account so-called "conservative" amino acid substitutions, which can generally be described as amino acid substitutions in which an amino acid residue is replaced with another amino acid residue of similar chemical structure and which has little or essentially no influence on the function, activity or other biological properties of the polypeptide. Such conservative amino acid substitutions are well known in the art, for example from WO 04/037999, GB-A-4 357 768, WO 98/49185, WO 00/46383 and WO 01/09300; and (preferred) types and/or combinations of such substitutions may be selected on the basis of the pertinent teachings from WO 04/037999 as well as WO 98/49185 and from the further references cited therein.

Such conservative substitutions preferably are substitutions in which one amino acid within the following groups (a) – (e) is substituted by another amino acid residue within the same group: (a) small aliphatic, nonpolar or slightly polar residues: Ala, Ser, Thr, Pro and Gly; (b) polar, negatively charged residues and their (uncharged) amides: Asp, Asn, Glu and Gln; (c) polar, positively charged residues: His, Arg and Lys; (d) large aliphatic, nonpolar residues: Met, Leu, Ile, Val and Cys; and (e) aromatic residues: Phe, Tyr and Trp.

Particularly preferred conservative substitutions are as follows: Ala into Gly or into Ser; Arg into Lys; Asn into Gln or into His; Asp into Glu; Cys into Ser; Gln into Asn; Glu into Asp; Gly into Ala or into Pro; His into Asn or into Gln; Ile into Leu or into Val; Leu into Ile or into Val; Lys into Arg, into Gln or into Glu; Met into Leu, into Tyr or into Ile; Phe into Met, into Leu or into Tyr; Ser into Thr; Thr into Ser; Trp into Tyr; Tyr into Trp; and/or Phe into Val, into Ile or into Leu.

Any amino acid substitutions applied to the polypeptides described herein may also be based on the analysis of the frequencies of amino acid variations between homologous proteins of different species developed by Schulz et al., Principles of Protein Structure, Springer-Verlag, 1978, on the analyses of structure forming potentials developed by Chou and Fasman, Biochemistry 13: 211, 1974 and Adv. Enzymol., 47: 45-149, 1978, and on the analysis of hydrophobicity patterns in proteins developed by Eisenberg et al., Proc. Nad. Acad Sci. USA 81: 140-144, 1984; Kyte & Doolittle; J Molec. Biol. 157: 105-132, 198 1, and Goldman et al., Ann. Rev. Biophys. Chem. 15: 321-353, 1986, all incorporated herein in their entirety by reference. Information on the primary, secondary and tertiary structure of Nanobodies is given in the description herein and in the general background art cited above. Also, for this purpose, the crystal structure of a V_{HH} domain from a llama is for example given by Desmyter et al., Nature Structural Biology, Vol. 3, 9, 803 (1996); Spinelli et al., Natural Structural Biology (1996); 3, 752-757; and Decanniere et al., Structure, Vol. 7, 4, 361 (1999). Further information about some of the amino acid residues that in conventional V_H domains form the V_H/V_L interface and potential camelizing substitutions on these positions can be found in the prior art cited above.

g) Amino acid sequences and nucleic acid sequences are said to be "*exactly the same*" if they have 100% sequence identity (as defined herein) over their entire length;

h) When comparing two amino acid sequences, the term "*amino acid difference*" refers to an insertion, deletion or substitution of a single amino acid residue on a position of the first sequence, compared to the second sequence; it being understood that two amino acid sequences can contain one, two or more such amino acid differences;

i) When a nucleotide sequence or amino acid sequence is said to "comprise" another nucleotide sequence or amino acid sequence, respectively, or to "essentially consist of" another nucleotide sequence or amino acid sequence, this may mean that the latter nucleotide sequence or amino acid sequence has been incorporated into the firstmentioned nucleotide sequence or amino acid sequence, respectively, but more usually this generally means that the firstmentioned nucleotide sequence or amino acid sequence comprises within its sequence a stretch of nucleotides or amino acid residues, respectively, that has the same nucleotide sequence or amino acid sequence, respectively, as the latter sequence, irrespective of how the firstmentioned sequence has

actually been generated or obtained (which may for example be by any suitable method described herein). By means of a non-limiting example, when a Nanobody of the invention is said to comprise a CDR sequence, this may mean that said CDR sequence has been incorporated into the Nanobody of the invention, but more usually this generally means that the Nanobody of the invention contains within its sequence a stretch of amino acid residues with the same amino acid sequence as said CDR sequence, irrespective of how said Nanobody of the invention has been generated or obtained. It should also be noted that when the latter amino acid sequence has a specific biological or structural function, it preferably has essentially the same, a similar or an equivalent biological or structural function in the firstmentioned amino acid sequence (in other words, the firstmentioned amino acid sequence is preferably such that the latter sequence is capable of performing essentially the same, a similar or an equivalent biological or structural function). For example, when a Nanobody of the invention is said to comprise a CDR sequence or framework sequence, respectively, the CDR sequence and framework are preferably capable, in said Nanobody, of functioning as a CDR sequence or framework sequence, respectively. Also, when a nucleotide sequence is said to comprise another nucleotide sequence, the firstmentioned nucleotide sequence is preferably such that, when it is expressed into an expression product (e.g. a polypeptide), the amino acid sequence encoded by the latter nucleotide sequence forms part of said expression product (in other words, that the latter nucleotide sequence is in the same reading frame as the firstmentioned, larger nucleotide sequence).

j) A nucleic acid sequence or amino acid sequence is considered to be "*(in) essentially isolated (form)*" - for example, compared to its native biological source and/or the reaction medium or cultivation medium from which it has been obtained - when it has been separated from at least one other component with which it is usually associated in said source or medium, such as another nucleic acid, another protein/polypeptide, another biological component or macromolecule or at least one contaminant, impurity or minor component. In particular, a nucleic acid sequence or amino acid sequence is considered "essentially isolated" when it has been purified at least 2-fold, in particular at least 10-fold, more in particular at least 100-fold, and up to 1000-fold or more. A nucleic acid sequence or amino acid sequence that is "in essentially isolated form" is

preferably essentially homogeneous, as determined using a suitable technique, such as a suitable chromatographical technique, such as polyacrylamide-gel electrophoresis;

k) The term "*domain*" as used herein generally refers to a globular region of an amino acid sequence (such as an antibody chain, and in particular to a globular region of a heavy chain antibody), or to a polypeptide that essentially consists of such a globular region. Usually, such a domain will comprise peptide loops (for example 3 or 4 peptide loops) stabilized, for example, as a sheet or by disulfide bonds. The term "*binding domain*" refers to such a domain that is directed against an antigenic determinant (as defined herein);

l) The term "*antigenic determinant*" refers to the epitope on the antigen recognized by the antigen-binding molecule (such as a Nanobody or a polypeptide of the invention) and more in particular by the antigen-binding site of said molecule. The terms "*antigenic determinant*" and "*epitope*" may also be used interchangeably herein.

m) An amino acid sequence (such as a Nanobody, an antibody, a polypeptide of the invention, or generally an antigen binding protein or polypeptide or a fragment thereof) that can (specifically) bind to, that has affinity for and/or that has specificity for a specific antigenic determinant, epitope, antigen or protein (or for at least one part, fragment or epitope thereof) is said to be "*against*", "*directed against*" *or "directed to"* said antigenic determinant, epitope, antigen or protein.

n) The term "*specificity*" refers to the number of different types of antigens or antigenic determinants to which a particular antigen-binding molecule or antigen-binding protein (such as a Nanobody or a polypeptide of the invention) molecule can bind. The specificity of an antigen-binding protein can be determined based on affinity and/or avidity. The affinity, represented by the equilibrium constant for the dissociation of an antigen with an antigen-binding protein (K_D), is a measure for the binding strength between an antigenic determinant and an antigen-binding site on the antigen-binding protein: the lesser the value of the K_D, the stronger the binding strength between an antigenic determinant and the antigen-binding molecule (alternatively, the affinity can also be expressed as the affinity constant (K_A), which is $1/K_D$). As will be clear to the skilled person (for example on the basis of the further disclosure herein), affinity can be determined in a manner known per se, depending on the specific antigen of interest. Avidity is the measure of the strength of binding between an antigen-binding molecule

(such as a Nanobody or polypeptide of the invention) and the pertinent antigen. Avidity is related to both the affinity between an antigenic determinant and its antigen binding site on the antigen-binding molecule and the number of pertinent binding sites present on the antigen-binding molecule. Typically, antigen-binding proteins (such as the amino acid sequences, Nanobodies and/or polypeptides of the invention) will bind to their antigen with a dissociation constant (K_D) of 10^{-5} to 10^{-12} moles/liter or less, and preferably 10^{-7} to 10^{-12} moles/liter or less and more preferably 10^{-8} to 10^{-12} moles/liter (i.e. with an association constant (K_A) of 10^5 to 10^{12} liter/ moles or more, and preferably 10^7 to 10^{12} liter/moles or more and more preferably 10^8 to 10^{12} liter/moles). Any K_D value greater than 10^{-4} mol/liter (or any K_A value lower than 10^4 M^{-1}) liters/mol is generally considered to indicate non-specific binding. Preferably, a monovalent immunoglobulin sequence of the invention will bind to the desired antigen with an affinity less than 500 nM, preferably less than 200 nM, more preferably less than 10 nM, such as less than 500 pM. Specific binding of an antigen-binding protein to an antigen or antigenic determinant can be determined in any suitable manner known per se, including, for example, Scatchard analysis and/or competitive binding assays, such as radioimmunoassays (RIA), enzyme immunoassays (EIA) and sandwich competition assays, and the different variants thereof known per se in the art; as well as the other techniques mentioned herein.

The dissociation constant may be the actual or apparent dissociation constant, as will be clear to the skilled person. Methods for determining the dissociation constant will be clear to the skilled person, and for example include the techniques mentioned herein. In this respect, it will also be clear that it may not be possible to measure dissociation constants of more then 10^{-4} moles/liter or 10^{-3} moles/liter (e,g, of 10^{-2} moles/liter). Optionally, as will also be clear to the skilled person, the (actual or apparent) dissociation constant may be calculated on the basis of the (actual or apparent) association constant (K_A), by means of the relationship [$K_D = 1/K_A$].

The affinity denotes the strength or stability of a molecular interaction. The affinity is commonly given as by the K_D, or dissociation constant, which has units of mol/liter (or M). The affinity can also be expressed as an association constant, K_A, which equals $1/K_D$ and has units of $(mol/liter)^{-1}$ (or M^{-1}). In the present specification, the stability of the interaction between two molecules (such as an amino acid sequence,

Nanobody or polypeptide of the invention and its intended target) will mainly be expressed in terms of the K_D value of their interaction; it being clear to the skilled person that in view of the relation $K_A = 1/K_D$, specifying the strength of molecular interaction by its K_D value can also be used to calculate the corresponding K_A value. The K_D-value characterizes the strength of a molecular interaction also in a thermodynamic sense as it is related to the free energy (DG) of binding by the well known relation $DG=RT.\ln(K_D)$ (equivalently $DG=-RT.\ln(K_A)$), where R equals the gas constant, T equals the absolute temperature and ln denotes the natural logarithm.

The K_D for biological interactions which are considered meaningful (e.g. specific) are typically in the range of 10^{-10}M (0.1 nM) to 10^{-5}M (10000 nM). The stronger an interaction is, the lower is its K_D.

The K_D can also be expressed as the ratio of the dissociation rate constant of a complex, denoted as k_{off}, to the rate of its association, denoted k_{on} (so that $K_D = k_{off}/k_{on}$ and $K_A = k_{on}/k_{off}$). The off-rate k_{off} has units s^{-1} (where s is the SI unit notation of second). The on-rate k_{on} has units $M^{-1}s^{-1}$. The on-rate may vary between 10^2 $M^{-1}s^{-1}$ to about 10^7 $M^{-1}s^{-1}$, approaching the diffusion-limited association rate constant for bimolecular interactions. The off-rate is related to the half-life of a given molecular interaction by the relation $t_{1/2}=\ln(2)/k_{off}$. The off-rate may vary between 10^{-6} s^{-1} (near irreversible complex with a $t_{1/2}$ of multiple days) to 1 s^{-1} ($t_{1/2}$=0.69 s).

The affinity of a molecular interaction between two molecules can be measured via different techniques known per se, such as the well known surface plasmon resonance (SPR) biosensor technique (see for example Ober *et al.*, Intern. Immunology, 13, 1551-1559, 2001) where one molecule is immobilized on the biosensor chip and the other molecule is passed over the immobilized molecule under flow conditions yielding k_{on}, k_{off} measurements and hence K_D (or K_A) values. This can for example be performed using the well-known Biacore instruments (see for example Example 12 or 20),

It will also be clear to the skilled person that the measured K_D may correspond to the apparent K_D if the measuring process somehow influences the intrinsic binding affinity of the implied molecules for example by artefacts related to the coating on the biosensor of one molecule. Also, an apparent K_D may be measured if one molecule contains more than one recognition sites for the other molecule. In such situation the

measured affinity may be affected by the avidity of the interaction by the two molecules.

Another approach that may be used to assess affinity is the 2-step ELISA (Enzyme-Linked Immunosorbent Assay) procedure of Friguet *et al.* (J. Immunol. Methods, 77, 305-19, 1985). This method establishes a solution phase binding equilibrium measurement and avoids possible artefacts relating to adsorption of one of the molecules on a support such as plastic.

However, the accurate measurement of K_D may be quite labor-intensive and as consequence, often apparent K_D values are determined to assess the binding strength of two molecules. It should be noted that as long all measurements are made in a consistent way (e.g. keeping the assay conditions unchanged) apparent K_D measurements can be used as an approximation of the true K_D and hence in the present document K_D and apparent K_D should be treated with equal importance or relevance.

Finally, it should be noted that in many situations the experienced scientist may judge it to be convenient to determine the binding affinity relative to some reference molecule. For example, to assess the binding strength between molecules A and B, one may e.g. use a reference molecule C that is known to bind to B and that is suitably labelled with a fluorophore or chromophore group or other chemical moiety, such as biotin for easy detection in an ELISA or FACS (Fluorescent activated cell sorting) or other format (the fluorophore for fluorescence detection, the chromophore for light absorption detection, the biotin for streptavidin-mediated ELISA detection). Typically, the reference molecule C is kept at a fixed concentration and the concentration of A is varied for a given concentration or amount of B. As a result an IC_{50} value is obtained corresponding to the concentration of A at which the signal measured for C in absence of A is halved. Provided $K_{D\,ref}$, the K_D of the reference molecule, is known, as well as the total concentration c_{ref} of the reference molecule, the apparent K_D for the interaction A-B can be obtained from following formula: $K_D = IC_{50}/(1+c_{ref}/K_{D\,ref})$. Note that if $c_{ref} << K_{D\,ref}$, $K_D \approx IC_{50}$. Provided the measurement of the IC_{50} is performed in a consistent way (e.g. keeping c_{ref} fixed) for the binders that are compared, the strength or stability of a molecular interaction can be assessed by the IC_{50} and this measurement is judged as equivalent to K_D or to apparent K_D throughout this text.

o) The half-life of an amino acid sequence, compound or polypeptide of the invention can generally be defined as the time taken for the serum concentration of the amino acid sequence, compound or polypeptide to be reduced by 50%, in vivo, for example due to degradation of the sequence or compound and/or clearance or sequestration of the sequence or compound by natural mechanisms. The in vivo half-life of an amino acid sequence, compound or polypeptide of the invention can be determined in any manner known per se, such as by pharmacokinetic analysis. Suitable techniques will be clear to the person skilled in the art, and may for example generally involve the steps of suitably administering to a warm-blooded animal (i.e. to a human or to another suitable mammal, such as a mouse, rabbit, rat, pig, dog or a primate, for example monkeys from the genus *Macaca* (such as, and in particular, cynomologus monkeys (*Macaca fascicularis*) and/or rhesus monkeys (*Macaca mulatta*)) and baboon (*Papio ursinus*)) a suitable dose of the amino acid sequence, compound or polypeptide of the invention; collecting blood samples or other samples from said animal; determining the level or concentration of the amino acid sequence, compound or polypeptide of the invention in said blood sample; and calculating, from (a plot of) the data thus obtained, the time until the level or concentration of the amino acid sequence, compound or polypeptide of the invention has been reduced by 50% compared to the initial level upon dosing. Reference is for example made to the Experimental Part below, as well as to Dennis et al., J. Biol. Chem 277:35035-42 (2002), and to the standard handbooks, such as Kenneth, A et al: Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists and Peters et al, Pharmacokinete analysis: A Practical Approach (1996). Reference is also made to "Pharmacokinetics", M Gibaldi & D Perron, published by Marcel Dekker, 2nd Rev. edition (1982).

As will also be clear to the skilled person (see for example pages 6 and 7 of WO 04/003019 and in the further references cited therein), the half-life can be expressed using parameters such as the t1/2-alpha, t1/2-beta and the area under the curve (AUC). In the present specification, an "increase in half-life" refers to an increase in any one of these parameters, such as any two of these parameters, or essentially all three these parameters. As used herein "increase in half-life" or "increased half-life" in particular refers to an increase in the t1/2-beta, either with or without an increase in the t1/2-alpha and/or the AUC or both.

For example, the half-life of an amino acid sequence or polypeptide of the invention may be determined by means of a pharmacokinetic study, performed in a rodent or non-human primate model, as follows. Groups of animals (n=2-10) are given an intravenous bolus injection of 1mg/kg or 10 mg/kg 2D3-17D12 fusion protein. Plasma samples are obtained via a vein at different timepoints after dosing (eg. 1, 2, 4, 6, 8, 12, 24, 48,144, 192, 240, 288 and 336 h after dosing) and analyzed for the presence of the 2D3-17D12 fusion protein by ELISA. Plasma concentration versus time are fitted to a two-compartment elimination model. The pharmacokinetic parameters of clearance, V1, steady state volume (Vss), T½, AUC, and AUC corrected for actual dose administered (AUC/dose) are averaged for each treatment group. Differences between groups are determined by analysis of variance.

p) In the context of the present invention, "modulating" or "to modulate" generally means either reducing or inhibiting the activity of, or alternatively increasing the activity of, a target or antigen, as measured using a suitable in vitro, cellular or in vivo assay. In particular, "modulating" or "to modulate" may mean either reducing or inhibiting the activity of, or alternatively increasing a (relevant or intended) biological activity of, a target or antigen, as measured using a suitable in vitro, cellular or in vivo assay (which will usually depend on the target or antigen involved), by at least 1%, preferably at least 5%, such as at least 10% or at least 25%, for example by at least 50%, at least 60%, at least 70%, at least 80%, or 90% or more, compared to activity of the target or antigen in the same assay under the same conditions but without the presence of the construct of the invention.

As will be clear to the skilled person, "modulating" may also involve effecting a change (which may either be an increase or a decrease) in affinity, avidity, specificity and/or selectivity of a target or antigen for one or more of its ligands, binding partners, partners for association into a homomultimeric or heteromultimeric form, or substrates; and/or effecting a change (which may either be an increase or a decrease) in the sensitivity of the target or antigen for one or more conditions in the medium or surroundings in which the target or antigen is present (such as pH, ion strength, the presence of co-factors, etc.), compared to the same conditions but without the presence of the construct of the invention. As will be clear to the skilled person, this may again

be determined in any suitable manner and/or using any suitable assay known per se, depending on the target or antigen involved.

"Modulating" may also mean effecting a change (i.e. an activity as an agonist, as an antagonist or as a reverse agonist, respectively, depending on the target or antigen and the desired biological or physiological effect) with respect to one or more biological or physiological mechanisms, effects, responses, functions, pathways or activities in which the target or antigen (or in which its substrate(s), ligand(s) or pathway(s) are involved, such as its signalling pathway or metabolic pathway and their associated biological or physiological effects) is involved. Again, as will be clear to the skilled person, such an action as an agonist or an antagonist may be determined in any suitable manner and/or using any suitable (in vitro and usually cellular or in assay) assay known per se, depending on the target or antigen involved. In particular, an action as an agonist or antagonist may be such that an intended biological or physiological activity is increased or decreased, respectively, by at least 1%, preferably at least 5%, such as at least 10% or at least 25%, for example by at least 50%, at least 60%, at least 70%, at least 80%, or 90% or more, compared to the biological or physiological activity in the same assay under the same conditions but without the presence of the construct of the invention.

Modulating may for example also involve allosteric modulation of the target or antigen; and/or reducing or inhibiting the binding of the target or antigen to one of its substrates or ligands and/or competing with a natural ligand, substrate for binding to the target or antigen. Modulating may also involve activating the target or antigen or the mechanism or pathway in which it is involved. Modulating may for example also involve effecting a change in respect of the folding or confirmation of the target or antigen, or in respect of the ability of the target or antigen to fold, to change its confirmation (for example, upon binding of a ligand), to associate with other (sub)units, or to disassociate. Modulating may for example also involve effecting a change in the ability of the target or antigen to transport other compounds or to serve as a channel for other compounds (such as ions).

Modulating may be reversible or irreversible, but for pharmaceutical and pharmacological purposes will usually be in a reversible manner.

q) In respect of a target or antigen, the term "interaction site" on the target or antigen means a site, epitope, antigenic determinant, part, domain or stretch of amino acid residues on the target or antigen that is a site for binding to a ligand, receptor or other binding partner, a catalytic site, a cleavage site, a site for allosteric interaction, a site involved in multimerisation (such as homomerization or heterodimerization) of the target or antigen; or any other site, epitope, antigenic determinant, part, domain or stretch of amino acid residues on the target or antigen that is involved in a biological action or mechanism of the target or antigen. More generally, an "interaction site" can be any site, epitope, antigenic determinant, part, domain or stretch of amino acid residues on the target or antigen to which an amino acid sequence or polypeptide of the invention can bind such that the target or antigen (and/or any pathway, interaction, signalling, biological mechanism or biological effect in which the target or antigen is involved) is modulated (as defined herein).

r) An amino acid sequence or polypeptide is said to be "*specific for*" a first target or antigen compared to a second target or antigen when is binds to the first antigen with an affinity (as described above, and suitably expressed as a K_D value, K_A value, K_{off} rate and/or K_{on} rate) that is at least 10 times, such as at least 100 times, and preferably at least 1000 times, and up to 10.000 times or more better than the affinity with which said amino acid sequence or polypeptide binds to the second target or polypeptide. For example, the first antigen may bind to the target or antigen with a K_D value that is at least 10 times less, such as at least 100 times less, and preferably at least 1000 times less, such as 10.000 times less or even less than that, than the K_D with which said amino acid sequence or polypeptide binds to the second target or polypeptide. Preferably, when an amino acid sequence or polypeptide is "specific for" a first target or antigen compared to a second target or antigen, it is directed against (as defined herein) said first target or antigen, but not directed against said second target or antigen.

s) The terms "cross-block", "cross-blocked" and "cross-blocking" are used interchangeably herein to mean the ability of an amino acid sequence or other binding agents (such as a polypeptide of the invention) to interfere with the binding of other amino acid sequences or binding agents of the invention to a given target. The extend to which an amino acid sequence or other binding agents of the invention is able to interfere with the binding of another to [target], and therefore whether it can be said to

cross-block according to the invention, can be determined using competition binding assays. One particularly suitable quantitative assay uses a Biacore machine which can measure the extent of interactions using surface plasmon resonance technology. Another suitable quantitative cross-blocking assay uses an ELISA-based approach to measure competition between amino acid sequence or another binding agents in terms of their binding to the target.

The following generally describes a suitable Biacore assay for determining whether an amino acid sequence or other binding agent cross-blocks or is capable of cross-blocking according to the invention. It will be appreciated that the assay can be used with any of the amino acid sequence or other binding agents described herein. The Biacore machine (for example the Biacore 3000) is operated in line with the manufacturer's recommendations. Thus in one cross-blocking assay, the target protein is coupled to a CM5 Biacore chip using standard amine coupling chemistry to generate a surface that is coated with the target. Typically 200- 800 resonance units of the target would be coupled to the chip (an amount that gives easily measurable levels of binding but that is readily saturable by the concentrations of test reagent being used). Two test amino acid sequences (termed A* and B*) to be assessed for their ability to cross-block each other are mixed at a one to one molar ratio of binding sites in a suitable buffer to create the test mixture. When calculating the concentrations on a binding site basis the molecular weight of an amino acid sequence is assumed to be the total molecular weight of the amino acid sequence divided by the number of target binding sites on that amino acid sequence. The concentration of each amino acid sequence in the test mix should be high enough to readily saturate the binding sites for that amino acid sequence on the target molecules captured on the Biacore chip. The amino acid sequences in the mixture are at the same molar concentration (on a binding basis) and that concentration would typically be between 1.00 and 1.5 micromolar (on a binding site basis). Separate solutions containing A* alone and B* alone are also prepared. A* and B* in these solutions should be in the same buffer and at the same concentration as in the test mix. The test mixture is passed over the target-coated Biacore chip and the total amount of binding recorded. The chip is then treated in such a way as to remove the bound amino acid sequences without damaging the chip-bound target. Typically this is done by treating the chip with 30 mM HCl for 60 seconds. The solution of A*

alone is then passed over the target-coated surface and the amount of binding recorded. The chip is again treated to remove all of the bound amino acid sequences without damaging the chip-bound target. The solution of B* alone is then passed over the target-coated surface and the amount of binding recorded. The maximum theoretical binding of the mixture of A* and B* is next calculated, and is the sum of the binding of each amino acid sequence when passed over the target surface alone. If the actual recorded binding of the mixture is less than this theoretical maximum then the two amino acid sequences are cross-blocking each other. Thus, in general, a cross-blocking amino acid sequence or other binding agent according to the invention is one which will bind to the target in the above Biacore cross-blocking assay such that during the assay and in the presence of a second amino acid sequence or other binding agent of the invention the recorded binding is between 80% and 0.1% (e.g. 80% to 4%) of the maximum theoretical binding, specifically between 75% and 0.1% (e.g. 75% to 4%) of the maximum theoretical binding, and more specifically between 70% and 0.1% (e.g. 70% to 4%) of maximum theoretical binding (as just defined above) of the two amino acid sequences or binding agents in combination. The Biacore assay described above is a primary assay used to determine if amino acid sequences or other binding agents cross-block each other according to the invention. On rare occasions particular amino acid sequences or other binding agents may not bind to target coupled via amine chemistry to a CM5 Biacore chip (this usually occurs when the relevant binding site on target is masked or destroyed by the coupling to the chip). In such cases cross-blocking can be determined using a tagged version of the target, for example a N-terminal His-tagged version. In this particular format, an anti-His amino acid sequence would be coupled to the Biacore chip and then the His-tagged target would be passed over the surface of the chip and captured by the anti-His amino acid sequence. The cross blocking analysis would be carried out essentially as described above, except that after each chip regeneration cycle, new His-tagged target would be loaded back onto the anti-His amino acid sequence coated surface. In addition to the example given using N-terminal His-tagged [target], C-terminal His-tagged target could alternatively be used. Furthermore, various other tags and tag binding protein combinations that are known in the art could be used for such a cross-blocking analysis (e.g. HA tag with anti-HA antibodies; FLAG tag with anti-FLAG antibodies; biotin tag with streptavidin).

The following generally describes an ELISA assay for determining whether an amino acid sequence or other binding agent directed against a target cross-blocks or is capable of cross-blocking as defined herein. It will be appreciated that the assay can be used with any of the amino acid sequences (or other binding agents such as polypeptides of the invention) described herein. The general principal of the assay is to have an amino acid sequence or binding agent that is directed against the target coated onto the wells of an ELISA plate. An excess amount of a second, potentially cross-blocking, anti-target amino acid sequence is added in solution (i.e. not bound to the ELISA plate). A limited amount of the target is then added to the wells. The coated amino acid sequence and the amino acid sequence in solution compete for binding of the limited number of target molecules. The plate is washed to remove excess target that has not been bound by the coated amino acid sequence and to also remove the second, solution phase amino acid sequence as well as any complexes formed between the second, solution phase amino acid sequence and target. The amount of bound target is then measured using a reagent that is appropriate to detect the target. An amino acid sequence in solution that is able to cross-block the coated amino acid sequence will be able to cause a decrease in the number of target molecules that the coated amino acid sequence can bind relative to the number of target molecules that the coated amino acid sequence can bind in the absence of the second, solution phase, amino acid sequence. In the instance where the first amino acid sequence, e.g. an Ab-X, is chosen to be the immobilized amino acid sequence, it is coated onto the wells of the ELISA plate, after which the plates are blocked with a suitable blocking solution to minimize non-specific binding of reagents that are subsequently added. An excess amount of the second amino acid sequence, i.e. Ab-Y, is then added to the ELISA plate such that the moles of Ab-Y [target] binding sites per well are at least 10 fold higher than the moles of Ab-X [target] binding sites that were used, per well, during the coating of the ELISA plate. [target] is then added such that the moles of [target] added per well are at least 25-fold lower than the moles of Ab-X [target] binding sites that were used for coating each well. Following a suitable incubation period the ELISA plate is washed and a reagent for detecting the target is added to measure the amount of target specifically bound by the coated anti-[target] amino acid sequence (in this case Ab-X). The background signal for the assay is defined as the signal obtained in wells with the coated amino acid sequence

(in this case Ab-X), second solution phase amino acid sequence (in this case Ab-Y), [target] buffer only (i.e. no target) and target detection reagents. The positive control signal for the assay is defined as the signal obtained in wells with the coated amino acid sequence (in this case Ab-X), second solution phase amino acid sequence buffer only (i.e. no second solution phase amino acid sequence), target and target detection reagents. The ELISA assay may be run in such a manner so as to have the positive control signal be at least 6 times the background signal. To avoid any artefacts (e.g. significantly different affinities between Ab-X and Ab-Y for [target]) resulting from the choice of which amino acid sequence to use as the coating amino acid sequence and which to use as the second (competitor) amino acid sequence, the cross-blocking assay may to be run in two formats: 1) format 1 is where Ab-X is the amino acid sequence that is coated onto the ELISA plate and Ab-Y is the competitor amino acid sequence that is in solution and 2) format 2 is where Ab-Y is the amino acid sequence that is coated onto the ELISA plate and Ab-X is the competitor amino acid sequence that is in solution. Ab-X and Ab-Y are defined as cross-blocking if, either in format 1 or in format 2, the solution phase anti-target amino acid sequence is able to cause a reduction of between 60% and 100%, specifically between 70% and 100%, and more specifically between 80% and 100%, of the target detection signal {i.e. the amount of target bound by the coated amino acid sequence) as compared to the target detection signal obtained in the absence of the solution phase anti- target amino acid sequence (i.e. the positive control wells).

t) An amino acid sequence is said to be "*cross-reactive*" for two different antigens or antigenic determinants (such as serum albumin from two different species of mammal, such as human serum albumin and cyno serum albumin) if it is specific for (as defined herein) both these different antigens or antigenic determinants.

u) By binding that is "*essentially independent of the pH*" is generally meant herein that the association constant (K_A) of the amino acid sequence with respect to the serum protein (such as serum albumin) at the pH value(s) that occur in a cell of an animal or human body (as further described herein) is at least 5%, such as at least 10%, preferably at least 25%, more preferably at least 50%, even more preferably at least 60%, such as even more preferably at least 70%, such as at least 80% or 90% or more (or even more than 100%, such as more than 110%, more than 120% or even 130% or more, or even

more than 150%, or even more than 200%) of the association constant (K_A) of the amino acid sequence with respect to the same serum protein at the pH value(s) that occur outside said cell. Alternatively, by binding that is "*essentially independent of the pH*" is generally meant herein that the k_{off} rate (measured by Biacore) of the amino acid sequence with respect to the serum protein (such as serum albumin) at the pH value(s) that occur in a cell of an animal or human body (as e.g. further described herein, e.g. pH around 5.5, e.g. 5.3 to 5.7) is at least 5%, such as at least 10%, preferably at least 25%, more preferably at least 50%, even more preferably at least 60%, such as even more preferably at least 70%, such as at least 80% or 90% or more (or even more than 100%, such as more than 110%, more than 120% or even 130% or more, or even more than 150%, or even more than 200%) of the k_{off} rate of the amino acid sequence with respect to the same serum protein at the pH value(s) that occur outside said cell, e.g. pH 7.2 to 7.4. By "*the pH value(s) that occur in a cell of an animal or human body*" is meant the pH value(s) that may occur inside a cell, and in particular inside a cell that is involved in the recycling of the serum protein. In particular, by "*the pH value(s) that occur in a cell of an animal or human body*" is meant the pH value(s) that may occur inside a (sub)cellular compartment or vesicle that is involved in recycling of the serum protein (e.g. as a result of pinocytosis, endocytosis, transcytosis, exocytosis and phagocytosis or a similar mechanism of uptake or internalization into said cell), such as an endosome, lysosome or pinosome.

v) As further described herein, the total number of amino acid residues in a Nanobody can be in the region of 110-120, is preferably 112-115, and is most preferably 113. It should however be noted that parts, fragments, analogs or derivatives (as further described herein) of a Nanobody are not particularly limited as to their length and/or size, as long as such parts, fragments, analogs or derivatives meet the further requirements outlined herein and are also preferably suitable for the purposes described herein;

w) The amino acid residues of a Nanobody are numbered according to the general numbering for V_H domains given by Kabat et al. ("Sequence of proteins of immunological interest", US Public Health Services, NIH Bethesda, MD, Publication No. 91), as applied to V_{HH} domains from Camelids in the article of Riechmann and Muyldermans, J. Immunol. Methods 2000 Jun 23; 240 (1-2): 185-195 (see for example Figure 2 of this publication); or referred to herein. According to this numbering, FR1

of a Nanobody comprises the amino acid residues at positions 1-30, CDR1 of a Nanobody comprises the amino acid residues at positions 31-35, FR2 of a Nanobody comprises the amino acids at positions 36-49, CDR2 of a Nanobody comprises the amino acid residues at positions 50-65, FR3 of a Nanobody comprises the amino acid residues at positions 66-94, CDR3 of a Nanobody comprises the amino acid residues at positions 95-102, and FR4 of a Nanobody comprises the amino acid residues at positions 103-113. [In this respect, it should be noted that - as is well known in the art for V_H domains and for V_{HH} domains - the total number of amino acid residues in each of the CDR's may vary and may not correspond to the total number of amino acid residues indicated by the Kabat numbering (that is, one or more positions according to the Kabat numbering may not be occupied in the actual sequence, or the actual sequence may contain more amino acid residues than the number allowed for by the Kabat numbering). This means that, generally, the numbering according to Kabat may or may not correspond to the actual numbering of the amino acid residues in the actual sequence. Generally, however, it can be said that, according to the numbering of Kabat and irrespective of the number of amino acid residues in the CDR's, position 1 according to the Kabat numbering corresponds to the start of FR1 and vice versa, position 36 according to the Kabat numbering corresponds to the start of FR2 and vice versa, position 66 according to the Kabat numbering corresponds to the start of FR3 and vice versa, and position 103 according to the Kabat numbering corresponds to the start of FR4 and vice versa.].

Alternative methods for numbering the amino acid residues of V_H domains, which methods can also be applied in an analogous manner to V_{HH} domains from Camelids and to Nanobodies, are the method described by Chothia et al. (Nature 342, 877-883 (1989)), the so-called "AbM definition" and the so-called "contact definition". However, in the present description, claims and figures, the numbering according to Kabat as applied to V_{HH} domains by Riechmann and Muyldermans will be followed, unless indicated otherwise; and

x) In respect of any amino acid sequence described herein that is a CDR sequence (such as any of the CDR sequences from the CDR1 Sequences Groups 2, 9, 16, 23, 30, 37, 44, 51 and/or 58 (see Table A-1); from the CDR2 Sequences Groups 4, 11, 18, 25, 32, 39, 46, 53, and/or 60 (see Table A-1); and/or from the CDR3 Sequences Groups 6, 13, 20,

27, 34, 41, 48, 54 and/or 62 (see Table A-1)), "*Optional Condition I*" means that when said amino acid sequence contains an amino acid substitution, such an amino acid substitution is preferably, and compared to the original amino acid sequence without said substitution, a conservative amino acid substitution (as defined herein): "*Optional Condition II*"means that said preferably only contains amino acid substitutions, and no amino acid deletions or insertions, compared to the original amino acid sequence without said substitution; "*Optional Condition III*" means that said amino acid sequence may be an amino acid sequence that is derived from the corresponding amino acid sequence by means of affinity maturation using one or more techniques of affinity maturation known per se.

y) In respect of any amino acid sequence described herein that is a framework sequence, "*Optional Condition I*" means that when said amino acid sequence contains an amino acid substitution, such an amino acid substitution is preferably, and compared to the original amino acid sequence without said substitution, a conservative amino acid substitution (as defined herein): "*Optional Condition II*"means that said preferably only contains amino acid substitutions, and no amino acid deletions or insertions, compared to the original amino acid sequence without said substitution; and "*Optional Condition IV*" means that where such an amino acid sequence contains any amino acid differences, these amino acid differences are preferably not present at one of the Hallmark Residues (although the presence of an amino acid difference at a position of a Hallmark Residue is not excluded, provided the favourable properties of a VHH or nanobody as described herein are essentially maintained or not affected to an extent that would make the resulting amino acid sequence no longer suitable for use as a single antigen binding domain or unit (for example, as a nanobody);

z) The Figures, Sequence Listing and the Experimental Part/Examples are only given to further illustrate the invention and should not be interpreted or construed as limiting the scope of the invention and/or of the appended claims in any way, unless explicitly indicated otherwise herein. Also, generally, the amino acid sequences and polypeptides of the invention that are explicitly referred to in the Experimental Part are preferered examples of amino acid sequences and polypeptides of the invention. Further preferences from within these amino acid sequences and polypeptides will become clear from the data presented in the Experimental Part,

For a general description of heavy chain antibodies and the variable domains thereof, reference is inter alia made to the prior art cited herein, to the review article by Muyldermans in Reviews in Molecular Biotechnology 74(2001), 277-302; as well as to the following patent applications, which are mentioned as general background art: WO 94/04678, WO 95/04079 and WO 96/34103 of the Vrije Universiteit Brussel; WO 94/25591, WO 99/37681, WO 00/40968, WO 00/43507, WO 00/65057, WO 01/40310, WO 01/44301, EP 1134231 and WO 02/48193 of Unilever; WO 97/49805, WO 01/21817, WO 03/035694, WO 03/054016 and WO 03/055527 of the Vlaams Instituut voor Biotechnologie (VIB); WO 03/050531 of Algonomics N.V. and Ablynx N.V.; WO 01/90190 by the National Research Council of Canada; WO 03/025020 (= EP 1 433 793) by the Institute of Antibodies; as well as WO 04/041867, WO 04/041862, WO 04/041865, WO 04/041863, WO 04/062551, WO 05/044858, WO 06/40153, WO 06/079372, WO 06/122786, WO 06/122787 and WO 06/122825, by Ablynx N.V. and the further published patent applications by Ablynx N.V. Reference is also made to the further prior art mentioned in these applications, and in particular to the list of references mentioned on pages 41-43 of the International application WO 06/040153, which list and references are incorporated herein by reference.

In accordance with the terminology used in the art (see the above references), the variable domains present in naturally occurring heavy chain antibodies will also be referred to as "*V_{HH} domains*", in order to distinguish them from the heavy chain variable domains that are present in conventional 4-chain antibodies (which will be referred to hereinbelow as "*V_H domains*") and from the light chain variable domains that are present in conventional 4-chain antibodies (which will be referred to hereinbelow as "*V_L domains*").

As mentioned in the prior art referred to above, V_{HH} domains have a number of unique structural characteristics and functional properties which make isolated V_{HH} domains (as well as Nanobodies based thereon, which share these structural characteristics and functional properties with the naturally occurring V_{HH} domains) and proteins containing the same highly advantageous for use as functional antigen-binding domains or proteins. In particular, and without being limited thereto, V_{HH} domains (which have been "designed" by nature to functionally bind to an antigen without the presence of, and without any interaction with, a light chain variable domain) and Nanobodies can function as a single, relatively small, functional antigen-binding structural unit, domain or protein. This distinguishes the V_{HH} domains from the V_H and V_L domains of conventional 4-chain antibodies, which by

themselves are generally not suited for practical application as single antigen-binding proteins or domains, but need to be combined in some form or another to provide a functional antigen-binding unit (as in for example conventional antibody fragments such as Fab fragments; in ScFv's fragments, which consist of a V_H domain covalently linked to a V_L domain).

Because of these unique properties, the use of V_{HH} domains and Nanobodies as single antigen-binding proteins or as antigen-binding domains (i.e. as part of a larger protein or polypeptide) offers a number of significant advantages over the use of conventional V_H and V_L domains, scFv's or conventional antibody fragments (such as Fab- or $F(ab')_2$-fragments):

- only a single domain is required to bind an antigen with high affinity and with high selectivity, so that there is no need to have two separate domains present, nor to assure that these two domains are present in the right spacial conformation and configuration (i.e. through the use of especially designed linkers, as with scFv's);
- V_{HH} domains and Nanobodies can be expressed from a single gene and require no post-translational folding or modifications;
- V_{HH} domains and Nanobodies can easily be engineered into multivalent and multispecific formats (as further discussed herein);
- V_{HH} domains and Nanobodies are highly soluble and do not have a tendency to aggregate (as with the mouse-derived "dAb's" described by Ward et al., Nature, Vol. 341, 1989, p. 544);
- V_{HH} domains and Nanobodies are highly stable to heat, pH, proteases and other denaturing agents or conditions (see for example Ewert et al, supra);
- V_{HH} domains and Nanobodies are easy and relatively cheap to prepare, even on a scale required for production. For example, V_{HH} domains, Nanobodies and proteins/polypeptides containing the same can be produced using microbial fermentation (e.g. as further described below) and do not require the use of mammalian expression systems, as with for example conventional antibody fragments;
- V_{HH} domains and Nanobodies are relatively small (approximately 15 kDa, or 10 times smaller than a conventional IgG) compared to conventional 4-chain antibodies and antigen-binding fragments thereof, and therefore show high(er) penetration into tissues (including but not limited to solid tumors and other dense tissues) than such conventional 4-chain antibodies and antigen-binding fragments thereof;

- V_{HH} domains and Nanobodies can show so-called cavity-binding properties (inter alia due to their extended CDR3 loop, compared to conventional V_H domains) and can therefore also access targets and epitopes not accessable to conventional 4-chain antibodies and antigen-binding fragments thereof. For example, it has been shown that V_{HH} domains and Nanobodies can inhibit enzymes (see for example WO 97/49805; Transue et al., Proteins 1998 Sep 1; 32(4): 515-22; Lauwereys et al., EMBO J. 1998 Jul 1; 17(13): 3512-20).

In a specific and preferred aspect, the invention provides Nanobodies against heterodimeric cytokines and/or their receptors, and in particular Nanobodies against heterodimeric cytokines and/or their receptors from a warm-blooded animal, and more in particular Nanobodies against heterodimeric cytokines and/or their receptors from a mammal, and especially Nanobodies against human heterodimeric cytokines and/or their receptors; as well as proteins and/or polypeptides comprising at least one such Nanobody.

In particular, the invention provides Nanobodies against heterodimeric cytokines and/or their receptors, and proteins and/or polypeptides comprising the same, that have improved therapeutic and/or pharmacological properties and/or other advantageous properties (such as, for example, improved ease of preparation and/or reduced costs of goods), compared to conventional antibodies against heterodimeric cytokines and/or their receptors or fragments thereof, compared to constructs that could be based on such conventional antibodies or antibody fragments (such as Fab' fragments, $F(ab')_2$ fragments, ScFv constructs, "diabodies" and other multispecific constructs (see for example the review by Holliger and Hudson, Nat Biotechnol. 2005 Sep;23(9):1126-36)), and also compared to the so-called "dAb's" or similar (single) domain antibodies that may be derived from variable domains of conventional antibodies. These improved and advantageous properties will become clear from the further description herein, and for example include, without limitation, one or more of:

- increased affinity and/or avidity for heterodimeric cytokines and/or their receptors, either in a monovalent format, in a multivalent format (for example in a bivalent format) and/or in a multispecific format (for example one of the multispecific formats described hereinbelow);
- better suitability for formatting in a multivalent format (for example in a bivalent format);

- better suitability for formatting in a multispecific format (for example one of the multispecific formats described hereinbelow);
- improved suitability or susceptibility for "humanizing" substitutions (as defined herein);
- less immunogenicity, either in a monovalent format, in a multivalent format (for example in a bivalent format) and/or in a multispecific format (for example one of the multispecific formats described hereinbelow);
- increased stability, either in a monovalent format, in a multivalent format (for example in a bivalent format) and/or in a multispecific format (for example one of the multispecific formats described hereinbelow);
- increased specificity towards heterodimeric cytokines and/or their receptors, either in a monovalent format, in a multivalent format (for example in a bivalent format) and/or in a multispecific format (for example one of the multispecific formats described hereinbelow);
- decreased or where desired increased cross-reactivity with heterodimeric cytokines and/or their receptors from different species;

and/or

- one or more other improved properties desirable for pharmaceutical use (including prophylactic use and/or therapeutic use) and/or for diagnostic use (including but not limited to use for imaging purposes), either in a monovalent format, in a multivalent format (for example in a bivalent format) and/or in a multispecific format (for example one of the multispecific formats described hereinbelow).

As generally described herein for the amino acid sequences of the invention, the Nanobodies of the invention are preferably in essentially isolated form (as defined herein), or form part of a protein or polypeptide of the invention (as defined herein), which may comprise or essentially consist of one or more Nanobodies of the invention and which may optionally further comprise one or more further amino acid sequences (all optionally linked via one or more suitable linkers). For example, and without limitation, the one or more amino acid sequences of the invention may be used as a binding unit in such a protein or polypeptide, which may optionally contain one or more further amino acid sequences that can serve as a binding unit (i.e. against one or more other targets than heterodimeric cytokines and/or their receptors), so as to provide a monovalent, multivalent or multispecific

polypeptide of the invention, respectively, all as described herein. In particular, such a protein or polypeptide may comprise or essentially consist of one or more Nanobodies of the invention and optionally one or more (other) Nanobodies (i.e. directed against other targets than heterodimeric cytokines and/or their receptors), all optionally linked via one or more suitable linkers, so as to provide a monovalent, multivalent or multispecific Nanobody construct, respectively, as further described herein. Such proteins or polypeptides may also be in essentially isolated form (as defined herein).

In a Nanobody of the invention, the binding site for binding against heterodimeric cytokines and/or their receptors is preferably formed by the CDR sequences. Optionally, a Nanobody of the invention may also, and in addition to the at least one binding site for binding against heterodimeric cytokines and/or their receptors, contain one or more further binding sites for binding against other antigens, proteins or targets. For methods and positions for introducing such second binding sites, reference is for example made to Keck and Huston, Biophysical Journal, 71, October 1996, 2002-2011; EP 0 640 130; WO 06/07260.

As generally described herein for the amino acid sequences of the invention, when a Nanobody of the invention (or a polypeptide of the invention comprising the same) is intended for administration to a subject (for example for therapeutic and/or diagnostic purposes as described herein), it is preferably directed against human heterodimeric cytokines and/or their receptors; whereas for veterinary purposes, it is preferably directed against heterodimeric cytokines and/or their receptors from the species to be treated. Also, as with the amino acid sequences of the invention, a Nanobody of the invention may or may not be cross-reactive (i.e. directed against heterodimeric cytokines and/or their receptors from two or more species of mammal, such as against human heterodimeric cytokines and/or their receptors and heterodimeric cytokines and/or their receptors from at least one of the species of mammal mentioned herein).

Also, again as generally described herein for the amino acid sequences of the invention, the Nanobodies of the invention may generally be directed against any antigenic determinant, epitope, part, domain, subunit or confirmation (where applicable) of heterodimeric cytokines and/or their receptors, such as an interaction site (as defined herein) or a site, antigenic determinant, epitope, part, domain that is not an interaction site.

As already described herein, the amino acid sequence and structure of a Nanobody can be considered - without however being limited thereto - to be comprised of four

framework regions or "FR's" (or sometimes also referred to as "FW's"), which are referred to in the art and herein as "Framework region 1" or "FR1"; as "Framework region 2" or "FR2"; as "Framework region 3" or "FR3"; and as "Framework region 4" or "FR4", respectively; which framework regions are interrupted by three complementary determining regions or "CDR's", which are referred to in the art as "Complementarity Determining Region 1"or "CDR1"; as "Complementarity Determining Region 2" or "CDR2"; and as "Complementarity Determining Region 3" or "CDR3", respectively. Some preferred framework sequences and CDR's (and combinations thereof) that are present in the Nanobodies of the invention are as described herein. Other suitable CDR sequences can be obtained by the methods described herein.

According to a non-limiting but preferred aspect of the invention, (the CDR sequences present in) the Nanobodies of the invention are such that:

- the Nanobodies can bind to heterodimeric cytokines and/or their receptors with a dissociation constant (K_D) of 10^{-5} to 10^{-12} moles/liter or less, and preferably 10^{-7} to 10^{-12} moles/liter or less and more preferably 10^{-8} to 10^{-12} moles/liter (i.e. with an association constant (K_A) of 10^{5} to 10^{12} liter/ moles or more, and preferably 10^{7} to 10^{12} liter/moles or more and more preferably 10^{8} to 10^{12} liter/moles);

and/or such that:

- the Nanobodies can bind to heterodimeric cytokines and/or their receptors with a k_{on}-rate of between 10^{2} $M^{-1}s^{-1}$ to about 10^{7} $M^{-1}s^{-1}$, preferably between 10^{3} $M^{-1}s^{-1}$ and 10^{7} $M^{-1}s^{-1}$, more preferably between 10^{4} $M^{-1}s^{-1}$ and 10^{7} $M^{-1}s^{-1}$, such as between 10^{5} $M^{-1}s^{-1}$ and 10^{7} $M^{-1}s^{-1}$;

and/or such that they:

- the Nanobodies can bind to heterodimeric cytokines and/or their receptors with a k_{off} rate between $1s^{-1}$ ($t_{1/2}$=0.69 s) and 10^{-6} s^{-1} (providing a near irreversible complex with a $t_{1/2}$ of multiple days), preferably between 10^{-2} s^{-1} and 10^{-6} s^{-1}, more preferably between 10^{-3} s^{-1} and 10^{-6} s^{-1}, such as between 10^{-4} s^{-1} and 10^{-6} s^{-1}.

Preferably, (the CDR sequences present in) the Nanobodies of the invention are such that: a monovalent Nanobody of the invention (or a polypeptide that contains only one Nanobody of the invention) is preferably such that it will bind to heterodimeric cytokines and/or their receptors with an affinity less than 500 nM, preferably less than 200 nM, more preferably less than 10 nM, such as less than 500 pM.

The affinity of the Nanobody of the invention against heterodimeric cytokines and/or their receptors can be determined in a manner known per se, for example using the general techniques for measuring K_D. K_A, k_{off} or k_{on} mentioned herein, as well as some of the specific assays described herein.

Some preferred IC50 values for binding of the Nanobodies of the invention (and of polypeptides comprising the same) to heterodimeric cytokines and/or their receptors will become clear from the further description and examples herein.

In a preferred but non-limiting aspect, the invention relates to a (single) domain antibody and/or a Nanobody (as defined herein) which is a p19+ sequence (as defined herein), which consists of 4 framework regions (FR1 to FR4 respectively) and 3 complementarity determining regions (CDR1 to CDR3 respectively), in which:

- CDR1 is chosen from the group consisting of:

a) the amino acid sequences from the CDR1 Sequences Group 2 (see Table A-1 and Figure 11);

b) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the CDR1 Sequences Group 2;

c) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the CDR1 Sequences Group 2;

and/or

- CDR2 is chosen from the group consisting of:

d) the amino acid sequences from the CDR2 Sequences Group 4;

e) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the CDR2 Sequences Group 4;

f) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the CDR2 Sequences Group 4;

and/or

- CDR3 is chosen from the group consisting of:

g) the amino acid sequences from the CDR3 Sequences Group 6;

h) amino acid sequences that have at least 80% amino acid identity with at least one of the amino acid sequences from the CDR3 Sequences Group 6;

i) amino acid sequences that have 3, 2, or 1 amino acid difference with at least one of the amino acid sequences from the CDR3 Sequences Group 6;

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JUMBO APPLICATIONS/PATENTS

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CLAIMS

1. Protein or polypeptide, comprising at least one amino acid sequence that is directed against the p19 subunit and at least one amino acid sequence that is directed against the p40 subunit, optionally linked via a suitable linker, and optionally comprising one or more further amino acid sequences, binding domains and/or binding units.

2. Protein or polypeptide according to claim 1, in which the amino acid sequence that is directed against the p19 subunit is a p19+ sequence (i.e. an amino acid sequence that is capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p19 subunit to its receptor), and in which the amino acid sequence that is directed against the p40 subunit is a p40+ sequence (i.e. an amino acid sequence that is capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p40 subunit to its receptor).

3. Protein or polypeptide according to claim 1, in which the amino acid sequence that is directed against the p19 subunit is a p19+ sequence (i.e. an amino acid sequence that is capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p19 subunit to its receptor), and in which the amino acid sequence that is directed against the p40 subunit is a p40- sequence (i.e. an amino acid sequence that is essentially not capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p40 subunit to its receptor).

4. Protein or polypeptide according to claim 1, in which the amino acid sequence that is directed against the p19 subunit is a p19+ sequence (i.e. an amino acid sequence that is essentially not capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p19 subunit to its receptor), and in which the amino acid sequence that is directed against the p40 subunit is a p40+ sequence (i.e. an amino acid sequence that is capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p40 subunit to its receptor).

5. Protein or polypeptide, comprising at least one amino acid sequence that is directed against the p35 subunit and at least one amino acid sequence that is directed against the p40

subunit, optionally linked via a suitable linker, and optionally comprising one or more further amino acid sequences, binding domains and/or binding units.

6. Protein or polypeptide, comprising at least one amino acid sequence that is directed against a first epitope or antigenic determinant on the p19 subunit and at least one further amino acid sequence that is directed against a second epitope or antigenic determinant on the p19 subunit different from the first, optionally linked via a suitable linker, and optionally comprising one or more further amino acid sequences, binding domains and/or binding units.

7. Protein or polypeptide according to claim 6, in which the first amino acid sequence is a p19+ sequence (i.e. an amino acid sequence that is essentially not capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p19 subunit to its receptor), and in which the second amino acid sequence is a p19- sequence (i.e. an amino acid sequence that is essentially not capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p19 subunit to its receptor).

8. Protein or polypeptide, comprising at least one amino acid sequence that is directed against a first epitope or antigenic determinant on the p40 subunit and at least one further amino acid sequence that is directed against a second epitope or antigenic determinant on the p40 subunit different from the first, optionally linked via a suitable linker, and optionally comprising one or more further amino acid sequences, binding domains and/or binding units.

9. Protein or polypeptide, in which the first amino acid sequence is a p40+ sequence (i.e. an amino acid sequence that is essentially not capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p40 subunit to its receptor), and in which the second amino acid sequence is a p40- sequence (i.e. an amino acid sequence that is essentially not capable of modulating, neutralizing, blocking and/or inhibiting the binding of a heterodimeric cytokine comprising a p40 subunit to its receptor).

10. Protein or polypeptide according to any of claims 1 to 9, in which each amino acid sequence that is comprised within said protein or polypeptide and that is directed against a subunit forms and/or essentially consist of a single (antigen) binding domain or binding unit, and/or is capable of forming and/or of functioning as a single (antigen) binding domain or binding unit (optionally after suitable folding).

11. Protein or polypeptide according to any of claims 1 to 10, in which each amino acid sequence that is comprised within said protein or polypeptide and that is directed against a subunit comprises an immunoglobulin fold or is capable of, under suitable conditions, forming an immunoglobulin fold.

12. Protein or polypeptide according to any of claims 1 to 11, in which each amino acid sequence that is comprised within said protein or polypeptide and that is directed against a subunit essentially consist of 4 framework regions (FR1 to FR4 respectively) and 3 complementarity determining regions.

13. Protein or polypeptide according to any of claims 1 to 12, in which each amino acid sequence that is comprised within said protein or polypeptide and that is directed against a subunit is a domain antibody (or an amino acid sequence that is suitable for use as a domain antibody), a single domain antibody (or an amino acid sequence that is suitable for use as a single domain antibody), a "dAb" (or an amino acid sequence that is suitable for use as a dAb) or a Nanobody™ (including but not limited to a V_{HH} sequence) or another single variable domain, or any suitable fragment of any one thereof.

14. Protein or polypeptide that is directed against a heterodimeric protein, polypeptide, ligand or receptor that comprises:

- at least a first subunit;

and

- at least a second subunit;

wherein said protein or polypeptide at least comprises a first binding domain or binding unit that is directed against said first subunit and a second binding domain or binding unit that is directed against said second subunit.

15. Protein or polypeptide that is directed against a first heterodimeric protein, polypeptide, ligand or receptor that comprises:

- at least a first subunit that is shared between said first heterodimeric protein, polypeptide, ligand or receptor and at least a second, different heterodimeric protein, polypeptide, ligand or receptor;

and

- at least a second subunit that is not shared between said first heterodimeric protein, polypeptide, ligand or receptor and said second, different heterodimeric protein, polypeptide, ligand or receptor;

wherein said protein or polypeptide at least comprises a first binding domain or binding unit that is directed against said first (i.e. shared) subunit and a second binding domain or binding unit that is directed against said second (i.e. not shared) subunit.

16. Protein or polypeptide that is directed against a first heterodimeric protein, polypeptide, ligand or receptor that comprises:

- at least a first subunit;

and

- at least a second subunit;

wherein said protein or polypeptide at least comprises a first binding domain or binding unit that is directed against said first subunit and a second binding domain or binding unit different from said first binding domain or binding unit that is also directed against said first subunit, but against a different epitope, antigenic determinant or binding site on said first subunit.

17. Protein or polypeptide according to claim 15 or 16, which is directed against a ligand for a receptor, and which comprises at least one binding domain or binding unit that is capable of modulating, neutralizing, blocking and/or inhibiting the binding of the ligand to its (cognate) receptor and at least one binding domain or binding unit that is essentially not capable of modulating, neutralizing, blocking and/or inhibiting the binding of the ligand to its (cognate) receptor.

18. Protein or polypeptide according to claim 15, which is directed against a ligand for a receptor, in which both the first binding domain or binding unit as well as the second binding domain or binding unit are capable of modulating, neutralizing, blocking and/or inhibiting the binding of the ligand to its (cognate) receptor.

19. Protein or polypeptide according to any of claims 14 to 18, in which each binding domain or binding unit comprises an immunoglobulin fold or is capable of, under suitable conditions, forming an immunoglobulin fold.

20. Protein or polypeptide according to any of claims 14 to 19, in which each binding domain or binding unit essentially consist of 4 framework regions (FR1 to FR4 respectively) and 3 complementarity determining regions.

21. Protein or polypeptide according to any of claims 14 to 20, in which each binding domain or binding unit is a domain antibody (or an amino acid sequence that is suitable for use as a domain antibody), a single domain antibody (or an amino acid sequence that is suitable for use as a single domain antibody), a "dAb" (or an amino acid sequence that is suitable for use as a dAb) or a Nanobody™ (including but not limited to a V_{HH} sequence) or another single variable domain, or any suitable fragment of any one thereof.

22. Nucleotide sequence or nucleic acid encoding a protein or polypeptide according to any of claims 1 to 21.

23. Composition comprising at least one protein or polypeptide according to any of claims 1 to 21 or a nucleotide sequence or nucleic acid according to claim 22.

24. Pharmaceutical composition comprising at least one protein or polypeptide according to any of claims 1 to 21 and at least one pharmaceutically acceptable carrier, diluent or excipient and/or adjuvant.

25. Use of (a nucleotide sequence and/or nucleic acid that encodes) a p19+ sequence in providing, constructing, and/or as part of (a nucleotide sequence and/or nucleic acid that encodes) a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that comprises said p19+ sequence (one or more) and one or more further binding domains or binding units.

26. Use of (a nucleotide sequence and/or nucleic acid that encodes) a p19- sequence in providing, constructing, and/or as part of (a nucleotide sequence and/or nucleic acid that encodes) a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that comprises said p19- sequence (one or more) and one or more further binding domains or binding units.

27. Use of (a nucleotide sequence and/or nucleic acid that encodes) a p40- sequence in providing, constructing, and/or as part of (a nucleotide sequence and/or nucleic acid that

encodes) a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that comprises said p40- sequence (one or more) and one or more further binding domains or binding units.

28. Use of (a nucleotide sequence and/or nucleic acid that encodes) a p40+ sequence in providing, constructing, and/or as part of (a nucleotide sequence and/or nucleic acid that encodes) a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that comprises said p40+ sequence (one or more) and one or more further binding domains or binding units.

10

29. Use of (a nucleotide sequence and/or nucleic acid that encodes) a p35 sequence in providing, constructing, and/or as part of (a nucleotide sequence and/or nucleic acid that encodes) a multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide that comprises said p35 sequence (one or more) and one or more further binding domains or binding units.

30. Use according to any of claims 25 to 29, in which the multivalent, multispecific and/or multiparatopic construct, protein and/or polypeptide is directed against a heterodimeric cytokine.

20

31. Use according to any of claims 25 to 30, in which the construct, protein and/or polypeptide is a biparatopic construct, protein and/or polypeptide that is directed against one subunit of the heterodimeric cytokine.

32. Use according to any of claims 30 and 31, in which the construct, protein and/or polypeptide is a multispecific construct, protein and/or polypeptide comprising at least one binding domain or binding unit that is directed against a first subunit of said heterodimeric cytokine and at least one binding domain or binding unit that is directed against a second subunit of said heterodimeric cytokine.

30

33. Use according to any of claims 30 to 32, in which the construct, protein and/or polypeptide comprises at least one least one binding domain or binding unit that is capable of modulating, neutralizing, blocking and/or inhibiting the binding of the heterodimeric cytokine to its (cognate) receptor.

34. Use of (a nucleotide sequence and/or nucleic acid that encodes) an amino acid sequence that comprises or essentially consists of a single binding domain or binding unit in providing, constructing, and/or as part of (a nucleotide sequence and/or nucleic acid that encodes) a multispecific construct, protein and/or polypeptide that is directed against a heterodimeric protein, polypeptide, ligand or receptor, wherein said construct, protein and/or polypeptide comprises said amino acid sequence (one or more) and at least one further binding domain or binding unit, and wherein said one or more amino acid sequences are directed against a first subunit of the heterodimeric protein, polypeptide, ligand or receptor and at least one of said further binding domains or binding units is directed against a second subunit of the heterodimeric protein, polypeptide, ligand or receptor different from the first subunit.

35. Use according to claim 34, in which the construct, protein and/or polypeptide is a directed against a heterodimeric cytokine or against a heterodimeric receptor for a heterodimeric cytokine.

36. Use of (a nucleotide sequence and/or nucleic acid that encodes) an amino acid sequence that comprises or essentially consists of a single binding domain or binding unit in providing, constructing, and/or as part of (a nucleotide sequence and/or nucleic acid that encodes) a biparatopic construct, protein and/or polypeptide that is directed against a heterodimeric protein, polypeptide, ligand or receptor, wherein said construct, protein and/or polypeptide comprises said amino acid sequence (one or more) and at least one further binding domain or binding unit, and wherein said one or more amino acid sequences are directed against a first subunit of the heterodimeric protein, polypeptide, ligand or receptor and at least one of said further binding domains or binding units is also directed against said first subunit, but to a different epitope or antigenic determinant on sais subunit.

37. Use according to claim 36, in which the construct, protein and/or polypeptide is directed against a ligand for a receptor and comprises at least one binding domain or binding unit that is capable of modulating, neutralizing, blocking and/or inhibiting the binding of the ligand to its (cognate) receptor and at least one binding domain or binding unit that is essentially not capable of modulating, neutralizing, blocking and/or inhibiting the binding of the ligand to its (cognate) receptor.

Figure 1

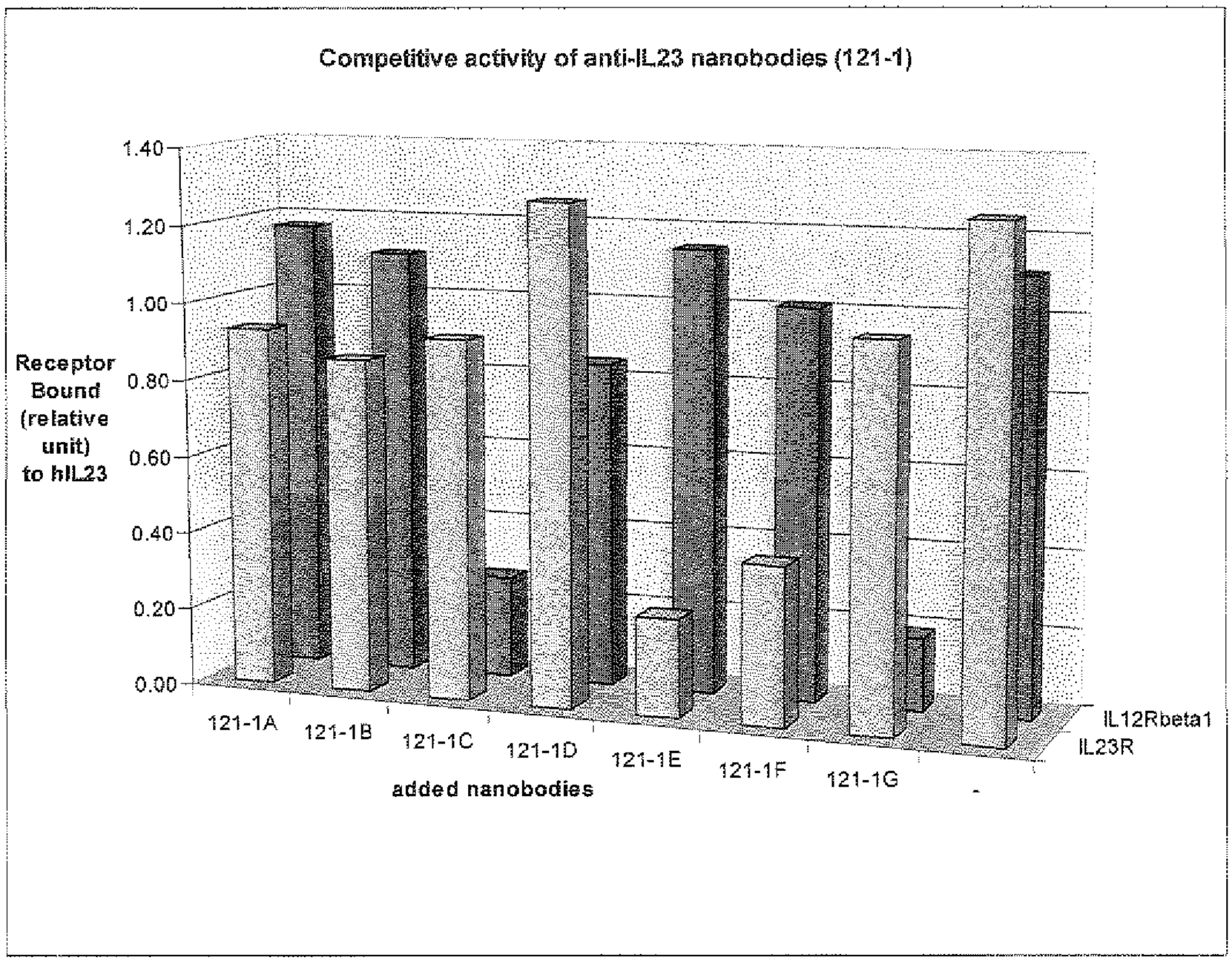

Competitive activity of anti-IL23 nanobodies (121-1)
Receptor Bound (relative unit) to hIL23
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
121-1A
121-1B
121-1C
121-1D
121-1E
121-1F
121-1G
-
added nanobodies
IL12Rbeta1
IL23R

Figure 2

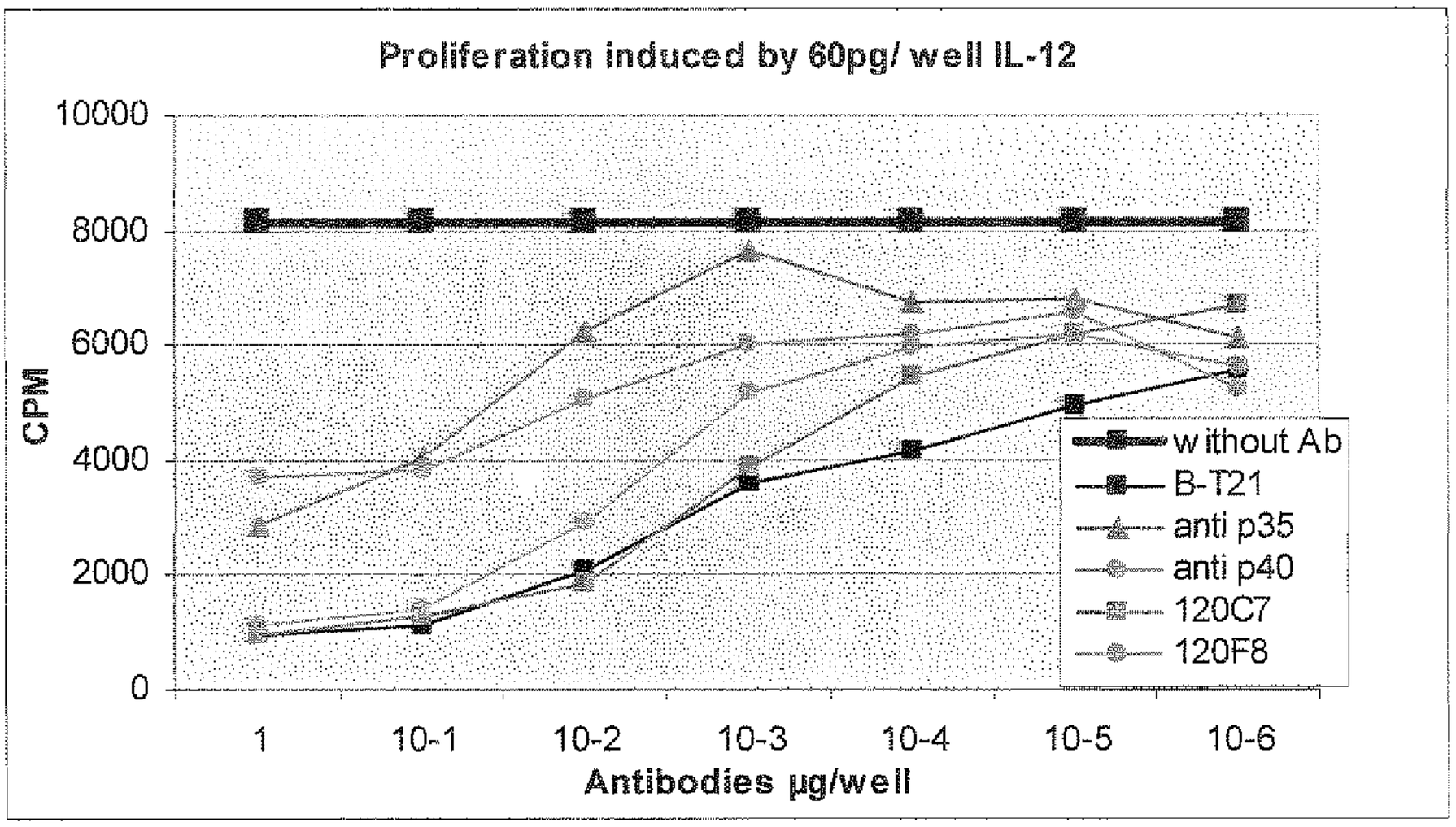

Proliferation induced by 60pg/ well IL-12
CPM
10000
8000
6000
4000
2000
0
1
10-1
10-2
10-3
10-4
10-5
10-6
Antibodies µg/well
without Ab
B-T21
anti p35
anti p40
120C7
120F8

Figure 3

Type	Clone	Biacore offrate (s-1) R&D hIL23	Biacore on rate (s-1) R&D hIL23	Biacore affinity Kd R&D hIL23	Biacore offrate (s-1) eBiosc hIL23	Biacore offrate (s-1) hIL12
p19+	119A3	3,47E-03	6,39E+05	5,42E-09	1,25E-03	nb
p19+	121A2	9,01E-05	7,03E+04	1,28E-09	7,43E-05	nb
p40-	80D10	4,12E-05	5,06E+04	8,14E-10		3,30E-05
p40-	80C10	5,01E-04	8,79E+04	5,70E-09		5,78E-04
p40+	81E10	2,63E-03	1,35E+05	1,95E-08		2,66E-03
p40+	121C1	3,63E-02	1,07E+06	3,38E-08		3,71E-02

Figure 4

Nanobody type	Nb id	Epitope group	hIL-23 (R&D)	hIL-23 (eBioSc)	Cyno IL-23 X-reactivity	mIL-23 (R&D)
p19+	121A2	X	9×10^{-9}	7.4×10^{-9}	YES	Nb
	119A3	X	3.4×10^{-9}	1.25×10^{-8}	YES	Nb
p19-	124H2*	B	1.1×10^{-8}	6.0×10^{-9}	YES	2.9×10^{-8}
Bind when 121A2 is bound (epitope competition studies)	124H5*	B	2.5×10^{-8}	3.5×10^{-9}	YES	3.0×10^{-8}
	124C4*	B	1.5×10^{-8}		YES	7.6×10^{-8}
	81A12	A	nt	1.1×10^{-8}	YES	nb
	123F1		nt	3.8×10^{-8}	YES	nb
	119G7	C	nt	4.8×10^{-8}	NO	nb
	81G2	A	nt	2.8×10^{-8}	YES	nb
	119C9	B	nt	1.2×10^{-8}	YES	nb
p40-	119B2	N	nt	2.9×10^{-8}	NT	nb

Figure 5A

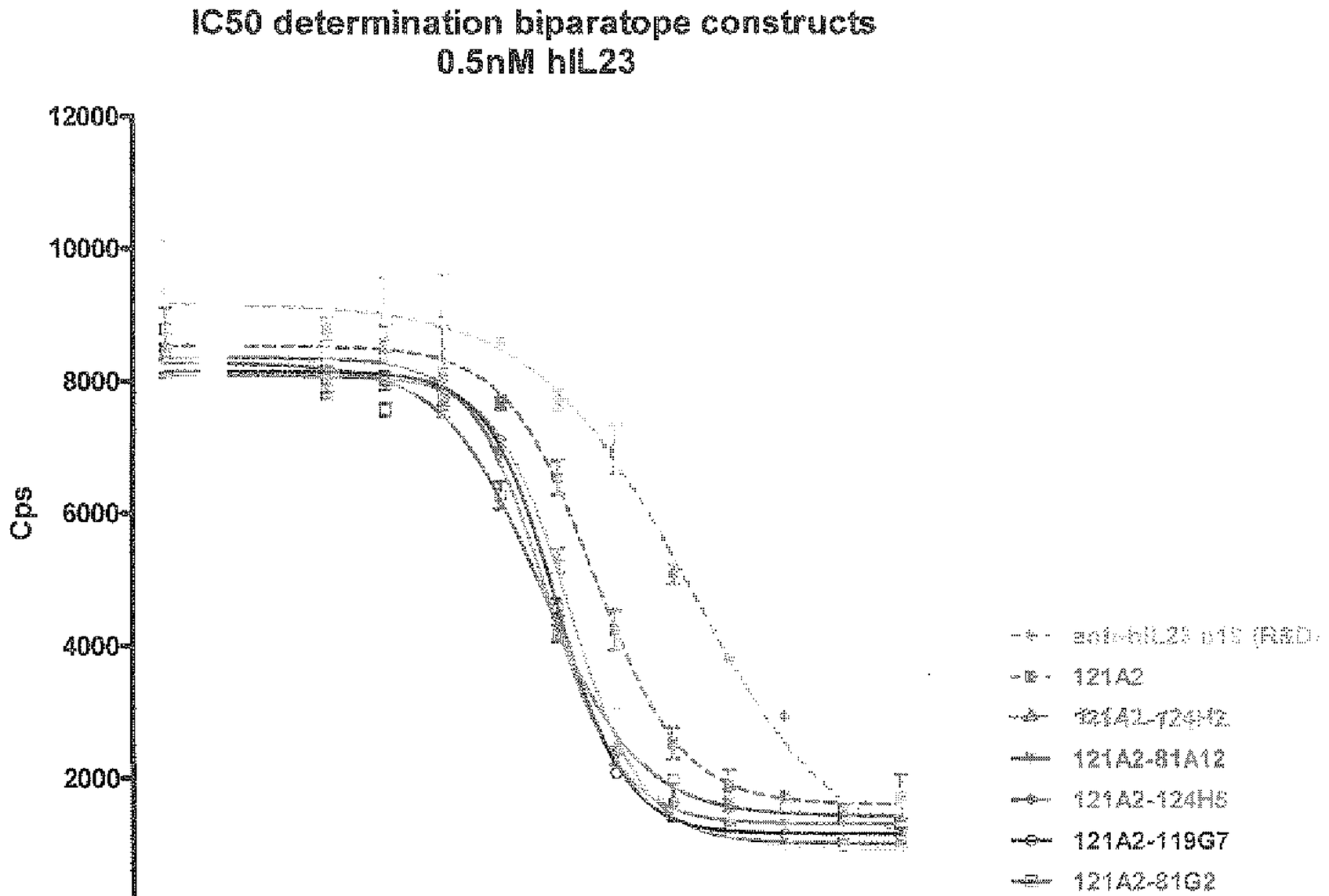


Figure 5B

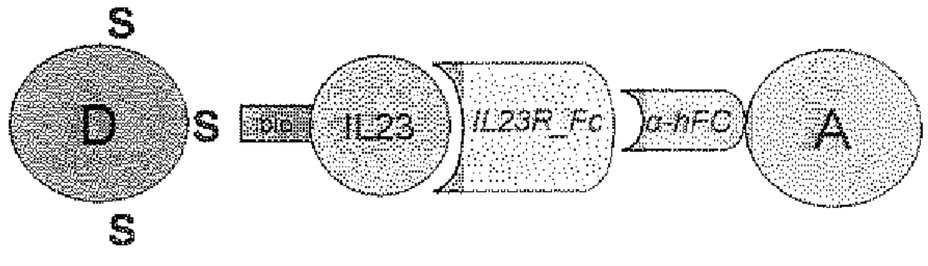


Figure 6

Nanobodies	IC50 (pM)
121A2	299
121A2-124H2	161
121A2-81A12	104
121A2-124H5	175
121A2-119G7	131
121A2-81G2	94
Anti hIL-23 p19	2390

Figure 7

Nanobodies	IC50 (pM)
121A2	270
119A3	670
121A2-119B2	270
121A2-124C4	189
119A3-81G2	54
119A3-119B2	670
119A3-119G7	132
119A3-124C4	193
Anti hIL-23 p19	18000

Figure 8

			3 days incub	4 days incubation				7 days incub	
			0,13 nM hIL23	0,13 nM hIL23	0,13 nM hIL23	0,016 nM hIL23	0,016 nM hIL23	0,016 nM hIL23	0,004 nM hIL23
	construct	linker	IC50 (nM)	IC50 (nM)	IC50 (nM)	IC50 (nM)	IC50 (nM)	IC50 (nM)	IC50 (nM)
MAB 1510 (anti p40)				25 *	5,360	1,4700			
p19+	121A2		2,600	2,300	1,470	0,7695			
	119A3		15,000				nb		
p19+/p19-	121A2-81A12	35GS		0,053	0,057	0,0052			
	121A2-81G2	35GS		0,056	0,027	0,0057	0,0062	0,0140	0,0029
	121A2-119G7	35GS		0,032	0,020	0,0087	0,0172	0,0087	0,0014
	121A2-124H2	35GS		0,075	0,095	0,0176			
	121A2-124H5	35GS		0,115	0,096	0,0222			
	121A2-124C4	35GS					0,0250	0,0130	
	119A3-81G2	35GS					0,0019	0,0021	
	119A3-119G7	35GS					nb		
	119A3-124C4	35GS					nb		
p19+/p40-	121A2-119B2	35GS					0,0710	0,0650	
	119A3-119B2	35GS					0,1060	0,1110	
				* not enough points			nb= not blocking at used concentrations		

Figure 9

function	Clone	Biacore offrate (s-1) R&D hIL23	Biacore on rate (s 1) R&D hIL23	Biacore affinity Kd R&D hIL23	Biacore offrate (s-1) eBiosc hIL23	Biacore offrate (s-1) hIL12	R&D mIL23 Biacore off rate (s-1)
						nb = not binding	
p19-	119C9				1,20E-03		
	119G7				4,79E-04		
	123F1				3,77E-04		
	12A11	1,34E-04			1,34E-04	nb	
	124H5	2,46E-04			3,54E-05	nb	3,04E-03
	119H1				1,06E-02		
	81D1				1,14E-02		
	119B3				1,50E-04		
	121C7				1,12E-04		
	124C3	1,23E-04				nb	
	124E5	1,87E-04				nb	
	12D2	1,01 E-04			1,25E-04	nb	
	4A11	3,20E-04				nb	
	12G7	2,42E-04				nb	
	124C5	3,57E-04				nb	
	124F9	3,10E-04				nb	
	119C3				3,34E-02		binding
	124B5	2,20E-04				nb	1,05E-03
	124C4	1,55E-04				nb	7,65E-04
	124D11	2,59E-04				nb	7,44E-03
	124G4	1,46E-04				nb	3,29E-03
	124H2	1,16E-04			5,88E-05	nb	2,91E-03
	124D4	3,48E-04				nb	2,90E-03
	81G2				2,57E-04		
	81A12				1,13E-04		
	124D2	9,08E-05			1,03E-04	nb	
	124F7	3,82E-04				nb	
p19+	4D2	1,11 E-04				nb	
	4E11	1,26 E-04				nb	
	124H1	1,58E-04				nb	
	12D11	1,21E-04				nb	
	12H2	1,26 E-04				nb	
	121A2	9,01E-05	7,03E+04	1,28E-09	7,43E-05	nb	
	4E3	1,64E-04				nb	
	121B2	1,64E-04	1,07E+05	1,54E-09		nb	
	124F10	1,69E-04				nb	
	124G2	6,55E-05			9,28E-05	nb	
	12A4	2,95E-04				nb	
	12C10	2,89E-04				nb	
	12E11	2,37E-04				nb	
	12F11	2,35E-04				nb	
	119A3	3,47E-03	6,39E+05	5,42E-09	1,25E-03	nb	
	4E7	1,01E-04				nb	
	124E3	2,61E-04				nb	
	124B6	2,49E-04				nb	

Figure 10

function	Clone	Biacore offrate (s-1) R&D hIL23	Biacore on rate (s-1) R&D hIL23	Biacore affinity Kd R&D hIL23	Biacore offrate (s-1) eBiosc hIL23	Biacore offrate (s-1) hIL12
p40-	80D10	4,12E-05	5,06E+04	8,14E-10		3,30E-05
	80C10	5,01E-04	8,79E+04	5,70E-09		5,78E-04
	119B2				1,52E-02	~E-02
p40+	3B8				3,50E-03	2,43E-03
	121C1 = 84D3	3,63E-02	1,07E+06	3,38E-08		3,71E-02
	3A11				5,13E-03	6,36E-03
	3A7				5,07E-03	5,88E-03
	3A10				2,86E-03	3,53E-03
	3G10				1,97E-03	2,44E-03
	4F3				2,08E-03	2,55E-03
	3C7				1,02E-02	1,19E-02
	3D4				6,20E-03	7,14E-03
	3G9				6,72E-03	7,68E-03
	3H5				3,33E-03	3,75E-03
	3F11				1,46E-03	1,34E-03
	3C1				2,94E-04	2,79E-04
	3E1				8,66E-03	9,56E-03
	81E10	2,63E-03	1,35E+05	1,95E-08		2,66E-03
	1G8				2,23E-03	7,79E-04

Figure 11

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P23ILp19+PMP121A2	126	EVQLVESGGGLVQAGGSLRLSCAASGSIFN	378	FNYMG	630	WFRQAPGKEREFVA	882	AIRWSGSSTYYADSVKG	1134	RFTISRDDAKNTVALQMNSLKPEDTAIYYCAL	1386	RKGIPYSTSDRVIKGVNDYDY	1638	WGQGTQVTVSS
P23ILp19+PMP121D3	127	RGAAGGVWGGLVQAGGSLRLSCAASGSIFN	379	FNYMG	631	WFRQAPGKEREFVA	883	AIRWSGSSTYYADSVKG	1135	RFTISRDDAKNTVALQMNSLKPEDTAIYYCAL	1387	RKGIPYSTSDRVIKGVNDYDY	1639	WGQGTQVTVSS
P23ILp19+PMP04E3	128	EVQLVESGGGLVQAGGSLRLSCAASGSIFN	380	FNYMG	632	WFRQAPGKEREFVS	884	AIRWSGISTYYADSVKG	1136	RFTISRDDAKNTVYLQMNSLKPEDTAIYYCAL	1388	RKGIPYSTSDRYIKGVNDYDY	1640	WGQGTQVTVSS
P23ILp19+PMP124F10	129	EVQLVESGGGLVQAGGSLRLSCAASGSIFN	381	FNYMG	633	WFRQAPGKEREFVA	885	AIRWSGRSTYYADSVKG	1137	RFTISRDDAKNTVALQMNSLKPEDTAIYYCAL	1389	RKGIPYSTSDRVIKGVNDYEY	1641	WGQGTQVTVSS
P23ILp19+PMP124G2	130	EVQLVESGGGLVQAGGSLRLSCAASGSIFN	382	FNYMG	634	WFRQAPGKEREFVA	886	AIRWSGSSTYYADSVKG	1138	RFTISRDDAKNTVYLQMNSLKPEDTATYYCAL	1390	RKGIPYSISDRVIKGVNDYDY	1642	WGQGTQVTVSS
P23ILp19+PMP121E3	131	EVQLVESGGGLVQAGGSLRVSCAASGSIFA	383	FNYMG	635	WFRQAPGKEREFVA	887	AIRWSGSSTYYADSVKG	1139	RFSISRDDAKNTVYLQMNSLKPEDTAIYYCAL	1391	RKGTPYSTSYRVIKAVNDYEY	1643	WGQGTQVTVSS
P23ILp19+PMP12A4	132	EVQLVESGGGLVQAGGSLRLSCAASGSIFN	384	FNYMG	636	WFRQAPGKEREFVA	888	TIRWSGSSTDYADSVKG	1140	RFTISRDDAKNTVYLQMNSLKPEDAAIYYCAL	1392	RKGIPYSTSNRYIKGVNDYDY	1644	WGQGTQVTVSS

Figure 11 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P23ILp19+PMP12E11	133	EVQLVESGGGLVQAGGSLRLSCAASGSIFN	385	FNYMG	637	WFRQAPGKEREFVA	889	TIRWSGSSTYYADSVKG	1141	RFTISRDGAKNTVYLQMNSLKPEDTAIYYCAL	1393	RKGIPYSTSSLYIKGVNDYDY	1645	WGQGTQVTVSS
P23ILp19+PMP119A3	134	EVQLVESGGGLVQAGGSLRLSCAASGRIFS	386	LPASGNIFNLLTIA	638	WHRQAPGMQRELVA	890	TINSGSRTNYADSVKG	1142	RFTISRDNAQKTVYLQMNNLKPEDTAVYYCQT	1394	SGSGSPNF	1646	WGQGTQVTVSS
P23ILp19+PMP119A2	135	EVQLVESGGGLVQAGGSLRLSCAASGSIFS	387	LPASGNIFNLLTIA	639	WHRQTPGKQRELVA	891	TINSGGRTNYTDSVKG	1143	RFTISRDNAQKTVYLQMNNLKPEDTAVYYCQT	1395	SGSGSPNY	1647	WGQGTQVTVSS
P23ILp19+PMP02C04	136	EVQLVESGGGLVQPGGSLRLSCAGSGSILR	388	IASMG	640	WYRQAPGKQRELAA	892	VIGSEGDTDYADSMKG	1144	RFTISLDNAANTVYLQMNSLKPEDTAVYICSG	1396	LLLNGGGTWQRL	1648	WGQGTQVTVSS
P23ILPMP36A1	2170	EVQLVESGGGLVQPGGSLRLSCEASALTSF	2215	SNYAMY	2260	WVRQAPGKALEWVS	2305	AISRAGSNTYYADSVKG	2350	RFTISRDNAKDTLYLQMNSLRSEDTGVYYCAV	2395	DSSGTW	2440	RGQGTQVTVSS
P23ILPMP36G2	2171	EVQLVESGGGLVQAGGSLRLSCVASERTFS	2216	SSAMG	2261	WFRQAPGKEREFVA	2306	AIGWSGGGFIHYGDSVKG	2351	RFTISADNGKNTVYLQMNSLKPEDTAVYYCAA	2396	DSRLRGIALLKGSYDY	2441	RGQGTQVTVSS
P23ILPMP36B3	2172	EVQLVESGGGLVQPGGSLRLSCAASGFTVD	2217	YHGIA	2262	WFRQAPGKGPEGVS	2307	CIRNSDGRTYYADSVKG	2352	RFTISRDNAKNTVYLQMNSLKLEDTAIYYCAT	2397	TTGRIGVNCVPSNT	2442	RGQGTQVTVSS

Figure 11 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P23ILPMP36 B4	217 3	EVQLVESGGGLVQ PGGSLRLSCAASG FTVD	221 8	YHGIA	226 3	WFRQAPG KGPEGVS	230 8	CIRNSDGRTY YADSVKG	235 3	RFTISRDNAKNTVYLQ MNSLKPEDTAIYYCA T	239 8	TTGRIGVNC VPSNT	244 3	RGQGTQV TVSS
P23ILPMP36 E5	217 4	EVQLVESGGGLVQ AGGSLRLSCAASG RTIS	221 9	NYGMG	226 4	WFRQAPG KEREFVA	230 9	AISARSAMIG YSDSVKG	235 4	RFTISRDNAKNTVYLQ MNSLKPEDTAVYYCA A	239 9	DLNRRVPTA RPQEYDG	244 4	WGQGTQV TVSS
P23ILPMP37 D5	217 5	EVQLVESGGGLVQ PGGSLRLSCAASG FTLD	222 0	YLAIG	226 5	WFRQAPG KEREGVS	231 0	CVSSSGQYTY YADSVKG	235 5	RFTISRDNAESTVYLQ MNSLKPEDTAVYYCA T	240 0	DPECYRVRG YYNGEYDY	244 5	WGQGTQV TVSS

Figure 12

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P23Ilp19-PMP119C09	137	EVQLVESGGGLVQAGGSLTLSCAASVRTFS	389	TSAMG	641	WFRQAPGKEREFVA	893	AINWNAGSTYHADSVKG	1145	RFTISGDNAKNSVFLQMNGLKPEDTAVYYCAA	1397	QASGRVTYFDYAYRRGSNYDY	1649	WGQGTQVTVSS
P23Ilp19-PMP119G07	138	EVQLVESGGGLVQAGGSLTLSCAVSGLTFN	390	NYAMG	642	WFRQVPGKEREFVA	894	AISRSGLRTFYSDSVK	1146	GRFTISRDSAKSTVYVQMNNLKPEDTAVYFCAA	1398	DRRTYYSEGPSLTDTLRYDY	1650	WGQGTQVTVSS
P23Ilp19-PMP123F01	139	EVQLVESGGGLVQAGGSLRLSCAASGRTSS	391	SYSMG	643	WFRQAPGKEREFVA	895	YISGGGLTIYYAHSVKG	1147	RFTISRDNAKNTVYLQMNSLNSADTAVYSCAA	1399	PKRDLYLGSRYPVPESYDY	1651	WGQGTQVTVSS
P23ILp19-PMP12A11	140	EVQLVESGGGLVQAGDSLKLSCAASGRTSS	392	SYAMG	644	WFRQAPGKEREFVA	896	AIIWSRGNTYYADSVKG	1148	RFTISRDNAKNTMYLQMNNLKPEDTAVYYCAA	1400	HRGDSIYYYTVWGKYDA	1652	WGQGTQVTVSS
P23Ilp19-PMP119C08	141	EVQLVESGGGLVQAGASLRLSCAASGRSFD	393	SNVMG	645	WFRQYPGKLREFVA	897	AIWWSAGTTKYYADSVKG	1149	RFTISRDNAKNTVHLQMNSLELEDTALYYCAA	1401	DRVSSSIQTMAGTYDY	1653	WGQGTQVTVSS
P23ILp19-PMP124H05	142	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	394	NYWMY	646	WVRQAPGKGLERVA	898	PLNPGGTITLYADFVKS	1150	RFTISRDNAKNTVYLQMNSLKPEDTAVYYCAA	1402	PSGTLYTRNKSGYIY	1654	WGQGTQVTVSS
P23ILp19-PMP119H01	143	EVQLVESGGGLVQAGGSLRLSCAASGSISE	395	FNVIG	647	WHRQAPGKERELVA	899	SITGHDSTYYTGSVKG	1151	RFTISRDNAKTTVYLQMNSLKPEDTAVYYCAV	1403	RQILRREYDY	1655	WGQGTQVTVSS

Figure 12 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P23ILp19-PMP81D01	144	EVQLVESGGGLVQAGGSLRLSCAASGRTFS	396	TYAAG	648	WFRQDPGEEREFVS	900	TISRGGGTTGYADAVKG	1152	RFTISRDNAKNTVYLQMNNLKPEDTAVYYCAA	1404	ADVSYGTTTDDPKRYDY	1656	WGQGTQVTVSS
P23ILp19-PMP81H02	145	EVQLVESGGGLVQAGGSLRLSCSASGRTFS	397	TYAAG	649	WFRQAPGKDREFVS	901	TISRGGGGTYSADAVTG	1153	RFTISRDNAKNTVYLQMNNLKPEDTAVYYCAA	1405	ADVSYGTTTDDPKRYDY	1657	WGQGTQVTVSS
P23ILp19-PMP84C03	146	EVQLVESGGGLVQAGGSLELSCSASGGTLR	398	TYAMG	650	WFRQAPGKEREFVS	902	TISRGGGSTDYADAVKG	1154	RFTISRDNAKNTVYLQMNSLKPEDTAEYICTA	1406	ADVSYGVTTDDPKRYDY	1658	WGQGTQVTVSS
P23ILp19-PMP119B03	147	EVQLVESGGGLVQAGGSLRLSCAASGTISS	399	INTMA	651	WFRQAPGKEREFVA	903	ALVKGFSWGSGSSIYADSVRG	1155	RFTISRDNAKNTQSLQMNSLELEDTAIYYCAA	1407	GRRSSVRSGYEF	1659	WGQGTQVTVSS
P23ILp19-PMP119E1	148	EVQLVESGGGLVQAGGSLRLSCAASGTISS	400	INTMA	652	WFRQAPGKEREFVA	904	ALVKGFSWGSGSSIYADSVRG	1156	RFTISRDNAKNTQSLQMNSLELEDTAIYYCAA	1408	GRRSSVRSGYEF	1660	WGQGTQVTVSS
P23ILp19-PMP121A1	149	EVQLVESGGGLVQAGGSLRLSCAASGTISS	401	INAMG	653	WFRQAPGKEREFVA	905	AIVKGFSWGSGSTIYADSVKG	1157	RFTISRDNAQNTMSLQMNSLELEDTAIYYCAH	1409	GRRSSGRSGYEY	1661	WGQGTQVTVSS
P23ILp19-PMP121B1	150	EVQLVESGGGLVQAGGSLRLSCVASGTISA	402	INTMG	654	WFRQAPGKEREFVA	906	ALVKGFSWGSGSTIYADSVKG	1158	RFTISRDNAKNTMSLQMNSLKLEDTAIYYCAQ	1410	GRRSSGRSGSGYEY	1662	WGQGTQVTVSS

Figure 12 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P23ILp19-PMP121C7	151	EVQLVESGGGLVQAGGSLRLSCAASGTISS	403	INVMG	655	WFRQAPGKEREFVA	907	ALVKGFSWGSGSSIYADSVRG	1159	RFTISRDNAKNTQSLQMNSLELEDTAIYYCAA	1411	GRRSSARSGYEF	1663	WGQGTQVTVSS
P23ILp19-PMP121F8	152	EVQLVESGGGLVQAGGSLRLSCAASGTISS	404	INAMG	656	WFRQAPGKEREFVA	908	AIVKGFSWGSGSTIYADSVKG	1160	RATISRDNAKNTMSLQMSSLELEDTAIYYCAH	1412	GRRSSGRSASGYEY	1664	WGQGTQVTVSS
P23ILp19-PMP121G8	153	EVQLVESGGGLVQAGGSLRLSCAASGTISS	405	INAMG	657	WFRQAPGKEREFVA	909	AIVKGFSWGSGSIMYADSVKG	1161	RFTISRVNAKNTMSLQMNSLELEDTAIYYCAA	1413	GRRSSGRSGSGYEY	1665	WGQGTQVTVSS
P23ILp19-PMP121H8	154	EVQLVESGGGLVQAGGSLRLSCAASGTISS	406	INTMG	658	WFRQAPGKEREFVA	910	ALVKGFSWGSGSNIVADSVKG	1162	RFTISRDNAKNTMSLQMNSLELEDTAIYYCAA	1414	GRRSSGRSGYEY	1666	WGQGTQVTVSS
P23Hlp19-PMP124C3	155	EVQLVESGGGLVQAGGSLRLSCAASGTISS	407	INAMG	659	WFRQAPGKEREFVA	911	AIVKGFSWGSGSTIYADSVKG	1163	RATISRDNAKNTMSLQMSSLELEDTAIYYCAH	1415	GRRSSGRSASGYEY	1667	WGQGTQVTVSS
P23Hlp19-PMP124E5	156	EVQLVESGGGLVQAGGSLRLSCAASGTISS	408	INAMG	660	WFRQAPGKEREFVA	912	AIVKGFSWGSGSVIYADSVKG	1164	RFTISRDNAKNTMSLQMNSLELEDTAIYYCAN	1416	GRRSSARSGANYEY	1668	WGQGTQVTVSS
P23Hlp19-PMP12D2	157	EVQLVESGGGLVQAGGSLRLSCAASGTISS	409	INTMG	661	WFRQAPGKEREFVA	913	AIVKGFSWGSGSTIYADSVKG	1165	RFTISRDNAQNTMSLQMNSLELEDTAIYYCAH	1417	GRRSSGRSGYEY	1669	WGQGTQVTVSS

Figure 12 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P23ILp19-PMP04A11	158	EVQLVESGGGLVQAGGSLRLSCAASGTISS	410	INAMG	662	WFRQAPGKEREFVA	914	AIVKGFSWGSGSTIYADSVKG	1166	RFTISRDNAQNTMSLQTNSLELEDTAIYYCAH	1418	GRRSSGRSGYEY	1670	WGQGTQVTVSS
P23ILp19-PMP12G7	159	EVQLVESGGGLVQAGGSLRLSCAASGTISS	411	INAMG	663	WFRQAPGKEREFVA	915	AIVKGFSWGSGSTIYADSVKG	1167	RFTISRDNAQNTMSLQMNSLELEDTAIYYCAH	1419	GRRSSGRSGYEY	1671	WGQGTQVTVSS
P23ILp19-PMP124C5	160	EVQLVESGGGLVQAGGSLRLSCAASGAISS	412	INAMG	664	WFRQAPGKEREFVA	916	AIVKGFSWGSGSTIYADSVKG	1168	RFTISRDNAKNTMSLQMSSLELEDTAIYYCAH	1420	GRRSSGRSGYEY	1672	WGQGTQVTVSS
P23Ilp19-PMP119G08	161	EVQLVESGGGLVQPGGSLRLSCAASGRPVG	413	GYGMG	665	WFRQGPGKEREFLA	917	TTAWNGDFTYYADSVKD	1169	RFTISRDNPKNTIYLQMNSLKPEDTAKYYCAA	1421	SISKGSTSYRXYGF	1673	WGQGTQVTVSS
P23ILp19-PMP119G02	162	EVQLVESGGGLVQPGGSLRLSCAASGRTFG	414	GYGMG	666	WFRQGPGKEREFLA	918	TTAWNGDFTYYADSVKD	1170	RFTISADNPKNTVYLQMNSLKPEDTAKYYCAA	1422	SIAKGSRSSRSYGY	1674	WGQGTQVTVSS
P23ILp19-PMP119C03	163	EVQLVESGGGLVQAGSSLRLSCAASGRTFS	415	TFRDYVMG	667	WFRQAPGKEREFVA	919	VISRGGGRTDYDDSVKG	1171	RFTISRDNVNNMVYLQMNSLNSEDTGVYYCAA	1423	DQDRSYGSIGMLPNEYDY	1675	WGQGTQVTVSS
P23ILp19-PMP123H1	164	EVQLVESGGGWVQAGSSLRLSCAASGRTFS	416	DYAMG	668	WFRQVPGKEREFVA	920	AISRGGGKTYYVDSEKG	1172	RFTISRDNAKNTVYLQMNSLNSEDTAVYYCAA	1424	DQDRSYGSIGTLPNDYDY	1676	WGQGTQVTVSS

Figure 12 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P23ILp19-PMP119D2	165	EVQLVESGGGLVQAGGSLRLSCIASGLPFS	417	TKSMG	669	WFRQAPGKEREFVA	921	RISPGGTSRYYGDFVKG	1173	RFAISRDNAKNTAWLQMNSLKAEDTAVYYCAS	1425	GERSSYIGSNYYRTNEYDY	1677	WGTGTQVTVSS
P23ILp19-PMP81G2	166	EVQLVESGGGLVQPGGSLRLSCIASGLPFS	418	TKSMG	670	WFRQAPGKEREFVA	922	RISPGGTSRYYGDFVKG	1174	RFAISRDNAKNTTWLQMNSLKAEDTAVYYCAS	1426	GERSTYIGSNYYRTNEYDY	1678	WGTGTQVTVSS
P23ILp19-PMP124B5	167	QVQLVESGGGLVQPGGSLRLSCAASGFTLA	419	DFAIA	671	WFRQAPGKEREGVS	923	GIDSGDGSTYYADSVKG	1175	RFTISSDNAKNTVYLQMNSLRPEDTAVYYCAR	1427	VRTGWGLNAPDYAMDY	1679	WGKGTLVTVSS
P23Ilp19-PMP124C4	168	EVQLVESGGGLVQPGGSLRLSCAASGFTLD	420	DYAIA	672	WFRQAPGKEREGVS	924	GIDSGDGSAYYADSVKG	1176	RFTISSDNAKNTVYLQMNSLRPEDTAVYYCAR	1428	VRTGWGLNAPDYAMDY	1680	WGKGTLVTVSS
P23Ilp19-PMP124D11	169	EVQLVESGGGLVQPGGSLRLSCAASGFTLD	421	DYAIA	673	WFRQAPGKEREGVS	925	GIDCSDGSTYYANSVKG	1177	RFTISSDNAKNTVYLQMNSLRPEDTAVYYCAR	1429	VRTGWGLRAPDYAMDY	1681	WGKGTLVTVSS
P23ILp19-PMP124G4	170	EVQLVESRGGLVQPGGSLRLSCAASGFYLD	422	DYAIA	674	WFRQAPGKEREGVS	926	GVDSGDGSTYYADSVKG	1178	RFTISSDNAKNTVYLQMNSLRPEDTAVYYCAR	1430	VRTGWGLNAPDYAMDY	1682	WGKGTLVTVSS
P23ILp19-PMP124H2	171	EVQLVESGGGLVQPGGSLRLSCAASGFYLD	423	DYAIA	675	WFRQAPGKEREGVS	927	GIDSGDGSTYYADSVKG	1179	RFTISSDNAKNTVYLQMNSLRPEDTAVYYCAR	1431	VRTGWGLNAPDYAMDY	1683	WGKGTLVTVSS

Figure 12 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P23ILp19-PMP81A12	172	EVQLVESGGGLVQAGGSLRLSCAASGRTLS	424	SYAMG	676	WFRQAPGKEREFVA	928	RISQGGTAIYYADSVKG	1180	RFTISRDNAKNTVYLQMNSLKPEDTAVYYCAK	1432	DPSPYYRGSAYLLSGSYDS	1684	WGQGTQVTVSS
P23Ilp19-PMP124D2	173	EVQLVESGGGLVQAGGSLRLSCAASGRTLS	425	SYSMG	677	WFRQAPGKEREFVA	929	RISPSGSAIYYADSVKG	1181	RFTISRDNAKNTVYLQMNSLKPEDTAVYYCAK	1433	DPSPYYRGSAYLLSGSYDS	1685	WGQGTQVTVSS
P23Ilp19-PMP121F7	174	EVQLVESEGGLVQPGGSLRLSCAASGFAFS	426	NYWMY	678	WIRQAPGKGLEWVS	930	TIKTSGSAAYADFVKG	1182	RFTISRDNAKNTLYLQMNSLKPEDTALYYCST	1434	DYAGTV	1686	RGQGTQVTVSS
P23Ilp19-PMP121D1	175	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	427	SYRMY	679	WVRQAPGKGLEWVS	931	SIGAVGSLPAYADFVKG	1183	RFTISRDNAKNTLYLQMSSLKVEDTALYYCAR	1435	DYQGAV	1687	RGKGTLVTVSS
P23ILPMP20B11	2187	EVQLVESGGGLVQAGGSLRLSCAVSGDTFS	2232	VYGMG	2277	WFRQAPGMEREFVA	2322	GISWNAGITAYTDTLKG	2367	RFTISRDRAKNTMYLQMNSLQPEDTAVYYCAA	2412	DVTRHYIATRSKVDASMYDY	2457	WGQGTQVTVSS
P23ILPMP20H9	2188	EVQLVESGGGSVQAGGSLRLSCVASGLYFN	2233	GNGLG	2278	WFRQAPGKEREFVA	2323	AIAWNGARINYADSVKG	2368	RFTVSRDNIKNTVYLQMNSLKPEDTAVYYCAS	2413	ARSGYASISNEYDY	2458	WGQGTQVTVSS

Figure 13

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P23ILp40-PMP80D10	176	EVQLVESGGGLVQAGGSLRLSCAASGRTFE	428	GNPMG	680	WFRQASGKKREFVA	932	SIDWSGGITSYADSVKG	1184	RFTISRDNAKNTVYLQMNSLKPEDTAVYYCAA	1436	SARFGSGSYYDLMYDY	1688	WGQGTQVTVSS
P23ILp40-PMP80C10	177	EVQLVESGGGLVQAGGSLRLSCAASGRTFD	429	SNPMG	681	WFRQAPEKKREFVA	933	IISGNGGITNYANSVKG	1185	RFTISRDNAKNTIYLQMNSLKPEDTAVYYCAA	1437	SDLYGSGSNYDLMYDY	1689	WGQGTQVTVSS
P23ILp40-PMP84G12	178	EVQLVESGGRLVQAGGSLRLSCAASGRTFD	430	SNPMG	682	WFRQAPGKKREFVA	934	IISGNGGITNYANSVKG	1186	RFTISRDNAKNTIYLQMNSLKPEDTAVYYCAA	1438	SGLYGSGSVYDLMYDY	1690	WGQGTQVTVSS
P23ILp40-PMP119H2	179	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	431	SSWMY	683	WVRRAPGKGLEWVS	935	TIKSGGGSTVYADFVKG	1187	RFTISRDNAKNTLYLQMNSLKSEDTAVYYCAK	1439	DWGASTFV	1691	RGQGTQVTVSS
P23ILp40-PMP121A3	180	EVXLVESGGGLVEPGGSLRLSCAASGFTFS	432	SSWMY	684	WVRQAPGKGLEWVA	936	TIKASSSAVYADFVKG	1188	RFTISRDNAKNTLYLQMNSLKPEDTALYYCAK	1440	DYAGRL	1692	RGQGTHVTVSS
P23ILp40-PMP119B02	181	EVQLMESGGGLVQAGGSLRLSCAAPGRTFS	433	EYAMG	685	WFRQNPGNEREFVA	937	AISRGGGFTDYADSVKG	1189	RFTISRDNAKNTVYLQMNSLKPEDTAVYYCAA	1441	DGRSSFGIAKRSRYEYDS	1693	WGQGTQVTVSS

Figure 13 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P12ILPMP80 H3	191	EVQLVESGGGLVQ AGDSLRLSCTASG RTFS	443	SHTMA	695	WFRQAPG KEREFVG	947	TIVRIFGDTYY ADSVKG	1199	RFTISRDNAKNTVYLQ MNSLKPEDTAVYYCA A	1451	ALRGTSSDW RAAATYDD	1703	WGQGTQV TVSS
P12ILPMP80 B3	194	EVQLVESGGGLVQ AGGSLRLSCAASG RTFS	446	SYAMG	698	WFRQAPG KEREFVA	950	GSNWSGGSTP YADSVVG	1202	RFAISRDNAKNTVHL QMNSLKPEDTAVYYC AA	1454	GRFSYSTRIP NDYAY	1706	WGQGTQV TVSS
P23ILPMP81 F3	204	EVQLVESGGGLVQ AGGSLRLSCAASG LTFS	456	TTAMA	708	WFRQAPG KEREFVA	960	ATNWSGGSTP YGDSVIG	1212	RFTISRNNAKNTVYLQ MNSLKPEDTAVYICA A	1464	DVSGWAHK GAKEYEY	1716	WGQGTQV TVSS
P23ILPMP84 A4	207	EVQLVESGGGLVQ AGGSRRVSCAASG LTFS	459	DYSMA	711	WFRQAPG KEREFVA	963	AHAWLASTT DYADSVKG	1215	RFTISRDNAKNTVYLQ MNSLKPEDTAAYYCA A	1467	GQRYLSRVS QGYEY	1719	WGQGTQV TVSS
P23ILPMP84 A5	208	EVQLVESGGGLVQ AGGSLRLSCEASE RTFS	460	TYRMG	712	WFRQSPGR EREFVT	964	SFNWSGGSTY YADSVKG	1216	RFIIATDDAKNTVYLR MNSLKPEDTAVYYCA G	1468	YSSGSYYSP RSYGV	1720	WGQGTQV TVSS
P23ILPMP84 B2	210	EVQLVESGGGLVQ PGGSLRLSCAASG FTLD	462	DYTMS	714	WVRQAPG KGLEWVS	966	SISRDGGRTY YAGSMKG	1218	RFTISRDNAKNTLYLQ MSSLKPEDTAVYYCA A	1470	ATFYTTSTYI SLYDY	1722	WGQGTQV TVSS
P23ILPMP84 B3	211	EVQLVESGGGLVQ PGGSLRLSCAASG SFFS	463	IKSMG	715	WYRQAPG KQRELVA	967	GIASGVTNYA DSVKG	1219	RFTISRDGAKNTVYLQ MNSLKPEDTAVYYCN A	1471	VGERLANTG VTEYDY	1723	WGQGTLV TVSS

Figure 13 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P23ILPMP84 B5	212	EVQLVESGGGLVQ PGGSLRLSCAASG RFFS	464	TYAMG	716	WFRQVPG KEREPVA	968	AVNWNGISTY YADSVKG	1220	RFTISRDNAENTVYLQ MNSLKPEDTAVYLCA R	1472	KRFQYIFGSQ QPESDFDS	1724	WGQGTQV TVSS
P23ILPMP84 B6	213	EVQLVESGGGLVQ SGDPLRLSCAASG PTYT	465	MA	717	WFRQAPG EEREFVA	969	VISGGSTNYA DSVKG	1221	RFTVSADNAKNTMYL QMNSLKPEDTAVYYC AG	1473	AGFYTTGTY YSLYDY	1725	WGQGTQV TVSS
P23ILPMP84 B8	214	KVQLVESGGGLVQ AGGSLRLSCAASG RSFS	466	TYAMG	718	WFRQAPG KEREFVA	970	ASNWSGGSK NYADSVLG	1222	RFTISRDNAKNTVYLQ MNSLKPTDTAVYYCA A	1474	KGSGDLRLR EYEYDY	1726	WGQGTQV TVSS
P23ILPMP84 C7	215	EVQLVESGGGSVQ AGGSLRLSCAASG RTIF	467	SDYAMG	719	WFRQAPG KEREFVS	971	AINWSGGSTT YADSVKG	1223	RFTISRDNYKNTVYLQ MNSLKPEDTAVYYCA S	1475	RAGGGLWT QTHEYVD	1727	WGQGTQV TVSS
P23ILPMP84 C9	216	EVQLVESGGGLVQ AGGSLRLSCAASG RTFS	468	TYAMG	720	WFRQAPG KEREFVA	972	ASNWSGGSK YYADSVKG	1224	RFTISRDNAKNTVYLQ MNSLKPEDTAVYYCA A	1476	RGSGELRLR EYEYDY	1728	WGQGTQV TVSS
P23ILPMP84 D7	219	EVQLVESGGGLVQ AGGSLRLSCAASGI IFS	471	DNVMG	723	WFRQAPG KEREFVA	975	AIAGRGSRLD YADSVKG	1227	RFTISRDNAKNTVYLQ MNSLKPEDTATYYCA A	1479	KPYGRVFYT EGSNYDF	1731	WGQGTQV TVSS
P23ILPMP84 E12	222	EVQLVESGGGLVQ AGDSLRLSCAASG RSFS	474	RDTMG	726	WFRQAPG KEREFVA	978	AINWSGGSRS YADSVLG	1230	RFTISRDNAKNTVYLQ MNRLKPEDTSIYYCAT	1482	DRGGHFSVG YYYPSDDSW DY	1734	WGQGTQV TVSS

Figure 13 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P23ILPMP84F5	225	EVQLVESGGGVVQAGESLRLSCAASGRSFS	477	DYEMG	729	WFRQAPGTEREFVA	981	AISWRGSSTYYADSVKG	1233	RFTISRDNAKNTVYLQMSSLKPEDTAVYYCAA	1485	GRLYPSSRSRDYDY	1737	WGQGTQVTVSS
P23ILPMP84F9	227	EVQLVESGGGLVQPGGSLRLSCAASGFSIS	479	DNWMY	731	WFRQAPGKGHEWVS	983	TIKTGTGSTAYADSVKG	1235	RFTISRDNAKNTLYLQMNSLKPEDTALYYCAR	1487	DWDGTV	1739	RGQGTQVTVSS
P23ILPMP84G1	228	EVQLVESGGGMVQAGGSLRLSCTASGLTDN	480	SYAMG	732	WFRRAPGKEREFLT	984	GLTLSGGSTYYADSVKG	1236	RFTTSRDSQKNTVSLQMNSLKPEDTAVYYCAA	1488	NRFGYGSAAYTPDNYNY	1740	WAQGTQVTVSS
P23ILPMP84H1	232	EVQLVESGGGVVQAGESLRLSCAASGRSFS	484	NFEMG	736	WFRQAPGTEREFVA	988	TINWRGSSTYYADSVKG	1240	RFTISRDNAENTVYLQMSSLKPEDTAVYYCAA	1492	GRLFPSSRSRDYDY	1744	WGQGTQVTVSS
P23ILPMP84F1	238	EVXLVESGGGVVQAGESLRLSCAASGRSFS	490	DYGMG	742	WFRQPPGTEREFVA	994	AINRRGSSTYYADSVKG	1246	RFTISRDSAKNTVYLQMSSLKPEDTAVYFCAA	1498	GQLYPSSASRDYDY	1750	WGQGTQVTVSS
P23ILPMP84A2	240	EVQLVESGGGLVQAGGSRRVSCAASGLTFS	492	DYSMA	744	WFRQAPGKEREFVA	996	AHAWLASRTDYADSVKG	1248	RFTISRDNAKNTVYLQMNSLKPEDTAAYYCAA	1500	GQRYLSRVSQGYEY	1752	WGQGTQVTVSS
PMP119A1	242	EVQLVESGGGLVQAGGSLRLSCAASGGTFS	494	TYAMG	746	WFRQAPGKEREFVA	998	ASNWSGGSTPYADSVMG	1250	RFTISRDNAKNTVYLQMGSLKPEDTAVYYCAA	1502	DVSGWAHKGAKEYEY	1754	WGQGTQVTVSS

Figure 13 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
PMP119C2	243	EVQLVESGGGLVQ PGGSLRLSCVASG SIF	495	TANDMA	747	WYRQAPG KQREWVA	999	TITRGDITLYA HSVKG	1251	RFTISRDYAANTVYLQ MNSLKPEDTAVYYCN A	1503	PNNYYGD	1755	WGQGTQV TVXS
PMP121B7	259	EVXLVESGGGVVQ AGESLRLSCAASG RSFS	511	NYEMG	763	WFRQAPG TEREFXG	1015	TISRRGSSTYY ADSVKG	1267	RFTISRDNAKNTVYLQ MSSLKPEDTAVYYCA A	1519	GQLFPSXHS RDYDY	1771	WGQGTQV TVSS
PMP121F1	260	EVQLVESGGGLVX PGGSLRLSCVASG FPFS	512	KTWMY	764	WFRQAPG KGLEQVS	1016	SIHTGFGVGV TYYADAVKG	1268	RFTISRDNAKNTLYLQ MNSLKPEDTALYYCA T	1520	DIQGTT	1772	RGQGTQV TVSS
PMP122H7	264	EVQLVESGGGVVQ AGESLRLSCAASG RSFS	516	NYEMG	768	WFRQAPG TEREFVG	1020	SINLRGSSTYY ADSVKG	1272	RFTISRDNAKNTVYLQ MSGLKPDDTAVYYCA A	1524	GWLYPSSRS RDYDY	1776	WGQGTQV TVSS
PMP123C1	269	EVQLVESGGGLVQ PGGSLRLSCAASG SFFS	521	IKSMG	773	WYRQAPG KQRELVA	1025	GITSGGTNYA DSVKG	1277	RFTISRDSAKNTVYLQ MNSLKPEDTAVYYCN A	1529	VGERLAYTG VTEYDY	1781	WGQGTLV TVSS
P23Ilp40-PMP20F2	2189	EVQLVESGGGLVQ PGGSLRLSCAASG FSLD	2234	YTAIG	2279	WFRQAPG KEREVVS	2324	CFTSVPGSTY HADSVKG	2369	RFTIASDNAKNTVYLQ MNDLKPEDTAVYYCA T	2414	DAQTYYSGS YCGRTPQEY PY	2459	WGQGTQV TVSS
P23Ilp40-PMP22D10	2190	EVQLVESGGGLVQ AGASLRLSCAASG RTFR	2235	SYNMG	2280	WLRQAPG KEREFVA	2325	TISWNAGIPY YADSVKG	2370	RFTISRDNAKNTVYLQ MNSLKPEDTAVYYCA A	2415	SNSWSSSAR FYDY	2460	WGQGTQV TVSS

Figure 13 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P23Ilp40-PMP23A11	2191	EVQLVESGGGLVPPGGSLRLSCAASGFTFS	236	SYAMS	2281	WVRRAPGRGLEWIS	2326	SISSGSDTTHVAGSVRG	2371	RFTISRDNAKNTLYLQMNSLKPDDTAVYYCVR	2416	AYDSIVPSPTQRTNYEY	2461	RGQGTQVTVSS
P23Ilp40-PMP21B9	2192	EVQLVESGGGLVQAGGSLRLSCAASGSIFS	237	INGMG	2282	WFRQAPGKEREFVS	2327	GINWSGSGNTYHADSVKG	2372	RATISRDNAKNTVYLQMNSLKPEDTAVYYCAA	2417	SERTYYSSSYYYRRFYDY	2462	WGQGTQVTVSS
P23Ilp40-PMP21H10	2193	EVQLVESGGGLVQAGGSLRLSCAASGRTFS	238	TYPMG	2283	YFRQAPGKERELVA	2328	AISRGGGSTYYEDSVKG	2373	RFTISRDNAKNTVYLQMNSLKPEDTAVYYCAV	2418	QLVGDSVSSYTRHYGY	2463	WGPGAQVTVSS
P23Ilp40-PMP22D6	2194	EVQLVESGGGLVQAGGSLRLSCAASGRTFN	239	NYLVG	2284	WFRQAPGKEREFVA	2329	AVRWEYGITEYADSVKG	2374	RFTISRDNAKNTVYLQMSSLRPEETAVYYCAA	2419	GTVRRSKFSNPIDYDY	2464	WGQGTQVTVSS

Figure 14

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P23ILp40-PMP84G12	178	EVQLVESGGRLVQAGGSLRLSCAASGRTFD	430	SNPMG	682	WFRQAPGKKREFVA	934	IISGNGGITNYANSVKG	1186	RFTISRDNAKNTIYLQMNSLKPEDTAVYYCAA	1438	SGLYGSGSVYDLMYDY	1690	WGQGTQVTVSS
P23ILp40+PMP81E10	182	EVQLVESGGGLVQAGGSLRLSCVASGRTFN	434	TYGMG	686	WFRQAPGKEREFVA	938	ANNWSGGATSYADSVKG	1190	RFTISRDNAKNTVFLQMNTLKPEDTAVYYCAA	1442	ADRGGGWLVVRENDYDY	1694	WGQGTQVTVSS
P23ILp40+PMP84D3	184	EVQLVESGGGLVQPGGSLRLSCAASGFSIS	436	NNWMY	688	WFRQAPGKGHEWVS	940	TIKTGAGSTAYADFVKG	1192	RFTISRDNAKNTLYLQMNSLKPEDTALYYCAR	1444	DWAGTV	1696	RGQGTQVTVSS
P23ILp40+PMP84E5	186	EVQLVESGGGLVQPGGSLRLSCAASGFAFS	438	NYWMY	690	WIRQAPGKGLEWVS	942	TIKTSGSAAYADFVKG	1194	RFTISRDNAKNTLYLQMNNLKPEDTALYYCSR	1446	DYAGTV	1698	RGQGTQVTVSS
P12ILPMP80A3	188	EVQLVESGGGLVQAGESLKLSCAASGRPFS	440	TYTMG	692	WFRQAPGKEREIVA	944	ASNWSGGSKYYSDSVKG	1196	RFTISRDNAKNTVYLQMNSLKPEDTAVYYCAT	1448	RESGELRIREYEYDY	1700	WGQGTQVTVSS
P12ILPMP80A10	189	EVQLVESGGGVVQAGESLRLSCAASGRSFS	441	NYEMG	693	WFRQAPGTEREFVG	945	TINRRGSSTYYADSVKG	1197	RFTISRDNAKNTVFLQMSSLKPEDTAVYYCAA	1449	GWLYPSSSSRDYDY	1701	WGQGTQVTVSS

Figure 14 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P12ILPMP80F10	190	EVQLVESGGGLVQPGGSLRLSCAASGFTLD	442	DYAIG	694	WFRQAPGKEREGVS	946	CISSSDGSTYYADSVKG	1198	RFTISRDNATNTVYLQMNSLKPEDTAVYRCAA	1450	VVDYYCPGYESGVFRYGMDY	1702	WGKGTLVTVSS
P12ILPMP80H10	192	EVQLVESGGGVVQAGESLRLSCAASGGSFS	444	NYEMG	696	WFRQAPGTEREFVG	948	TINRRGSSTYYEDSVKG	1200	RFTISRDNAKNTVYLQMSSLKPEDTANYYCAA	1452	GWLYPSSRSRDYDY	1704	WGQGTQVTVSS
P12ILPMP80E10	193	EVQLVESGGGLVQAGGSLXLSCAASGRTFS	445	DYGMG	697	WFRQAPGKEREFVA	949	VINWSGGSTGYAASVKG	1201	RFTISRDNYKNTVYLQMNSLKPDDTAVYYCAA	1453	DTLHGGAVTTTPARYDY	1705	WGQGTQVTVSS
P12ILPMP80B10	195	EVQLVESGGGLVQPGGSLRLSCAASGFTLS	447	GSWMY	699	WVRQAPGKGLEWVS	951	TIKPNGSTASADSVKG	1203	RFTISRDNAKNTLYLQMNSLKPEDTALYYCAR	1455	DFSGNQ	1707	RGQGTQVTVSS
P23ILPMP81A1	198	EVQLVESGGGLVQTGGSLRLSCAASVINFR	450	LADMD	702	WYRQALGKQRELVA	954	SISTGYRTNYADFVKG	1206	RFTISRDNAKNTVYLQMDSLKPEDTAVYYCAA	1458	RDLRGLRVDY	1710	WGQGTQVTVSS
P23ILPMP81B1	199	EVQLVESGGGLVQPGGSLRLSCAASGRFFS	451	TYSMG	703	WFRQVPGKEREPVA	955	AVNWNGISTYYADSVKG	1207	RFTISRDNAENTVYLQMNSLKPEDTAVYLCAR	1459	KRFQYIFGSQQPESDFDS	1711	WGQGTQVTVSS
P23ILPMP81C1	200	EVQLVESGGGSVQAGGSLRLSCAASGQITF	452	SDDAMG	704	WFRQAPGKEREFVS	956	AINWSGGSTSYTDSVRG	1208	RFTISRHNAKNTVYLQMNSLKPEDTAVYYCASS	1460	RPGGGLWTQTHEYAY	1712	WGQGTQVTVSS

Figure 14 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P23ILPMP81 H10	201	EVQLVESGGGVVR AGESLRLSCAASG RSFS	453	NYEMG	705	WFRQAPG TEREFVG	957	SINRRGSSTYY ADSVKG	1209	RFTISRDNAKNTVYLQ MSSLKPEDTAVYYCA A	1461	GWLYPSSRS RDYDY	1713	WGQGTQV TVSS
P23ILPMP81 F10	203	EVQLVESGGGLVQ PGGSLRLSCAASG FTFS	455	THWMY	707	WVRQAPG KGLEWVA	959	TSTFNILTGTE NTYYSDSVKG	1211	RFTISRDNAKNTLYLQ MNGLKPEDTALYYCA R	1463	DSSGNL	1715	KGQGTQV TVSS
P23ILPMP84 D5	205	EVQLVESGGGVVQ AGESLRLSCAASG RSFS	457	DYEMG	709	WFRQAPG TEREFVA	961	TINWRGSSTY YADSVKG	1213	RFTISRDSAKNTVYLQ MSSLKPLDTAVYYCA A	1465	GRLFPSSRSR DYDY	1717	WGQGTQV TVSS
P23ILPMP84 A12	206	EVQLVESGGGVVQ AGESLRLSCAASG RSFS	458	DYEMG	710	WFRQAPG TEREFVA	962	SINRRGSSTFY ADSVKG	1214	RFTISRDNTKNTVYLQ MSSLKPEDTAVYLCA A	1466	GWLFPSSRS RDYDY	1718	WGQGTQV TVSS
P23ILPMP84 A6	209	EVQLVESGGGLVQ AGGSLRLSCAASG RTFS	461	TYATG	713	WFRQAPG KEREFVA	965	ATRGSNGLAY YGNSAKG	1217	RFTISRDNAKNTVYLQ MNSLKPEDTAVYYCA S	1469	SNSRCIGDG CYDEPHEYA Y	1721	WGQGTQV TVSS
P23ILPMP84 D12	217	EVQLVESGGGVVQ AGESLRLSCAASG RIFS	469	DYEMG	721	WFRQAPG TEREFVA	973	AISWRGSSTY YADSVKG	1225	RFTISRDNAKNTVYLQ MSSLKPEDTAVYYCA A	1477	GRLFPSSRSR DYDY	1729	WGQGTQV TVSS
P23ILPMP84 D2	218	EVQLVESGGGLVQ PGGSLRLSCAASG FNFS	470	NYRMY	722	WVRQAPG KGLEWVS	974	SIGAIGNVPAY ADFVKG	1226	RFTISRDNAKNTLYLE MSSLKVEDTALYYCA R	1478	DYQGVV	1730	RGKGTLV TVSS

Figure 14 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P23ILPMP84 E1	220	EVQLVESGGGLVQ PGGSLRLSCAASG FTFS	472	GYWMY	724	WLRQAPG KGLEWVS	976	TIKTTGGGAY AEFVKG	1228	RFTISRDNAKNTLYLQ MNNLKPEDTALYYCA R	1480	DFEGTV	1732	RGQGTQV TVSS
P23ILPMP84 E10	221	EVQLVESGGGVVQ AGESLRLSCAASG YNVK	473	DYEMG	725	WFRQAPG TEREFAA	977	AINWRGSSTY YADSVKG	1229	RFTISRDNAKNTVYLQ MSSLKPEDTAVYYCA A	1481	GRLYPSSRSR DYDY	1733	WGQGTQV TVSS
P23ILPMP84 E8	223	EVQLVESGGGLVQ AGVSLRLSCAASG RAFS	475	NFDMG	727	WFRQAPG REREFVA	979	AINRSGSSTYV SASVKG	1231	RFTISRDNAKNTMSLQ MNNLKPEDTAVYVCA T	1483	GLLFPSSAER NYDY	1735	WGQGTQV TVSS
P23ILPMP84 F2	224	QVQLVESGGGLVQ PGGSLRLSCAASG FTFS	476	SSWMY	728	WVRQAPG KGLEWVA	980	TVKTNNSTVY ADFVKG	1232	RFTISRDNAKNTLYLR MNSLKPEDTALYYCA R	1484	DYAGRL	1736	RGQGTQV TVSS
P23ILPMP84 F6	226	EVQLVESGGGAVQ AGESLRLSCAASG RSFS	478	NYEMG	730	WFRQAPG TERAFVG	982	TISRRGSSTYY ADSVKG	1234	RFTISRDNAKNTVYLQ MSSLKPEDTAVYYCA A	1486	GQLFPSSNSR DYDY	1738	WGQGTQV TVSS
P23ILPMP84 G11	229	EVQLVESGGGLVQ AGGSLRLSCAASG RTFS	481	TYATG	733	WFRQAPG KEREFVS	985	AMRGSNGLA YYANSVKG	1237	RFTISRDNAKNTVYLQ MNSLKPEDTAVYYCA S	1489	SESRCIGDGC YDEPHEYAY	1741	WGQGTQV TVSS
P23ILPMP84 G4	230	EVQLVESGGGVVQ AGESLRLSCAASG RSFS	482	NYEMG	734	WFRQAPG TEREFVA	986	AISRRRSSTYY ADSVKG	1238	RFTISRDNAKNTVYLQ MSSLKPEDTAVYYCA A	1490	GALFPSSRSR DYDY	1742	WGQGTQV TVSS

Figure 14 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P23ILPMP84 G6	231	EVQLVESGGGVVQ AGESLRLSCAASG RSFS	483	NYEMG	735	WFRQAPG TEREFVS	987	TISRRGSSTYY ADSVKG	1239	RFTISRDNAKNTVYLQ MSSLKPEDTAVYYCA A	1491	GQLFPSSRPR DYDY	1743	WGQGTQV TVSS
P23ILPMP84 H2	233	EVQLVESGGGVVQ AGESLRLSCAASG RSFS	485	NYEMG	737	WFRQAPG TEREFVG	989	TINRRGSSTYY ADSVKG	1241	RFTISRDNAKNTVFLQ MSSLKPEDTAVYYCA A	1493	GWLFPSSLS RDYDF	1745	WGQGTQV TVSS
P23ILPMP84 H3	234	EVQLVESGGGLVQ PGGSLRLSCAASG FAFS	486	NRWMY	738	WVRQAPG KGLEWVS	990	TIKPNGSTAY ADFVKG	1242	RFTFSKDNAKNTLYL QMNSLKPEDTALYYC ST	1494	DYAGTV	1746	RGQGTQV TVSS
P23ILPMP84 H6	235	EVQLVESGGGVVQ AGESLRLSCAASG RSFS	487	NYEMG	739	WFRQAPG TEREFVG	991	TISRRGSSTYY ADSVKG	1243	RFTISRDNAKNTVYLQ MSSLKPEDTAVYYCA A	1495	GQLFPSSHSR DYDY	1747	WGQGTQV TVSS
P23ILPMP84 H8	236	EVQLVESGGGLVQ PGGSLRLSCAASG FTFS	488	SSVMF	740	WLRQAPG KGLEWVS	992	TIKPSGSTIYP NPAKG	1244	RFTISRDNAKNTLYLQ MDNLAPEDTALYYCA R	1496	DIGGAV	1748	RGQGTQV TVSS
P23ILPMP84 H9	237	EVQLVESGGGVVQ AGESLRLSCAASG RSLN	489	NEEMG	741	WFRQAPG TEREFVA	993	TISRRGTGTY YADSVKG	1245	RFTISRDNAKNTVYLQ MSSLKPEDTAVYYCA A	1497	GQLFPSSRSR DYDY	1749	WGQGTQV TVSS
P23ILPMP84 D8	239	EMQLVESGGGLV QPGGSLRLSCAAS GFSIS	491	NNWMY	743	WFRQAPG KGHEWVS	995	TIKTGAGSTA YADFVKG	1247	RFTISRDNAKNTLYLQ MNSLKPEDTALYYCA R	1499	DWAGTV	1751	RGQGTQV TVSS

Figure 14 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P23ILPMP84 E7	241	EVQLVESGGGLVQ PGGSLRLSCAASG FTFS	493	DSWMY	745	WVRQAPG KELEWVS	997	TISNSGFTTRY ADSVKG	1249	RFTISRDNAKNTLYLQ MNSLKPEDTSLYYCA R	1501	DLGGAL	1753	RGQGTQV TVSS
PMP122A8	266	EVXLVESGGGVVQ AGESLRLSCSASG RSFS	518	NYEMA	770	WFRQAPG TEREFVA	1022	TINRRGSSTYY ADSVKG	1274	RFTISRBNAKNTXVLQ MSSLKPEDTXVYYCA A	1526	GWLFPXSRS RDYDY	1778	WGQGTQV TVSS
P23Ilp40+21 C4	195	EVQLVESGGGLVQ AGGSLRLSCAASG RTFS	240	GYDMG	285	WFRQAPG KEREFVA	330	QISRHNSNTY YADAVKG	375	RFTISRDNAKNTVSLQ MNSLKPEDTAVYYCA I	420	GSLFPSSRER DYDY	465	WGQGTQV TVSS
P23Ilp40+22 D7,	196	EVQLVESGGGLVQ AGGSLRLSCASSG RTFS	241	IYARG	286	WFRQAPG KEREFVA	331	AIRSGLTTYSD SVKG	376	RFTISRDIAKNTVFLQ MNSLKSEDTAVYYCA A	421	AVNYFTDFT DYSKRDSYD Y	466	WGQGTQV TVSS
P23Ilp40+22 E11	197	EVQLVESGGGLVQ AGGSLRLSCAASG RTFS	242	WSAVG	287	WFRQAPG KEREFVA	332	AIRWSGGSPY YADSVKD	377	RFTISRDNAKNTVYLQ MNSLRPEDTAVYLCG E	422	TSLFPTSRGS HYDT	467	WGQGTQV TVSS
P23Ilp40+22 C7	198	EVQLVESGGGLVQ AGGSLRLSCAASG RTFS	243	SDAVG	288	WFRQAPG LERVFVA	333	AIRWSGGSAY YADSAKG	378	RFTISRDNAKNTVYLQ MNSLKPEDTAVYYCG A	423	TSLFPSSRGS HYDS	468	WGQGTQV TVSS
P23Ilp40+23 E3	199	EVQLVESGGELVQ AGGSLRLSCAASG SIVS	244	ISAMA	289	WYRQAPG KQRERVA	334	TITRGGTPDY ADSAKD	379	RFTISRDNAKNTVSLQ MNNLKPEDTAVYYCK A	424	ALRTPTHDY NYYDY	469	WGQGTQV TVSS

Figure 14 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P23Ilp40+23H3	2200	EVQLVESGGGLVQAGDSLRLSCAASGRSFS	2245	NDAMG	2290	WFRQAPGKERSFVA	2335	AINWSGELTGYAGSVKG	2380	RFTISRDGVENMVFLQMNSLVPEDTGVYYCAA	2425	VEGRDYYRGAQYYDY	2470	WGQGTQVTVSS
P23ILPMP3G10	2201	EVQLVESGGGVVQAGESLRLSCAASGYNVK	2246	DYEMG	2291	WFRQAPGMEREFAA	2336	AISWRGSSTYYADSVKG	2381	RFTISRDNAKNTVYLQMSSLKPEDTAVYYCAA	2426	GRLYPSSRSRDYDY	2471	WGQGTQVTVSS
P23ILPMP4F3	2202	EVQLVESGGGVVQAGESLRLSCAASGYNVK	2247	DYEMG	2292	WFRQAPGMEREFAA	2337	AISWRGSSTYYADSVKG	2382	RFTISRDNAKNTVYLQMSSLKPEDTAVYYCAA	2427	GRLYPSSRSRDYDY	2472	WGQGTQVTVSS
P23ILPMP3A10	2203	EVQLVESGGGVVQAGESLRLSCAASGYNFK	2248	DHDLG	2293	WFRQAPGMEREFVA	2338	AISWRGSSTYYADSVKG	2383	RFTISRDNAKNTVYLQMSSLKPEDTAVYYCAA	2428	GRLYPSSRSRDYDY	2473	WGQGTQVTVSS
P23ILPMP3C7	2204	EVQPVESGGGVVQAGESLRLSCAASGRSFS	2249	DYEMG	2294	WFRQAPGTEREFVA	2339	TINRRGSSTYYADSVKG	2384	RFTISRDNAKNTVYLQMSSLKSEDTAVYYCAA	2429	GWLYPSSRSRDYDY	2474	WGQGTQVTVSS
P23ILPMP3G9	2205	EVQLVESGGGVVQAGESLRLSCAASGRSFS	2250	NYEMG	2295	WFRQAPGTEREFVG	2340	SINRRGSSTYYADSVKG	2385	RFTISRDNAKNTVYLQMSSLKPEDTAVYYCAA	2430	GWLYPSSRSRDYDY	2475	WGQGTQVTVSS
P23ILPMP3D4	2206	EVQLVESGGGVVQAGETLRLSCAASGRSFS	2251	NYEMG	2296	WFRQAPGTEREFVG	2341	TINRRGSSTYYTDSVKG	2386	RFSISRDNAKNTMYLQMSSLKPEDTAVYYCAA	2431	GWLFPSSRSRDYDY	2476	WGQGTQVTVSS

Figure 14 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P23ILPMP3H5	207	EVQLVESGGGVVQAGESLRLSCAASGRSFS	252	NYEMG	297	WFRQAPGTEREFVG	342	AINRRGSSTYYADSAKG	387	RFTISRDNAKNTVFLQMSSLKPEDTAVYYCAA	432	GWLFPSSRSRDYDY	477	WGQGTQVTVSS
P23ILPMP3A11	208	EVQLVESGGGVVQAGESLRLSCAASGRTFS	253	NYEMG	298	WFRQAPGTEREFVA	343	SISRRYSTYYPDSVKG	388	RFTISRDNAKNTVYLQMSSLKPDDTAVYYCAA	433	GQLFPSSRSRDYDY	478	WGQGTQVTVSS
P23ILPMP3A7	209	EVQLVESGGGVVQAGESLRLSCAASGRSFS	254	NYEMG	299	WFRQAPGTEREFVA	344	AISRRRSSTYYADSVKG	389	RFTISRDNAKNTVYLQMSSLKPEDTAVYYCAA	434	GALFPSSRSRDYDY	479	WGQGTQVTVSS
P23ILPMP3F11	210	EVQLVESGGGLVQAGGSLRLSCAASGSIFS	255	INAMG	300	WFRQAPGKERQFVA	345	AINWSTGSTYYSDSVKG	390	RFTISRDNAKNTVYLQMNSLKPEDTAVYFCAS	435	GYLFPSSRGSQYDY	480	WGQGTQVTVSS
P23ILPMP3C1	211	EVQLVESGGGSVQAGGSLRLSCKVSGIMFS	256	DKGMG	301	WFRQAPGKERETVA	346	ATNWSGGSTYYADSVKG	391	RFTISRDNYKNTLHLQMASLKPEDTGIYYCAA	436	AGDSWNSRRIEDYDY	481	WGQGTPVTVSS
P23ILPMP3B8	212	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	257	SSVMF	302	WLRQAPGKGLEWLS	347	TIKPTGSTIYPGSGKG	392	RFTISRDNAKNTLYLQINNLKPEDTALYYCAR	437	DIGGTV	482	RGQGTQVTVSS
P23ILPMP3E1	213	EVQLVESGGGLVQAGGSLRLSCAASGIIFS	258	DNTMG	303	WFRQAPGKEREFVA	348	AIAGRGSRLNYADSVKG	393	RFTISRDNTKNTVYLQMNSLKPEDTAIYYCAA	438	KPYGRVYYTEGSNYDY	483	WGQGTQVTVSS

Figure 15

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P23ILp40+PMP122H9	183	EVQLVESGGGLVQAGGSLRLSCVASGRAFN	435	TYGMG	687	WFRQAPGKEREFVA	939	ANNWSGGATSYADSVKS	1191	RFTISRDNYKNTVFLQMNTLKPEDTAVYYCAA	1443	ANRGGGWLTVRENDYDY	1695	WGQGTQVTVSS
P23ILp40+PMP121A8	185	EVQLVESRGGLVQPGGSLRLSCAASGFTFS	437	SSWMY	689	WVRQAPGKGLEWVA	941	TIKTGGSAAYADFVKG	1193	RFTISRDDAKNTLYLQMNSLKPEDTAQYYCAR	1445	DYAGRL	1697	RGQGTQVTVSS
P23ILp40+PMP121H1	187	EVQLVESGGGLVQPGGSLRLSCAASGFAIT	439	SYYMY	691	WVRQAPGKGLEWVS	943	TITTTGGRAYADYVKG	1195	RFTISRDNAKNTLYLQMNSLKPEDTALYYCAR	1447	DLGGAV	1699	RGQGTQVTVSS
P12ILPMP80C3	196	EVQLVESGGGLVQPGGSLRLSCAASGRTFS	448	TYAMG	700	WFRQAPGKEREFVA	952	ASNWSGGSKHYADSVLG	1204	RFTISRDNYKNTVFLQMNSLKPEDTAVYFCAA	1456	RGSGELRLREYEYDY	1708	WGQGTQVTVSS
P12ILPMP80D3	197	EVQLVESGGGLVQAGGSLRLSCAASGGTFG	449	STFMG	701	WFRQTPGKEREFVA	953	AINWSGTFTWYSDSVKG	1205	RFSISRDNANNTVHLQMNKLKFEDTAVYYCAT	1457	DFNGGERRVPASYDS	1709	WGQGTQVTVSS
P23ILPMP81E2	202	RGALVESGGGLVQAGGSLRLSCAASGRPFS	454	SVAMG	706	WFRQAPGKEREFVA	958	AITGDSRSTYYSDSLKG	1210	RFTISRDNAKNTVYLQMNSLKPEDTAIYYCAA	1462	TTYISGTYYYLTKQDMYAY	1714	WGQGTQVTVSS
PMP119F3-b	244	EVQLVESGGGLVQPGGSLRLSCAASGFTLD	496	YYHIG	748	WFRQAPGKEREGVS	1000	CIDSSDGSTYYADSVKG	1252	RFTISRDNAKNTVYLQMNSLKPEDTAVYYCAA	1504	GPTWTQRNDRSWIFYEYDY	1756	WGQGTQVTVSS

Figure 15 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
PMP119F8	245	EVXLVESGGGSVQAGGSLGLSCTASEGTFS	497	RYTLA	749	WFRQEPGKEREFVA	1001	AISLSGTTAFYSNSVEG	1253	RFTVSRDNAKNTEYLQMNSLKSEDTAVYYCAA	1505	RSRDEFYYADDARYVY	1757	WGQGTQVTVSS
PMP119H3	246	EVQLVESGGGLVRAGGSLRLSCAASGRAFS	498	NYAMG	750	WFRRAPGRERELVG	1002	AITWSGGGTYYADSVKG	1254	RFTISRDNAKSTVYLQMNSLKPEDTAVYSCAA	1506	PRYERMMSRLEVDYGY	1758	WGQGTQVTVSS
PMP120C7	247	EVQLVESGGGFVQPGGSLRLSCAASASIFS	499	GYTMG	751	WYRQAPGKERELVT	1003	SISHRGGTNYADSVKG	1255	RFTISRENAKSTVYLQMNSLKPEDTGVYYCNR	1507	LINEAS	1759	WGQGTQVTVSS
PMP120A7	248	EVQLVESGGGFAQPGGSLRLSCAASASIFS	500	GYTMA	752	WYRQAPGKERELVT	1004	SISHRGGTNYADSVKG	1256	RFTISRENAKSTVYLQMDSLKPEDTGVYYCNR	1508	LINEAS	1760	WGQGTQVTVSS
PMP120F7	249	EVQLVESGGGFVQPGGSLRLSCAASASIFS	501	GYTMG	753	WYRQAPGKERELVT	1005	SISHRGGTNYADSVKG	1257	RFTISRENAKSTVYLQMNSLKPEDTGVYFCNR	1509	LINEAS	1761	WGQGTQVTVSS
PMP120H7	250	EVQLVESGGGLVQPGGSLRLTCAASGSIAS	502	NSAMG	754	WYRQLPGKQRELIA	1006	HITSRGHTTYADFVKG	1258	RFTISRDNVKNMVYLQMNSLKPEDTAVYYCNK	1510	ILHSDY	1762	WGQGTQVTVSS
PMP120H8	251	EVQLVESGGGLVQPGGSLRLPCVASGSIFR	503	GNTMG	755	WYRQTPGKQRELVA	1007	SITSRGYTSYADSVKG	1259	RFTISRDNAKNTVYLQMNSLKPEDTAVYYCNR	1511	IVVESQ	1763	WGQGTQVTVSS

Figure 15 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
PMP120H9	252	EVQLVESGGGLVQ PGGSPRLSCVASGS IFR	504	GNTMG	756	WYRQTPG KQRELVA	1008	SITSRGYTSYA DSVKG	1260	RFTISRDNAKNTVYLQ MNSLKPEDTAVYYCN R	1512	IVVESQ	1764	WGQGTQV TVSS
PMP120A8	253	EVQLVESGGGFVQ PGGSLXLSCAASA SIFS	505	GYTMG	757	WYRQAPG KERELVT	1009	SISHRGGTNY ADSVKG	1261	RFTISRENAKSTVYLQ MNSLKPEDTGVYYCN R	1513	LINEAS	1765	WGQGTQV TVSS
PMP120D7	254	EVQLVESGGGFVQ PGGSLRLSCAASA SIFS	506	GYTMG	758	WYRQAPG KERELVT	1010	SISHRGGTNY AESVKG	1262	RFTISRXNAKSTVYLE MNSLKPEDTGVYYCN R	1514	LINEAS	1766	WGQGTQV TVSS
PMP120 E7	255	EVXLVESGGGFVQ PGGSLRLSCAASA SIFS	507	GYTMG	759	WYRQAPG KERELVT	1011	SISHRGGTNY ADSVKG	1263	RFTISRXNAKSTVYLQ MNSLKPEDTGVYYCN R	1515	LINEAS	1767	WGQGTQV TVSS
PMP120 E8	256	EVQLVESGGGFVQ PGGSLXLSCAASA SIFS	508	GYTMA	760	WYRQAPG KERELVT	1012	SISHRGGTNY ADSVKG	1264	RFTISRENAKSTVYLQ MNSLKSEDTGVYYCN R	1516	LINEAS	1768	WGQGTQV TVSS
PMP120F9	257	EVQLVESGGGFVQ PGGSLRLSCAASA SIFS	509	GYTMG	761	WYRQAPG KERELVT	1013	SISHRGGTNY ADSVKG	1265	RFTISRENAKSTVYLQ MNSLKPEDTGVYYCN R	1517	LINEAS	1769	WGQGXQV TVSS
PMP121B3	258	EVQLVESGGGLVQ AGGSLRLSCAASIR TFS	510	SYNMA	762	WFRQAPG KEREFVT	1014	AIIQSGGTTYY DDSVKG	1266	RFTISRDNAKNTVYLQ MNSLKPEDTAVYYCA A	1518	RSAYASGIY YYTREVSYN Y	1770	WGQGTQV TVSS

Figure 15 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
PMP122C7	261	EVQLVESGGGLVQPGGSLRLSCAASGFTLD	513	DYTIA	765	WFRQAPGKEREGVS	1017	CISSSALITFYADSVKG	1269	RFTISRBNAKNTVYLQMNSLKPDDTAVYYCAA	1521	DRYYYCSGWPDESAY	1773	WGQGTQVTVSS
PMP122 E7	262	EVQLVESGGGLVQPGGSLRLSCAASGFTLD	514	DYTIA	766	WFRQAPGKEREGVS	1018	CISSSALITFYADSVKG	1270	RFTISRDNAKNTVYLQMNSLKPDDTAVYYCAA	1522	DRYYYCSGWPDESAY	1774	WGQGTQVTVSS
PMP122F7	263	EVQLVESGGGLVQPGGSLRISCAASGFTLD	515	DYTIA	767	WFRQAPGKEREGVS	1019	CISSSALITFYADSVKG	1271	RFTISRDNAKNTVYLQMNSLKPEDTAVYYCAA	1523	DRYYYCSGWPDESAY	1775	WGQGTQVTVSS
PMP122H8	265	EVQLVESGGGLVQPGGSLRLSCAASGFTLD	517	DYTIA	769	WFRQAPGKEREGVS	1021	CISSSALITFYADSVKG	1273	RFTISRDNAKNTVYLQMNSLKPEDTAVYYCAA	1525	DRYYYCSGWPDENAY	1777	WGQGTQVTVSS
PMP123A1	267	EVQLVESGGGLVQAGGSLRLSCAASGPLFE	519	NYVIG	771	WFRQGPGKEREGVS	1023	CIRCTGGSTTYADSVKG	1275	RFTLSRDNAKNTLYLQMNSLTPDDAAVYYCAK	1527	PRAGMAVYEYDA	1779	WGQGTQVTVSS
PMP123B1	268	EVQLVESGGGLVQPGGSLRLSCTASGLTFS	520	TYGMG	772	WFRQAPGKNREFVA	1024	AIKRGGSAYYSHPVRG	1276	RFTISRDNGKNTVYLQMNSLKPEDTAVYYCAA	1528	DQDPQELLPFGLANEYDY	1780	WGQGTQVTVSS
PMP124B1	270	EVQLVESGGGLVQPGSSLRLSCAASGFTLD	522	DYTIA	774	WFRQAPGKEREGVS	1026	CISSVDGSTNYGYPMKG	1278	RFTISTDNAKNMVYLQMNSLKPEDTAVYYCAA	1530	MKMCTRAFYGDPVDY	1782	WGKGTLVTVSS

Figure 15 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
PMP124C1	271	EVQLVESGGGLVQAGGSLRLACAASGLAFS	523	RSAMG	775	WFRQAPGKERENVA	1027	AISGGGLITDYTDSVKG	1279	RFTVSRDNAKNTVYLQMNNLKPEDTAVYYCAA	1531	SLXGSLTEYDY	1783	WGRGTQVTVSS
PMP124F1	272	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	524	SYMMS	776	WVRQAPGKGLEWVS	1028	FISSGGGISSYADSVEG	1280	RFTISRDNAKNTLYLHMNSLKPEDTAVYYCTK	1532	GRGDTRYDY	1784	RGQGTQVTVSS
PMP124G1	273	EVQLVESGGGLVQAGGSLRLSCAASGRTFS	525	SYVMG	777	WFRQAPGKEREFVA	1029	AISSGGSITDYGDSVKG	1281	RFTISRDNAKNTVNLQMNSLKPEDTAVYYCAA	1533	QDGRGILTRANHYDY	1785	WGQGTQVTVSS
P23ILPMP122G9	214	EVQLVESGGGLVQAGGSLRLSCAASGFTFS	259	SYWMY	304	WFRQAPGKGLEWVS	349	SINSGSGNTYYADSVKG	394	RFTISRDNAKNTVYLQMNSLKPEDTAIYYCAA	439	ARTFYSRTYYPVNRDEYDY	484	WGQGTQVTVSS

Figure 16

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P27ILPMP82-A1	274	EVQLVESGGGLVQAGGSLRLSCAASGFTFD	526	DYAIG	778	WFRQAPGKEREGVS	1030	CISSSDGSTYYADSVKG	1282	RFTISSDNAKNTVYLQMNSLKPEDTAVYYCAT	1534	GLLDCPQRYGSSWYKGIGY	1786	WGQGTQVTVSS
P27ILPMP82-A3	275	EVQLVESGGGLVQVGGSLRLSCAASEGTFN	527	SYTMG	779	WFRQAPGKEREFVA	1031	AISWIASVTEHSDSVKG	1283	RFAISRDDAKNTVYLEINTLKPEDTATYYCAR	1535	RRAPYYHISRRTDEYDF	1787	WGRGTQVTVSS
P27ILPMP82-A10	276	EVQLVESGGGLVQAGDSLRLSCAASGRAFS	528	TYTMG	780	WFRQAPGKEREFVA	1032	VRTGKTGGTRYADSVKG	1284	RFTISGDNAKNTVYLQMNRLEPEDTAVYHCAA	1536	SAIPVVVTTPEEYDY	1788	WGQGTQVTVSS
P27ILPMP82-A11	277	EVQLVESGGGLVQAGGSLRLSCAASGFTLD	529	DYAIG	781	WFRQAPGKEREGVS	1033	CISSSDGSTDYADSVKG	1285	RFTISSDNAKNTVYLQMNSLKPEDTAVYYCAA	1537	YYKPWKYYCSDYGSYEHDA	1789	WGQGTQVTVSS
P27ILPMP82-B1	278	EVQLVESGGGLVQAGGSLRLSCAASGLTFS	530	TYTMG	782	WFRQAPGKEREFVS	1034	TISGSGLIKDSVKD	1286	RFTISRDNAKNTVYLQMNSLKPEDTAVYYCAA	1538	RLSGWTSSRDKDYGY	1790	WGQGTQVTVSS
P27ILPMP82-B3	279	EVQLVESGGGLVQPGGSLTLSCAASGFTLD	531	RYAIG	783	WFRQAPGKQREGVA	1035	CISNLNSTDSKTYYADFVKG	1287	RFTISRDNAKNTVYLQMNSLKPEDTAVYYCAT	1539	PPYSDSYCLHREWVGLVPDDY	1791	WGQGTQVTVSS

Figure 16 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P27ILPMP82-B10	280	EVQLVESGGGLVQAGGSLRLSCAASGRTFS	532	SYTFG	784	WFRRAPDKDREFVA	1036	QISWIGGRTAYADSVKG	1288	RFTISRDNAKSTVYLQMNSLNTEDTAVYYCAA	1540	DRDVWVLSEHLYDY	1792	WGQGTQVTVSS
P27ILPMP82B11	281	EVQLVESGGGLVQAGGSLRLSCAASGGTVT	533	NYGRA	785	WFRQAPGKERDFVA	1037	GVNWSGSSTHYLDSVKG	1289	RFTISRDNAKNTVYLQMNNLKPEDTAVYYCAA	1541	AEGSTWYLESNLYNH	1793	WGQGTQVTVSS
P27ILPMP82-C1	282	EVQLVESGGGLVQVGGSLRLSCAASEHTFN	534	SYTMG	786	WFRQAPGKEREFVA	1038	AISWIASVTEYSDSVKG	1290	RFTISRDDAKKTVHLEINNLKPEDTATYYCAR	1542	RRMPYYHISRRADEYDF	1794	WGRGTQVTVSS
P27ILPMP82-C3	283	EVQLVESGGGLVQAGGSLELSCVASGLTFD	535	TYVTG	787	WFRQAPGKEREFVA	1039	TISGSGLITSYEDSVKD	1291	RVTISRDNAKNTVYLQMNSLKPGDTAVYYCAA	1543	RLSGWTSSRDYDYDY	1795	WGQGTQVTVSS
P27ILPMP82-C10	284	EVQLVESGGGLVQAGDSLRLSCAASGRTLA	536	NYGMG	788	WFRQAPGKEREFVA	1040	GVNWSGSSTYYLDSVKG	1292	RFTISRDNAKNTVYLQMNSLKPEDTAVYYCAA	1544	AEGSTWYLQPNLYNL	1796	WGQGTQVTVSS
P27ILPMP82-C11	285	EVQLVESGGGLVQAGGSLRLSCAASGRTFS	537	TYTMA	789	WFRQTPGKERDLVA	1041	GITGSGLRTYYADSVKG	1293	RFTISRDNAKNTVDLQMNSLKPEDTAVYYCAA	1545	SLTGWIPSSLQSYNY	1797	RGQGTQVTVSS
P27ILPMP82-D1	286	EVQLVESGGGLVQVGGSLRLSCAASERTFN	538	SYTMG	790	WFRQAPGKEREFVA	1042	AISWIASVTDYSDSVKG	1294	RFTISRDDDKNTVYLEINNLKPEDTATYYCAR	1546	RRMPYYHISRRTDEYDF	1798	WGRGTQVTVSS

Figure 16 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P27ILPMP82-D3	287	EVQLVESGGGLVQAGGSLRLSCAASGLTFS	539	TYTMG	791	WFRQAPGKEREFVA	1043	TISGSGLIKDSVKD	1295	RFTVSRDNAKNTVYLQMDSLKPEDTAVYYCAA	1547	RLSGWTSSRDYDYNY	1799	WGQGTQVTVSS
P27ILPMP82-D10	288	EVQLVESGGGLVQAGDSVRLSCAASGRTFS	540	VDTNTMG	792	WYRQAPGKEHEFVA	1044	AISWSGTTVYADSVKG	1296	RFTISKDNAKNTIYLQMNSLKPEDTAVYVCAA	1548	ERGKYATTGNYDY	1800	WGQGTQVTVSS
P27ILPMP82-D11	289	EVQLVESGGGLVQAGGSLRLSCAASGIIFT	541	NYAMA	793	WFRQAPGKEREFVA	1045	AISWRNSSTNYADSVKG	1297	RFTISRDNAKNTVYLQMNSLKPEDTALYTCAA	1549	RWRPQVDYVDHWSYTY	1801	WGQGAQVTVSS
P27ILPMP82-E1	290	EVQLVESGGDLVQPGGSLRLSCEASGRIFG	542	FNGMG	794	WYRQVQGKQRELVA	1046	RILSSISTYYVDSVKG	1298	RFTISRDNARNTVYLQMDSLKPEDTAIYYCNF	1550	EDY	1802	WGRGTQVTVSS
P27ILPMP82-E3	291	EVQLVESGGGLVQAGGSLRLSCVASGRTFR	543	SQSMG	795	WFRQAPGKEREIVA	1047	AISSDGISTFYTDSVKG	1299	RFTISRDNAKNTGYLQMNSLKPEDTAVYYCAA	1551	TTYSSYTTSGLLYPY	1803	WGQGTQVTVSS
P27ILPMP82-E10	292	EVQLVESGGGLVQPGGSLRLSCAASGITLD	544	DYATG	796	WFRQAPGKEREGVS	1048	CISGNHGSTYYADSVKG	1300	RFTISRDNAKNTVYLQMNSLKPEDTAVYYCAA	1552	LRWGCTLYGDYEGPYDY	1804	WGQGTQVTVSS
P27ILPMP82-E11	293	EVQLVESGGGLVQPGGSLRLSCAASGFTLD	545	DYPIG	797	WFRQAPGKEREGVS	1049	CISSSDGSTYYADSVKG	1301	RFTISRDNAKNTVYLQMNSLKPEDTAVYYCAA	1553	VPYRTCEGYDYIHYYPDDY	1805	WGQGTQVTVSS

Figure 16 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P27ILPMP82-F1	294	EVQLVESGGGLVQAGGSLRLSCAASGGTFS	546	TYVMA	798	WFRQAPGKEREFVT	1050	TISGSGLRTSYKDSVED	1302	RFTISRDNAKNTVYLQMNSLKPEDTAVYYCAA	1554	RLSGWTSSRDYDYNY	1806	WGQGTQVTVSS
P27ILPMP82-F3	295	EVQLVESGGGLVQAGDSLRLSCTASGGTFI	547	TTYVMG	799	WFRQAPGKEREFVA	1051	AIRRSGESGDTSYADSVKG	1303	RFTISRDNAKNTVYLQMNSLKPEDTAVYLCAA	1555	GTMRAYNY	1807	WGQGTQVTVSS
P27ILPMP82-F10	296	EVQLVESGGGLVQAGGSLSLSCAASGLTFS	548	TYGMG	800	WFRQAPGKEREFVA	1052	FISVSGIRTYYADSVKG	1304	RFTISRDNAKNTVYLQMNSLKPEDTAVYYCAA	1556	ALTGWIEARAEKYNY	1808	WGQGTQVTVSS
P27ILPMP82-F11	297	EVQLVESGGGLVQAGGSLRLSCAASGFTLD	549	DYAIG	801	WFRQAPGKEREGVS	1053	CISSSDGSTYYADSVKG	1305	RFTISRDNAKNTVYLQMNSLKPEDTAVYYCAA	1557	DLLRHRMSGWGPYWFLYEYDY	1809	WGQGTQVTVSS
P27ILPMP82-G3	298	KVQLVESGGGLVQVGGSLRLSCAASERTFD	550	SYAMA	802	WFRQAPGKEREFAA	1054	AISWIASVIEYSDSVKG	1306	RFTISRDDAKNTVYLEINNLKPEDTATYYCAR	1558	RRMPYYHISRRTDEYDF	1810	WGRGTQVTVSS
P27ILPMP82-G10	299	EVQLVESGGGLVQAGGSLRLSCAASGRTFS	551	NYPMG	803	WFRQAPGNEREFVA	1055	AISSSGLNTDYTDSVKG	1307	RFTISRDNAANTVYLQMNSLKPEDTAVYYCAR	1559	SSSGWMRARDFTS	1811	WGRGTQVTVSS
P27ILPMP82-G11	300	EVQLVESGGGLVQAGGSLRLSCAASGFTLD	552	DYAKG	804	WFRQAPGKEREGVS	1056	CISSSDGSTYYADSVKG	1308	RFTISSDNAKNTVYLQMNSLKPEDTAVYYCAA	1560	LPLPHCPPPPSLYYSGSFYPDDY	1812	WGQGTQVTVSS

Figure 16 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P27ILPMP82-H3	301	EVQLVESGGGLVQAGGSLSLSCEASGRIFN	553	LNGMG	805	WYRQAQGKQRELVA	1057	RILSSISTYYTDSVKG	1309	RFTISRDNARNTVYLQMDSLKPEDTAVYYCNF	1561	GDY	1813	WGQGTQVTVSS
P27ILPMP82-H10	302	EVQLVESGGGLVQAGGSLRLSCAASGFTLD	554	DYAIG	806	WFRQAPGKEREGVS	1058	CISSSIGSTYYADSVKG	1310	RFTISSDNAKNTVYLEMNSLKPEDTAVYYCAY	1562	LRWGCSLYLTDYDY	1814	WGQGTQVTVSS
P27ILPMP82-H11	303	EVQLVESGGGLVQAGGSLRLSCAASGFTLD	555	DYAIG	807	WFRQALGKEREGVS	1059	CISSSDGFTYYADSVKG	1311	RFTISSDNAKNTVYLQMNNLKPEDTADYYCAP	1563	FSATCNGDSSWWSVSRYFGS	1815	WGPGTQVTVSS
P27ILPMP82-G1	304	EVQLVESGGGLVQAGGSLRLSCAASGRTFS	556	DYAMG	808	WFRQAPGKERECVG	1060	AISKSGGSTIYADSVKG	1312	RFTISRDNAKNTLYLQMNSLKPEDSAVYYCAA	1564	DRRHGDVVAARASS	1816	WGQGTQVTVSS
P27ILPMPA2	305	EVQLVESGGGLVPAGDSLRLACAASERSFS	557	SYNTG	809	WFRQAPGKEREFVA	1061	ATSGSTFSTYYTDSVKG	1313	RFTISRDNAKNTVYLQMDNLKPEDTAVYYCAA	1565	STSGNAWFTVYYSTLGEYDY	1817	WGQGTQVTVSS
P27ILPMP82A8	306	EVQLVESGGGLVQAGGSLRLSCAASGFTLD	558	DYAIG	810	WFRQAPGKEREGIS	1062	CISSTDSSTYYVDSVKG	1314	RFTISSDNAKNTVYLQMNSLKPEDTAVYYCAA	1566	LRFGCSYYYTEYDY	1818	WGQGTQVTVSS
P27ILPMP82C8	307	EVQLVESGGGLVQPGGSLRLSCAASGFTLD	559	DYAIG	811	WFRQAPGKEREGVS	1063	FISSSGGSTYYADSVKG	1315	RFTISRDNAKNTVYLQMNSLKPEDTAVYYCAA	1567	DRRAGDLVRYEYDY	1819	RGQGTQVTVSS

Figure 16 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
P27ILPMP82 B5	308	EVQLVESGGGLVQ PGGSLTLSCAASGF SLE	560	HYAVG	812	WFRQAPG KEREGVS	1064	CIDMDGSSHY ADVVRG	1316	RFTISRBBAANTVTLQ MTGLKPEDAXXYNCA I	1568	EWACTAKX GTSRXDWR QWXYVD	1820	WTQGTQV TVSS
P27ILPMP82 D8	309	EVQLVESGGGLVQ AGGSLRLSCAASG FTLD	561	DYAIG	813	WFRQAPG KEREGVS	1065	CIXSSDGSTYY ADSVK	1317	GRFTMSSDNAKNTVY LQMNSLKPEDTAVYY CAD	1569	CDTVDGIWY QEGS	1821	RGQGTQV TVSS
P27ILPMP82 F5	310	EVQLVESGGGLVQ PGGSLRLSCAASG FTLD	562	YYAFG	814	WFRQAPG KEREGVS	1066	CISMVNDSTY YADSVK	1318	GRFTISRDNAKNTVYL QMNSLKPEDTXVYYC AA	1570	QPTYCETLL RVGEWPGGI IPYDY	1822	WGQGTQV TVSS
P27ILPMP82 F7	311	EVQLVESGGGLVQ PGGSLRLSCAASG FTLD	563	EHTIG	815	WFRQAPG KEREGVS	1067	CISSSDGSTYY ADSVK	1319	GRFTISRDNAKNTVYL QMNSLKPEDTAAYYC AA	1571	TMYNGVVA TAQFMGDM SADWYNY	1823	WGQGTXV TVSS
P27ILPMP82 H8	312	EVQLVESGGGLVQ AGGSLXLSCAVSG FTLD	564	DYAIG	816	WFRQAPG KEREGVS	1068	YISSSDGSTYY ADSVK	1320	GRFTISSDNAKNTVYL QMNSLKPEDTAVYYC AA	1572	ITWDTVVRT APFEYEPDY	1824	WGQGTQV TVSS

Figure 17

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
PMPIL12Rb1-134-5A	313	EVQLVESGGGLVQAGGSLRLSCAVSGIAFR	565	YNSVA	817	WSRQAPGSQRELVA	1069	RITNSARTNYADSVKG	1321	RFTISRDNDKNMVYLQMNSLKPEDTAVYYCGA	1573	GRSMTGDVAY	1825	WGQGTQVTVSS
PMPIL12Rb1-134-5B	314	EVQLVESGGGLVQAGGSLRLSCAASGITFD	566	DDYAIG	818	WFRQAPGKEREGVS	1070	LISSSDGSTYYADSVKG	1322	RFTITSDNAKNTVYLQMNSLKPEDTAVYYCAA	1574	DPTSGLPSDDEYDY	1826	WGQGTQVTVSS
PMPIL12Rb1-134-5C	315	EVQLVESGGGLVQAGGSLRLSCAASGIAFR	567	YNSVA	819	WSRQAPGSQREVVA	1071	GITNSARTNYADSVKG	1323	RFTISRDNDKKMVYLQMNSLKPEDTAVYYCGA	1575	GRSMAGDVAY	1827	WGQGTQVTVSS
PMPIL12Rb1-134-5E	316	EVQLVESGGGLVQAGGSLRLSCAASGIAFR	568	YNSVA	820	WSRQAPGSQRELVA	1072	SISNSARTKYADSVKG	1324	RFTISRDNEKKMLYLQMDSLKPEDTAVYYCGA	1576	GRSMAGDVAY	1828	WGQGTQVTVSS
PMPIL12Rb1-134-5F	317	EVQLVESGGGLVQPGGSLRLSCVASGRPLT	569	GSTMA	821	WFRQAPGKECEFVA	1073	RISGSGTINYADSLRG	1325	RFTISRDVPKNTVWLQMDSLKPDDTAVYYCAA	1577	VKVAGSYEY	1829	WGQGTQVTVSS
PMPIL12Rb1-134-5G	318	EVQLVESGGGSVQTGGSLTLSCTASGRTGS	570	TDGVG	822	WFRQAPGKEREFVS	1074	AIKWIGGSKYYSNSAEG	1326	RFTIAVDNAKNTVYLQMNSLNPEDTAVYYCAA	1578	GAIMFPSRPRDFDF	1830	WGQGTQVTVSS
PMPIL12Rb1-134-8B	319	EVQLVESGGGLVQAGGSLRLSCAASGRTFS	571	SYAMG	823	WFRQAPGKEREFVA	1075	HINWNGGNTYYADSVRG	1327	RFIISRDNAKNTLYLQMNRLKPEDTAVYYCAA	1579	RPDRVIVKWDEYDY	1831	WGQGTQVTVSS

Figure 17 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
PMPIL12Rb1-134-8D	320	EVQLVESGGGLVQPGESLTLSCAASGFTFS	572	SYWMY	824	WVRQAPGRELEWVA	1076	RIQPGSSYTAYADSVKG	1328	RFTISRDLAKNTLYLQMNRLKSDDTAVYYCAK	1580	DWEMAAPS	1832	LGQGTQVTVSS
PMPIL12Rb1-134-9B	321	EVQLVESGGGLVQAGGSLRLSCAASGTFLS	573	INRMG	825	WYRQAPGKERELVA	1077	VIISGGSTNYADSVKG	1329	RFTISRENAELTVYLQMNSLKPEDTAVYYCNV	1581	WINTDGIYTYEY	1833	WGQGTQVTVSS
PMPIL12Rb1-134-9C	322	EVQLVESGGGSVQPGGSLRLSCAASGLIVG	574	RPAMG	826	WYRQAPGKQRELVA	1078	IIGSGGNTNYPESVKG	1330	RFTIARENANNTVYLQMNSLKPEDTAVYHCNL	1582	HGTRF	1834	WGQGTQVTVSS
PMPIL12Rb1-148-2D	323	EVQLVESGGGLVQAGGSLRLSCAASGLTFS	575	SPAMA	827	WFRQVPGKEREFVA	1079	TIRRSSAWTDYADSVKG	1331	RFTISRDRPTNTAYLQMSSLKPEDTAVYYCAA	1583	DKISRGIDPNWTY	1835	WGRGTQVTVSS
PMPIL12Rb1-148-2F	324	EVQLVESGGGLVQPGGSLRLSCAVSGISVR	576	SSVVN	828	WYRQAPGKQRELVA	1080	LIMGGAIRKYADDVKG	1332	RFTISSDSAKNTVYLQMNSLRPEDTAVYYCSA	1584	LEY	1836	WGQGTQVTVSS
PMPIL12Rb1-148-2G	325	EVQLVESGGGLVQPGGSLRLSCAVSGISVR	577	SSVVN	829	WYRQAPGKQRELVA	1081	LIMGGAITKYADDVKG	1333	RFTISSDSARNTVYLQMNSLRPEDTAVYSCSA	1585	LEY	1837	WGQGTQVTVSS
PMPIL12Rb1-148-3C	326	EVQLVESGGGLAQEGGSLRLSCAASGRPLT	578	TYGMA	830	WFRQAPGKEREFVA	1082	RIGAEPGATVYGDSVKG	1334	RFTISRDNAKNTVYLQMNTLKPEDTAVYYCAA	1586	DAPPFGPYYRESVYDY	1838	WGQGTQVTVSS

Figure 17 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
PMPIL12Rb1-148-3F	327	EVQLVESGGGLVTAGGSLRLSCAASGFRFS	579	VYDMG	831	WFRQAPGKEREFVA	1083	VIVGSRTTDYADSVKG	1335	RFIIFRDNAKNTLYLQMNGLKPDDTAVYYCAR	1587	RVGTYETVLGYDK	1839	WGQGTQVTVSS
PMPIL12Rb1-148-5D	328	EVQLVESGGGLVQAGGSLRLSCAASGFTFD	580	DYAIG	832	WFRQAPGKEREGVS	1084	CISSSDGSTYYADSVKG	1336	RFTISSDNAKNTVYLQMNSLKPEDTAVYYCAA	1588	PLLRGGCPITYYSGSYPHVYHAMDY	1840	WGKGTLVTVSS
PMPIL12Rb1-148-7A	329	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	581	RAWMY	833	WVRQAPGETLEWVS	1085	RIQPGGGSTSYADSVKG	1337	RFTISRDNAKNTLYLQMNSLKSEDTAVYYCAK	1589	DWEMAAPS	1841	LGQGTLVTVSS
PMPIL12Rb1-148-7F	330	EVQLVESGGGLVQPGGSLRLSCKASRSIFS	582	INTMD	834	WHRQVPGKQRELVA	1086	AIVNGVWKNYADSVKG	1338	RFTISRDNAENTVYLQMNNLKPEDTAVYYCHA	1590	KRGVSDY	1842	WGQGTQVTVSS
PMPIL12Rb1-134-11G	331	EVXLVESGGGLVETGGSLRLSCAARGRIKS	583	IADMG	835	WYRQAPGKQRELVA	1087	TITFGGTTTYADSAKG	1339	RFTISRDNAENTVYLQMNSLKPEDTAVYFCNA	1591	DRILYVSEGLYRTEVDS	1843	WGQGTQVTVSS
PMPIL12Rb1-134-8A	332	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	584	RAWMY	836	WVRQAPGETLEWVS	1088	RIQPGGGSTSYADSVKG	1340	RFTISRDNAKNTLYLQMNSLKSEDTAVYYCAK	1592	DWEMAAPS	1844	LGQGTQVTVSS
PMPIL12Rb1-134-4c	333	EVQLMESGGGVVQVGGSLRLSCAASGGTLY	585	SYIVG	837	WFSQAPGQDREFVG	1089	AIEYSGGITDYKDSVKG	1341	RFTISKDNPKNTVFLQMDSLKPEDTAVYYCGL	1593	TRVVGARNPGDYAY	1845	WGQGTQVTVSS

Figure 17 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
PMPIL12Rb1-134-8C	334	EVQLVESGGGLAQTGGSLTLSCAASGRTPS	586	IVAMG	838	WFRQIPGKDREPVG	1090	EIILSKGFTYYADSVKG	1342	RFTISRANAKNTITMSLQMHSLKSEDTAVYYCAA	1594	RQNWSGNPTRPNEYEY	1846	WGQGTQVTVSS
PMPIL12Rb1-148-10E	335	EVQLVESGGGLVQTGGSLRLSCAASGRTSR	587	LVAMG	839	WFRQTPGKEREFVG	1091	EIILSKDFTYYADSVKG	1343	RFTISRANAKNTITMYLQMSSLKSEDTAVYYCAA	1595	RQNWSGHPARTNEYEY	1847	WGQGTQVTVSS
PMPIL12Rb1-148-11F	336	EVQLVESGGGLVQTGGSLRLSCAASGRTPS	588	IVAMG	840	WFRQTPGKEREFVG	1092	EIILSKGFTYYADSVKG	1344	RFTISRANAKNTITMYLQMHSLKSEDSAVYYCAA	1596	RQNWSGGPTRTNEYEY	1848	WGQGTQVTVSS
PMPIL12Rb1-148-12D	337	EVQLVESGGGLVQTGGSLRLSCAASGRTPS	589	IVAMG	841	WFRQTPGKERESVG	1093	EIILSKGFTYYADSVKG	1345	RFTISRANAKNTITMYLQMNSLKSEDTAVYYCAA	1597	RQNWSGNPTRTNEYEY	1849	WGQGTQVTVSS
PMPIL12Rb1-148-9C	338	EVQLVESGGGLVQTGGSLXLSCAASGRTPR	590	LVAMG	842	WFRQTPGKEREFVG	1094	EIILSKGFTYYADSVKG	1346	RFTISRVNAKNTITMYLQMNSLKSEDTAVYYCAG	1598	RQNWSGSPARTNEYEY	1850	WGQGTQVTVSS
PMPIL12Rb1-148-9F	339	EVQLVESGGGLVQTGGSLRLSCAASGRTPS	591	IIAMG	843	WFRQTPGKEREFVG	1095	EIILSKGFTYYADSVKG	1347	RFTISRANAKNTITMYLQMNSLKSEDTAVYYCAA	1599	RQNWSGNPTRTNEYEY	1851	WGQGTQVTVSS

Figure 18

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
PMPIL12Rb2-135-10B	340	EVQLVESGGGLVQTGGSLRLSCTHSGRPLS	592	MFAVG	844	WFRQAPGEQRVLVA	1096	AISRSGGATYYPDSVKG	1348	RFAISRDNAKNTVNLQMNSLTPEDTAVYYCAA	1600	ALGGVYNAIANDYKY	1852	WGQGTQVTVSS
PMPIL12Rb2-135-10C	341	EVQLVESGGGSVQAGGSLRLSCAASGRTFS	593	DYAMG	845	WFRQAPGKEREFVA	1097	GISRSGSTTGYAGSVKG	1349	RFSISRDNAKNAVYLQMNSLKPEDTAVYYCAS	1601	KRSPYTGIYYSDLSQSED	1853	WGQGTQVTVSS
PMPIL12Rb2-135-12A	342	EVQLVESGGGLVQAGGSLRLSCAASGFAFD	594	DYEIG	846	WFRQAPGKEREGVA	1098	CINNSDGSTYYIDSVKG	1350	RFTISKDSATNTVYLQMSSLKPEDTAVYYCAA	1602	DSWCTVVAGKIHPFDS	1854	WGQGTQVTVSS
PMPIL12Rb2-135-12B	343	EVQLVESGGGLVQAGGSLRLSCAASGRTSS	595	TYVMG	847	WFRQAPGKEREFVA	1099	GISWSAGNTRYADSVKG	1351	RFTISRDIAKNTFDLQMNSLKPEDTAVYYCAA	1603	DRRYGGSLDPSAWDF	1855	WGQGTQVTVSS
PMPIL12Rb2-135-12C	344	EVQLVESGGGSVQAGGSLRLSCAASGRTFS	596	SYVMG	848	WFRQAPGKEREFVA	1100	AVSWSAGNTRYANSVKG	1352	RFTISRDIAKNTFYLQMNSLKPEDTAVYYCVA	1604	DRRYGGSLDPSAWDF	1856	WGQGTQVTVSS
PMPIL12Rb2-135-1A	345	EVQLVESGGGLVQPGGSLRLSCAVSGFTSD	597	YYVIA	849	WFRQTPGHEREGVS	1101	SIRKGDGATYYADSVKG	1353	RFSISRDNAKNMVYLQMNSLKPEDTAVYTCAA	1605	RYDTLLGGGRPREFPY	1857	WGQGTQVTVSS
PMPIL12Rb2-135-1C	346	EVQLVESGGGLVQPGGSLRLSCAVSGFTSD	598	YYVVA	850	WFRQTPGHEREGVS	1102	SIRIGDYATYYADSVKG	1354	RFSISRDNAKNMVYLQMNSLKPEDTAVYTCAA	1606	RYDSHLGGGRPREFPY	1858	WGQGTQVTVSS

Figure 18 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
PMPIL12Rb2-135-1D	347	EVQLVESGGGLVQPGGSLRLSCAVSGFTSD	599	YYVIA	851	WFRQTPGHEREGVS	1103	SIRITDNATYYADSVKG	1355	RFSISRDNAKNMVFLQMNSLKPEDTAVYTCAA	1607	RYETLLGGGRPREFPY	1859	WGQGTQVTVSS
PMPIL12Rb2-135-1E	348	EVQLVESGGGLVQPGGSLILSCAVSGFTSD	600	YYVIA	852	WFRQTPGHEREGVS	1104	SIRIGDGATYYADSVKG	1356	RFSISRDNAKNMVYLQMNSLKPEDTAVYTCAA	1608	RYDTLLGGGRPREFPY	1860	WGQGTQVTVSS
PMPIL12Rb2-135-1F	349	EVQLVESGGGLVQPGGSLRLSCAASGFSFS	601	RNWMY	853	WVRQAPGKGLEWVG	1105	DISMEGTNTYYRDSVQG	1357	RFTISRDNAKNILYLQMNSLKSEDTAVYYCAR	1609	AKNEGFVPGGYDFDY	1861	RGQGTQVTVSS
PMPIL12Rb2-135-1H	350	EVQLVESGGGLVQPGGSLRLSCAVSGFTSD	602	YYVIA	854	WFRQTPGHEREGLS	1106	SIRIGDSATFYADSVKG	1358	RFSISRDNAKNMVYLQMNSLKPEDTAVYTCAG	1610	RYDTLLGGGRPREFPY	1862	WGQGTQVTVSS
PMPIL12Rb2-135-3A	351	EVQLVESGGGLVQPGGSLRLSCAVSGFTSD	603	FYVIA	855	WFRQTPGHEREGVS	1107	SIRIGDNAAYYADSVKG	1359	RFSISRDYAKNMVYLQMNSLKAEDTAVYTCAG	1611	RYDSNLGGGRPREFPY	1863	WGRGTQVTVSS
PMPIL12Rb2-135-3B	352	EVQLVESGGGLVQPGGSLRLSCAASGRTIA	604	AYKMA	856	WFRQAPDKARERVA	1108	LITSFGLTVYADSVKG	1360	RFTISRDNAYNTVYLQMNHLKFEDTAVYYCAA	1612	GQQDSSNYNS	1864	WGQGTQVTVSS
PMPIL12Rb2-135-3D	353	EVQLVESRGGLVQPGGSLRLSCAVSGFTSD	605	YYVIA	857	WFRQTPGHEREGVS	1109	SIRKGDGATYYADSVKG	1361	RFSISRDNAKNMVYLQMNSLKPEDTAVYTCAA	1613	RYDTLLGGGRPREFPY	1865	WGQGTQVTVSS

Figure 18 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
PMPIL12Rb2-135-7B	354	EVQLVESGGRLVQAGDSLRLSCAASGRTFT	606	SYRMG	858	WFRQAPGKEREFVS	1110	ALRWSSGNIDYTYYADSVKG	1362	RFSISGDYAKNTVYLQMNSLKAEDTAVYYCAA	1614	STRWGVMESDTEYTS	1866	WGQGTQVTVSS
PMPIL12Rb2-135-8A	355	EVQLVESGGGLVQAGGSLTLSCAASGRTFS	607	SYHMG	859	WFRQAPGKEREYVA	1111	AISWSGHMTYYKDSAKG	1363	RFTISRDNAKNTVYLQMNNLKPEDTAVYYCAA	1615	RNRDYWSDFDVPGRYAY	1867	WGQGTQVTVSS
PMPIL12Rb2-135-8C	356	EVQLVESGGRLVQAGDSLRLSCAASGRTFT	608	NYRVG	860	WFRQAPGKEREFVS	1112	ALRWSSSNIDYTYYADSVKG	1364	RFSISGDYAKNTVYLQMNSLKAEDTAVYYCAA	1616	STSWGVLESDTEYTS	1868	WGQGTQVTVSS
PMPIL12Rb2-135-1B	357	EVQLVESGGGLVQPGGSLRLSCAVSGFTSE	609	YYVIA	861	WFRQTPGHEREGVS	1113	SIRIRDNAAYYADSVKG	1365	RFSISRDNHKNMVYLQMNSLKPEDTAVYTCAG	1617	RYDTLLGGGRPREFPY	1869	WGQGTQVTXSX
PMPIL12Rb2-135-3C	358	EVXLVESGGALVQDGGSLRLSCAASGLTLS	610	NYVAA	862	WFRQAPGKEREYVG	1114	SIRWSSEQTYYANSVKG	1366	RFSISRDNAKNAVYLEMNTLKPEDTAVYYCAL	1618	GTSFSALPKLYNY	1870	WGQGTQVTVSS
PMPIL12Rb2-135-7A	359	EVXLVESGGRLVQAGDSLRLSCAASGRTFI	611	SYRMG	863	WFRQAPGKEREFVA	1115	ALRWSSSNIDYTYYADSVKG	1367	RFSISGDYAKNTVYLQMNSLKAEDTAVYYCAA	1619	STRWGVMESDTEYTS	1871	WGQGTQVTVSS
PMPIL12Rb2-136-4B	360	EVQLVESGGGLVQSGGSLRLSCAASEGTFT	612	IYPLG	864	WFRQAPGKDRKFVA	1116	ALPWSAGIPQYSDSVKG	1368	RFTISRDNAKNTVYLQMNNLKPEDTAVYYCAX	1620	KGRDDSYQPXNY	1872	WGQGTQVTVSS

Figure 19

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
PMPIL23R-136-11C	361	EVQLVESGGGSAQAGGSLRLSCAASGGTFS	613	SYTMA	865	WFRQAPEKEHEFVA	1117	VISGTGDSAYYADSAKG	1369	RFTISRDNAKHTVYLQMNVLKPEDTALYYCAG	1621	PCMVLGERCILMPHNY	1873	WGQGTQVTVSS
PMPIL23R-136-12A	362	EVQLVESGGGLVQAGGSLKLSCAASGRSFS	614	RYAMG	866	WFRQAPGKEREFVA	1118	ATRWNGGSTYYVDYADSVKG	1370	RFTVSRDNVKNTMYLQMNSLKPEDTAGYYCAG	1622	KGTVYSGSRPISDEYDYDY	1874	WGQGTQVTVSS
PMPIL23R-136-12B	363	EVPLVESGGGLVQSGGSLRLSCAASGSFDS	615	DTVMA	867	WYRQAPGKQRDFVA	1119	AVTGTGGTNYADSVKG	1371	RFSISRDNAKNTVYLQMNSLKPEDMGVYYCYM	1623	RILGGGRY	1875	WGQGTQVTVSS
PMPIL23R-136-12C	364	EVQLVESGGGLVQAGGSLRLSCAASERTVS	616	TYTSG	868	WFRQAPGKERDLVA	1120	AIRWSDDFTYYADSVKG	1372	RFTISRDNAKNTVYLQMNSLKVEDTAVYYCAG	1624	HSFSALIPPVSFWPS	1876	WGQGTQVTVSS
PMPIL23R-136-4C	365	EVQLVESGGGLVQAGGSLRLSCAASGTIFR	617	IENMY	869	WFRQAPGNQREWVA	1121	RISRESGTSYADSVKD	1373	RFTISRDNAKNTVYLQMNSLKPGDTAVYYCTA	1625	DVQTNSRGAQQIF	1877	RGQGTQVTVSS
PMPIL23R-136-4D	366	EVQLVESGGGLVQAGGSLRLSCAASGSIFR	618	INNMY	870	WFRQAHENQREWVA	1122	RITRESDTTYADSVKD	1374	RFTISRDNAKNTVYLQMNSLKPGDTAVYYCTA	1626	DVQTNSRDAQQIF	1878	RGQGTRVTVSS
PMPIL23R-150-11A	367	EVQLVESGGALVQPGESLRLSCVVSGDTST	619	YHAIG	871	WFRQAPGKGREGVS	1123	CINRSDGTTAYADSVKG	1375	RFTISRDKAKNTVYLQMNALRPEDTAVYSCAA	1627	DPMLYCDTDYEPQTTDFTS	1879	WGRGTQVTVSS

Figure 19 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
PMPIL23R-150-11F	368	EVQLVESGGGSVQVGASLRLSCAARGRALS	620	NYGVG	872	WFRQAPGKEREFVA	1124	SVSWNGGNKNYRSSVKG	1376	RFTISRDNANDTVFLQMNSLKPEDTAVYYCSA	1628	DVRPYGLGPRSDERVAD	1880	WGQGTQVTVSS
PMPIL23R-150-11G	369	EVQLVESGGGLVQAGGSLRVSCLASGNIVS	621	RNVMA	873	WYRQAPGKQRELVA	1125	SVDTGGSTLYADSVKG	1377	RFTISRDSAKSMVYLQMNSLKPEDTAVYYCNV	1629	PRYGY	1881	WGQGTQVTVSS
PMPIL23R-150-2C	370	EVQLVESGGGLVQSGGSLRLSCAASEGTFT	622	IYPLG	874	WFRQAPGKDRKFVA	1126	ALPWSAGIPQYSDSVKG	1378	RFTISRDNAKNTVYLQMNNLKPEDTAVYYCAA	1630	KGRDDSYQPWNY	1882	WGQGTQVTVSS
PMPIL23R-150-2D	371	EVQLVESGGGLVQPGGSLTLSCVASGRTFS	623	TDVMG	875	WFRQAPGKEREFVA	1127	AHRTSGISTVYAASVKG	1379	RFTISRDNAKNTVYLGMKSLKPEDTAVYYCAA	1631	GSDASGGYDY	1883	WGQGTQVTVSS
PMPIL23R-150-2G	372	EVQLVESGGGLVQPGGSLTLSCVASGRTFS	624	TDVMG	876	WFRQAPGKEREFVA	1128	AHRRNGISTVYAASVKG	1380	RFTISRDNAKNTVYLGMKSLKPEDTAVYYCAA	1632	GSDASGGYDY	1884	WGQGTQVTVSS
PMPIL23R-150-7H	373	EVQLVESGGGLVQAGGSLRLSCAASGRTFS	625	SYAMG	877	WFRQAPGKDREFVA	1129	AISWIGESTYYADSVKG	1381	RFTISRDNAKNTVYLRMNSLKPEDTAVYYCAA	1633	DLYYTAYVAAADEYDY	1885	WGQGTQVTVSS
PMPIL23R-150-9H	374	EVQLVESGGGLVQAGGSLKLSCAASGRSFS	626	RYAMG	878	WFRQAPGKEREFVA	1130	ATRWNGGSTYYADYADSVKG	1382	RFTVSRDNAKNTMYLQMNSLKPEDTAVYYCAG	1634	KGTVYSGSSPISDEYGYDY	1886	WGQGTQVTVSS

Figure 19 (continued)

	ID	Framework 1	ID	CDR 1	ID	Framework 2	ID	CDR 2	ID	Framework 3	ID	CDR 3	ID	Framework 4
PMPIL23R-150-1B	375	EVQLVESGGGLMQAGDSLRLSCAASGRTSY	627	IYTMA	879	WFRQAPGKEREFVA	1131	AIRWSDTTTYYADSVKG	1383	RFTASRDNAKNTMYLQMNSLKPMDTAVYYCAV	1635	KRDSSTYYRVRNYDY	1887	WGQGTQVTVSS
PMPIL23R-150-2B	376	EVQLVESGGGLVQAGGSLRLSCAAAERTFS	628	DYAVG	880	WFRQAPGKEREFVS	1132	AVSRFGTITNYADSVQG	1384	RFTISRDNAKNTVYLQMTGLKFEDTAVYYCAA	1636	ARTVYVGHLYYIDNEYAY	1888	WGQGTQVTVSS
PMPIL23R-136-4B	377	EVQLVESGGGLVQSGGSLRLSCAASEGTFT	629	IYPLG	881	WFRQAPGKDRKFVA	1133	ALPWSAGIPQYSDSVKG	1385	RFTISRDNAKNTVYLQMNNLKPEDTAVYYCAX	1637	KGRDDSYQPXNY	1889	WGQGTQVTVSS

Figure 20

SEQ ID NO: 1890 : P23ILP19+PMP121A2 EVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVA AIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGIPY STSDRVIKGVNDYDYWGQGTQVTVSS
SEQ ID NO: 1891 : P23ILP19+PMP121D3 RGAAGGVWGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFV AAIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGIP YSTSDRVIKGVNDYDYWGQGTQVTVSS
SEQ ID NO: 1892 : P23ILP19+PMP04E3 EVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVSA IRWSGISTYYADSVKGRFTISRDDAKNTVYLQMNSLKPEDTAIYYCALRKGIPYST SDRYIKGVNDYDYWGQGTQVTVSS
SEQ ID NO: 1893 : P23ILP19+PMP124F10 EVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVA AIRWSGRSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGIPY STSDRVIKGVNDYEYWGQGTQVTVSS
SEQ ID NO: 1894 : P23ILP19+PMP124G2 EVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVA AIRWSGSSTYYADSVKGRFTISRDDAKNTVYLQMNSLKPEDTATYYCALRKGIPY SISDRVIKGVNDYDYWGQGTQVTVSS
SEQ ID NO: 1895 : P23ILP19+PMP121E3 EVQLVESGGGLVQAGGSLRVSCAASGSIFAFNYMGWFRQAPGKEREFVA AIRWSGSSTYYADSVKGRFSISRDDAKNTVYLQMNSLKPEDTAIYYCALRKGTPY STSYRVIKAVNDYEYWGQGTQVTVSS
SEQ ID NO: 1896 : P23ILP19+PMP12A4 EVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVA TIRWSGSSTDYADSVKGRFTISRDDAKNTVYLQMNSLKPEDAAIYYCALRKGIPY STSNRYIKGVNDYDYWGQGTQVTVSS
SEQ ID NO: 1897 : P23ILP19+PMP12E11 EVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVA TIRWSGSSTYYADSVKGRFTISRDGAKNTVYLQMNSLKPEDTAIYYCALRKGIPY STSSLYIKGVNDYDYWGQGTQVTVSS
SEQ ID NO: 1898 : P23ILP19+PMP119A3 EVQLVESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAWHRQAPG MQRELVATINSGSRTNYADSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQ TSGSGSPNFWGQGTQVTVSS
SEQ ID NO: 1899 : P23ILP19+PMP119A2 EVQLVESGGGLVQAGGSLRLSCAASGSIFSLPASGNIFNLLTIAWHRQTPG KQRELVATINSGGRTNYTDSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQ TSGSGSPNYWGQGTQVTVSS

Figure 20 (continued)

SEQ ID NO: 1900 : P23ILP19+PMP02C04 EVQLVESGGGLVQPGGSLRLSCAGSGSILRIASMGWYRQAPGKQRELAAV IGSEGDTDYADSMKGRFTISLDNAANTVYLQMNSLKPEDTAVYICSGLLLNGGGT WQRLWGQGTQVTVSS
SEQ ID NO: 2485 : P23ILPMP36A1 EVQLVESGGGLVQPGGSLRLSCEASALTSFSNYAMYWVRQAPGKALEWV SAISRAGSNTYYADSVKGRFTISRDNAKDTLYLQMNSLRSEDTGVYYCAVDSSGT WRGQGTQVTVSS
SEQ ID NO: 2486 : P23ILPMP36G2 (=23IL36A4) EVQLVESGGGLVQAGGSLRLSCVASERTFSSSAMGWFRQAPGKEREFVA AIGWSGGGFIHYGDSVKGRFTISADNGKNTVYLQMNSLKPEDTAVYYCAADSRL RGIALLKGSYDYRGQGTQVTVSS
SEQ ID NO: 2487 : P23ILPMP36B3 EVQLVESGGGLVQPGGSLRLSCAASGFTVDYHGIAWFRQAPGKGPEGVSC IRNSDGRTYYADSVKGRFTISRDNAKNTVYLQMNSLKLEDTAIYYCATTTGRIGV NCVPSNTRGQGTQVTVSS
SEQ ID NO: 2488 : P23ILPMP36B4 EVQLVESGGGLVQPGGSLRLSCAASGFTVDYHGIAWFRQAPGKGPEGVSC IRNSDGRTYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAIYYCATTTGRIGV NCVPSNTRGQGTQVTVSS
SEQ ID NO: 2489 : P23ILPMP36E5 EVQLVESGGGLVQAGGSLRLSCAASGRTISNYGMGWFRQAPGKEREFVA AISARSAMIGYSDSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADLNRR VPTARPQEYDGWGQGTQVTVSS
SEQ ID NO: 2490 : P23ILPMP37D5 EVQLVESGGGLVQPGGSLRLSCAASGFTLDYLAIGWFRQAPGKEREGVSC VSSSGQYTYYADSVKGRFTISRDNAESTVYLQMNSLKPEDTAVYYCATDPECYR VRGYYYNGEYDYWGQGTQVTVSS

Figure 21

SEQ ID NO: 1901 : P23ILP19-PMP119C09 EVQLVESGGGLVQAGGSLTLSCAASVRTFSTSAMGWFRQAPGKEREFVA AINWNAGSTYHADSVKGRFTISGDNAKNSVFLQMNGLKPEDTAVYYCAAQASG RVTYFDYAYRRGSNYDYWGQGTQVTVSS
SEQ ID NO: 1902 : P23ILP19-PMP119G07 EVQLVESGGGLVQAGGSLTLSCAVSGLTFNNYAMGWFRQVPGKEREFVA AISRSGLRTFYSDSVKGRFTISRDSAKSTVYVQMNNLKPEDTAVYFCAADRRTYY SEGPSLTDTLRYDYWGQGTQVTVSS
SEQ ID NO: 1903 : P23ILP19-PMP123F01 EVQLVESGGGLVQAGGSLRLSCAASGRTSSSYSMGWFRQAPGKEREFVA YISGGGLTIYYAHSVKGRFTISRDNAKNTVYLQMNSLNSADTAVYSCAAPKRDL YLGSRYPVPESYDYWGQGTQVTVSS
SEQ ID NO: 1904 : P23ILP19-PMP12A11 EVQLVESGGGLVQAGDSLKLSCAASGRTSSSYAMGWFRQAPGKEREFVA AIIWSRGNTYYADSVKGRFTISRDNAKNTMYLQMNNLKPEDTAVYYCAAHRGD SIYYYTVWGKYDAWGQGTQVTVSS
SEQ ID NO: 1905 : P23ILP19-PMP119C08 EVQLVESGGGLVQAGASLRLSCAASGRSFDSNVMGWFRQYPGKLREFVA AIWWSAGTTKYADSVKGRFTISRDNAKNTVHLQMNSLELEDTALYYCAADRVS SSIQTMAGTYDYWGQGTQVTVSS
SEQ ID NO: 1906 : P23ILP19-PMP124H05 EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMYWVRQAPGKGLERV APLNPGGTITLYADFVKSRFTISRDNAKNTVYLQMNSLKPEDTAVYVCAAPSGTL YTRNKSGYIYWGQGTQVTVSS
SEQ ID NO: 1907 : P23ILP19-PMP119H01 EVQLVESGGGLVQAGGSLRLSCAASGSISEFNVIGWHRQAPGKERELVASI TGHDSTYYTGSVKGRFTISRDNAKTTVYLQMNSLKPEDTAVYYCAVRQILRREY DYWGQGTQVTVSS
SEQ ID NO: 1908 : P23ILP19-PMP81D01 EVQLVESGGGLVQAGGSLRLSCAASGRTFSTYAAGWFRQDPGEEREFVST ISRGGGTTGYADAVKGRFTISRDNAKNTVYLQMNNLKPEDTAVYYCAAADVSY GTTTDDPKRYDYWGQGTQVTVSS
SEQ ID NO: 1909 : P23ILP19-PMP81H02 EVQLVESGGGLVQAGGSLRLSCSASGRTFSTYAAGWFRQAPGKDREFVST ISRGGGGTYSADAVTGRFTISRDNAKNTVYLQMNNLKPEDTAVYYCAAADVSY GTTTDDPKRYDYWGQGTQVTVSS
SEQ ID NO: 1910 : P23ILP19-PMP84C03 EVQLVESGGGLVQAGGSLELSCSASGGTLRTYAMGWFRQAPGKEREFVS TISRGGGSTDYADAVKGRFTISRDNAKNTVYLQMNSLKPEDTAEYICTAADVSY GVTTDDPKRYDYWGQGTQVTVSS

Figure 21 (continued)

SEQ ID NO: 1911 : P23ILP19-PMP119B03 EVQLVESGGGLVQAGGSLRLSCAASGTISSINTMAWFRQAPGKEREFVAA LVKGFSWGSGSSIYADSVRGRFTISRDNAKNTQSLQMNSLELEDTAIYYCAAGRR SSVRSGYEFWGQGTQVTVSS
SEQ ID NO: 1912 : P23ILP19-PMP119E1 EVQLVESGGGLVQAGGSLRLSCAASGTISSINTMAWFRQAPGKEREFVAA LVKGFSWGSGSSIYADSVRGRFTISRDNAKNTQSLQMNSLELEDTAIYYCAAGRR SSVRSGYEFWGQGTQVTVSS
SEQ ID NO: 1913 : P23ILP19-PMP121A1 EVQLVESGGGLVQAGGSLRLSCAASGTISSINAMGWFRQAPGKEREFVAA IVKGFSWGSGSTIYADSVKGRFTISRDNAQNTMSLQMNSLELEDTAIYYCAHGRR SSGRSGYEYWGQGTQVTVSS
SEQ ID NO: 1914 : P23ILP19-PMP121B1 EVQLVESGGGLVQAGGSLRLSCVASGTISAINTMGWFRQAPGKEREFVAA LVKGFSWGSGSTIYADSVKGRFTISRDNAKNTMSLQMNSLKLEDTAIYYCAQGR RSSGRSGSGYEYWGQGTQVTVSS
SEQ ID NO: 1915 : P23ILP19-PMP121C7 EVQLVESGGGLVQAGGSLRLSCAASGTISSINVMGWFRQAPGKEREFVAA LVKGFSWGSGSSIYADSVRGRFTISRDNAKNTQSLQMNSLELEDTAIYYCAAGRR SSARSGYEFWGQGTQVTVSS
SEQ ID NO: 1916 : P23ILP19-PMP121F8 EVQLVESGGGLVQAGGSLRLSCAASGTISSINAMGWFRQAPGKEREFVAA IVKGFSWGSGSTIYADSVKGRATISRDNAKNTMSLQMSSLELEDTAIYYCAHGRR SSGRSASGYEYWGQGTQVTVSS
SEQ ID NO: 1917 : P23ILP19-PMP121G8 EVQLVESGGGLVQAGGSLRLSCAASGTISSINAMGWFRQAPGKEREFVAA IVKGFSWGSGSIMYADSVKGRFTISRVNAKNTMSLQMNSLELEDTAIYYCAAGR RSSGRSGSGYEYWGQGTQVTVSS
SEQ ID NO: 1918 : P23ILP19-PMP121H8 EVQLVESGGGLVQAGGSLRLSCAASGTISSINTMGWFRQAPGKEREFVAA LVKGFSWGSGSNIVADSVKGRFTISRDNAKNTMSLQMNSLELEDTAIYYCAAGR RSSGRSGYEYWGQGTQVTVSS
SEQ ID NO: 1919 : P23ILP19-PMP124C3 EVQLVESGGGLVQAGGSLRLSCAASGTISSINAMGWFRQAPGKEREFVAA IVKGFSWGSGSTIYADSVKGRATISRDNAKNTMSLQMSSLELEDTAIYYCAHGRR SSGRSASGYEYWGQGTQVTVSS
SEQ ID NO: 1920 : P23ILP19-PMP124E5 EVQLVESGGGLVQAGGSLRLSCAASGTISSINAMGWFRQAPGKEREFVAA IVKGFSWGSGSVIYADSVKGRFTISRDNAKNTMSLQMNSLELEDTAIYYCANGRR SSARSGANYEYWGQGTQVTVSS

Figure 21 (continued)

SEQ ID NO: 1921 : P23ILP19-PMP12D2 EVQLVESGGGLVQAGGSLRLSCAASGTISSINTMGWFRQAPGKEREFVAA IVKGFSWGSGSTIYADSVKGRFTISRDNAQNTMSLQMNSLELEDTAIYYCAHGRR SSGRSGYEYWGQGTQVTVSS
SEQ ID NO: 1922 : P23ILP19-PMP04A11 EVQLVESGGGLVQAGGSLRLSCAASGTISSINAMGWFRQAPGKEREFVAA IVKGFSWGSGSTIYADSVKGRFTISRDNAQNTMSLQTNSLELEDTAIYYCAHGRR SSGRSGYEYWGQGTQVTVSS
SEQ ID NO: 1923 : P23ILP19-PMP12G7 EVQLVESGGGLVQAGGSLRLSCAASGTISSINAMGWFRQAPGKEREFVAA IVKGFSWGSGSTIYADSVKGRFTISRDNAQNTMSLQMNSLELEDTAIYYCAHGRR SSGRSGYEYWGQGTQVTVSS
SEQ ID NO: 1924 : P23ILP19-PMP124C5 EVQLVESGGGLVQAGGSLRLSCAASGAISSINAMGWFRQAPGKEREFVAA IVKGFSWGSGSTIYADSVKGRFTISRDNAKNTMSLQMSSLELEDTAIYYCAHGRR SSGRSGYEYWGQGTQVTVSS
SEQ ID NO: 1925 : P23ILP19-PMP119G08 EVQLVESGGGLVQPGGSLRLSCAASGRPVGGYGMGWFRQGPGKEREFLA TTAWNGDFTYYADSVKDRFTISRDNPKNTIYLQMNSLKPEDTAKYYCAASISKGS TSYRXYGFWGQGTQVTVSS
SEQ ID NO: 1926 : P23ILP19-PMP119G02 EVQLVESGGGLVQPGGSLRLSCAASGRTFGGYGMGWFRQGPGKEREFLA TTAWNGDFTYYADSVKDRFTISADNPKNTVYLQMNSLKPEDTAKYYCAASIAKG SRSSRSYGYWGQGTQVTVSS
SEQ ID NO: 1927 : P23ILP19-PMP119C03 EVQLVESGGGLVQAGSSLRLSCAASGRTFSTFRDYVMGWFRQAPGKERE FVAVISRGGGRTDYDDSVKGRFTISRDNVNNMVYLQMNSLNSEDTGVYYCAAD QDRSYGSIGMLPNEYDYWGQGTQVTVSS
SEQ ID NO: 1928 : P23ILP19-PMP123H1 EVQLVESGGGWVQAGSSLRLSCAASGRTFSDYAMGWFRQVPGKEREFVA AISRGGGKTYYVDSEKGRFTISRDNAKNTVYLQMNSLNSEDTAVYYCAADQDRS YGSIGTLPNDYDYWGQGTQVTVSS
SEQ ID NO: 1929 : P23ILP19-PMP119D2 EVQLVESGGGLVQAGGSLRLSCIASGLPFSTKSMGWFRQAPGKEREFVAR ISPGGTSRYYGDFVKGRFAISRDNAKNTAWLQMNSLKAEDTAVYYCASGERSSY IGSNYYYRTNEYDYWGTGTQVTVSS
SEQ ID NO: 1930 : P23ILP19-PMP81G2 EVQLVESGGGLVQPGGSLRLSCIASGLPFSTKSMGWFRQAPGKEREFVARI SPGGTSRYYGDFVKGRFAISRDNAKNTTWLQMNSLKAEDTAVYYCASGERSTYI GSNYYYRTNEYDYWGTGTQVTVSS

Figure 21 (continued)

SEQ ID NO: 1931 : P23ILP19-PMP124B5 QVQLVESGGGLVQPGGSLRLSCAASGFTLADFAIAWFRQAPGKEREGVSG IDSGDGSTYYADSVKGRFTISSDNAKNTVYLQMNSLRPEDTAVYYCARVRTGWG LNAPDYAMDYWGKGTLVTVSS
SEQ ID NO: 1932 : P23ILP19-PMP124C4 EVQLVESGGGLVQPGGSLRLSCAASGFTLDDYAIAWFRQAPGKEREGVSG IDSGDGSAYYADSVKGRFTISSDNAKNTVYLQMNSLRPEDTAVYYCARVRTGW GLNAPDYAMDYWGKGTLVTVSS
SEQ ID NO: 1933 : P23ILP19-PMP124D11 EVQLVESGGGLVQPGGSLRLSCAASGFTLDDYAIAWFRQAPGKEREGVSG IDCSDGSTYYANSVKGRFTISSDNAKNTVYLQMNSLRPEDTAVYYCARVRTGWG LRAPDYAMDYWGKGTLVTVSS
SEQ ID NO: 1934 : P23ILP19-PMP124G4 EVQLVESRGGLVQPGGSLRLSCAASGFYLDDYAIAWFRQAPGKEREGVSG VDSGDGSTYYADSVKGRFTISSDNAKNTVYLQMNSLRPEDTAVYYCARVRTGW GLNAPDYAMDYWGKGTLVTVSS
SEQ ID NO: 1935 : P23ILP19-PMP124H2 EVQLVESGGGLVQPGGSLRLSCAASGFYLDDYAIAWFRQAPGKEREGVS GIDSGDGSTYYADSVKGRFTISSDNAKNTVYLQMNSLRPEDTAVYYCARVRTGW GLNAPDYAMDYWGKGTLVTVSS
SEQ ID NO: 1936 : P23ILP19-PMP81A12 EVQLVESGGGLVQAGGSLRLSCAASGRTLSSYAMGWFRQAPGKEREFVA RISQGGTAIYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAKDPSPY YRGSAYLLSGSYDSWGQGTQVTVSS
SEQ ID NO: 1937 : P23ILP19-PMP124D2 EVQLVESGGGLVQAGGSLRLSCAASGRTLSSYSMGWFRQAPGKEREFVA RISPSGSAIYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAKDPSPYY RGSAYLLSGSYDSWGQGTQVTVSS
SEQ ID NO: 1938 : P23ILP19-PMP121F7 EVQLVESEGGLVQPGGSLRLSCAASGFAFSNYWMYWIRQAPGKGLEWVS TIKTSGSAAYADFVKGRFTISRDNAKNTLYLQMNSLKPEDTALYYCSTDYAGTV RGQGTQVTVSS
SEQ ID NO: 1939 : P23ILP19-PMP121D1 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYRMYWVRQAPGKGLEWVS SIGAVGSLPAYADFVKGRFTISRDNAKNTLYLQMSSLKVEDTALYYCARDYQGA VRGKGTLVTVSS
SEQ ID NO: 2502 : P23ILPMP20B11 EVQLVESGGGLVQAGGSLRLSCAVSGDTFSVYGMGWFRQAPGMEREFV AGISWNAGITAYTDTLKGRFTISRDRAKNTMYLQMNSLQPEDTAVYYCAADVTR HYIATRSKVDASMYDYWGQGTQVTVSS
SEQ ID NO: 2503 : P23ILPMP20H9 EVQLVESGGGSVQAGGSLRLSCVASGLYFNGNGLGWFRQAPGKEREFVA AIAWNGARINYADSVKGRFTVSRDNIKNTVYLQMNSLKPEDTAVYYCASARSGY ASISINEYDYWGQGTQVTVSS

Figure 22

SEQ ID NO: 1940 : P23ILP40-PMP80D10 EVQLVESGGGLVQAGGSLRLSCAASGRTFEGNPMGWFRQASGKKREFVA SIDWSGGITSYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAASARFGS GSYYDLMYDYWGQGTQVTVSS
SEQ ID NO: 1941 : P23ILP40-PMP80C10 EVQLVESGGGLVQAGGSLRLSCAASGRTFDSNPMGWFRQAPEKKREFVAI ISGNGGITNYANSVKGRFTISRDNAKNTIYLQMNSLKPEDTAVYYCAASDLYGSG SNYDLMYDYWGQGTQVTVSS
SEQ ID NO: 1942 : P23ILP40-PMP84G12 EVQLVESGGRLVQAGGSLRLSCAASGRTFDSNPMGWFRQAPGKKREFVA IISGNGGITNYANSVKGRFTISRDNAKNTIYLQMNSLKPEDTAVYYCAASGLYGS GSVYDLMYDYWGQGTQVTVSS
SEQ ID NO: 1943 : P23ILP40-PMP119H2 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSSWMYWVRRAPGKGLEWVS TIKSGGGSTVYADFVKGRFTISRDNAKNTLYLQMNSLKSEDTAVYYCAKDWGAS TFVRGQGTQVTVSS
SEQ ID NO: 1944 : P23ILP40-PMP121A3 EVXLVESGGGLVEPGGSLRLSCAASGFTFSSSWMYWVRQAPGKGLEWVA TIKASSSAVYADFVKGRFTISRDNAKNTLYLQMNSLKPEDTALYYCAKDYAGRL RGQGTHVTVSS
SEQ ID NO: 1945 : P23ILP19-PMP119B02 EVQLMESGGGLVQAGGSLRLSCAAPGRTFSEYAMGWFRQNPGNEREFVA AISRGGGFTDYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADGRSS FGIAKRSRYEYDSWGQGTQVTVSS
SEQ ID NO: 1955 : P12ILPMP80H3 EVQLVESGGGLVQAGDSLRLSCTASGRTFSSHTMAWFRQAPGKEREFVG TIVRIFGDTYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAAALRGTS SDWRAAATYDDWGQGTQVTVSS
SEQ ID NO: 1958 : P12ILPMP80B3 EVQLVESGGGLVQAGGSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVA GSNWSGGSTPYADSVVGRFAISRDNAKNTVHLQMNSLKPEDTAVYYCAAGRFS YSTRIPNDYAYWGQGTQVTVSS
SEQ ID NO: 1968 : P23ILPMP81F3 EVQLVESGGGLVQAGGSLRLSCAASGLTFSTTAMAWFRQAPGKEREFVA ATNWSGGSTPYGDSVIGRFTISRNNAKNTVYLQMNSLKPEDTAVYICAADVSGW AHKGAKEYEYWGQGTQVTVSS
SEQ ID NO: 1971 : P23ILPMP84A4 EVQLVESGGGLVQAGGSRRVSCAASGLTFSDYSMAWFRQAPGKEREFVA AHAWLASTTDYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAAYYCAAGQRY LSRVSQGYEYWGQGTQVTVSS

Figure 22 (continued)

SEQ ID NO: 1972 : P23ILPMP84A5 EVQLVESGGGLVQAGGSLRLSCEASERTFSTYRMGWFRQSPGREREFVTS FNWSGGSTYYADSVKGRFIIATDDAKNTVYLRMNSLKPEDTAVYYCAGYSSGSY YSPRSYGVWGQGTQVTVSS
SEQ ID NO: 1974 : P23ILPMP84B2 EVQLVESGGGLVQPGGSLRLSCAASGFTLDDYTMSWVRQAPGKGLEWVS SISRDGGRTYYAGSMKGRFTISRDNAKNTLYLQMSSLKPEDTAVYYCAAATFYT TSTYISLYDYWGQGTQVTVSS
SEQ ID NO: 1975 : P23ILPMP84B3 EVQLVESGGGLVQPGGSLRLSCAASGSFFSIKSMGWYRQAPGKQRELVAG IASGVTNYADSVKGRFTISRDGAKNTVYLQMNSLKPEDTAVYYCNAVGERLANT GVTEYDYWGQGTLVTVSS
SEQ ID NO: 1976 : P23ILPMP84B5 EVQLVESGGGLVQPGGSLRLSCAASGRFFSTYAMGWFRQVPGKEREPVA AVNWNGISTYYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYLCARKRFQY IFGSQQPESDFDSWGQGTQVTVSS
SEQ ID NO: 1977 : P23ILPMP84B6 EVQLVESGGGLVQSGDPLRLSCAASGPTYTMAWFRQAPGEEREFVAVISG GSTNYADSVKGRFTVSADNAKNTMYLQMNSLKPEDTAVYYCAGAGFYTTGTY YSLYDYWGQGTQVTVSS
SEQ ID NO: 1978 : P23ILPMP84B8 KVQLVESGGGLVQAGGSLRLSCAASGRSFSTYAMGWFRQAPGKEREFVA ASNWSGGSKNYADSVLGRFTISRDNAKNTVYLQMNSLKPTDTAVYYCAAKGSG DLRLREYEYDYWGQGTQVTVSS
SEQ ID NO: 1979 : P23ILPMP84C7 EVQLVESGGGSVQAGGSLRLSCAASGRTIFSDYAMGWFRQAPGKEREFVS AINWSGGSTTYADSVKGRFTISRDNYKNTVYLQMNSLKPEDTAVYYCASRAGGG LWTQTHEYVDWGQGTQVTVS
SEQ ID NO: 1980 : P23ILPMP84C9 EVQLVESGGGLVQAGGSLRLSCAASGRTFSTYAMGWFRQAPGKEREFVA ASNWSGGSKYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAARGSG ELRLREYEYDYWGQGTQVTVSS
SEQ ID NO: 1983 : P23ILPMP84D7 EVQLVESGGGLVQAGGSLRLSCAASGIIFSDNVMGWFRQAPGKEREFVAA IAGRGSRLDYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTATYYCAAKPYGRV FYTEGSNYDFWGQGTQVTVSS
SEQ ID NO: 1986 : P23ILPMP84E12 EVQLVESGGGLVQAGDSLRLSCAASGRSFSRDTMGWFRQAPGKEREFVA AINWSGGSRSYADSVLGRFTISRDNAKNTVYLQMNRLKPEDTSIYYCATDRGGH FSVGYYYPSDDSWDYWGQGTQVTVSS

Figure 22 (continued)

SEQ ID NO: 1989 : P23ILPMP84F5 EVQLVESGGGVVQAGESLRLSCAASGRSFSDYEMGWFRQAPGTEREFVA AISWRGSSTYYADSVKGRFTISRDNAKNTVYLQMSSLKPEDTAVYYCAAGRLYP SSRSRDYDYWGQGTQVTVSS
SEQ ID NO: 1991 : P23ILPMP84F9 EVQLVESGGGLVQPGGSLRLSCAASGFSISDNWMYWFRQAPGKGHEWVS TIKTGTGSTAYADSVKGRFTISRDNAKNTLYLQMNSLKPEDTALYYCARDWDGT VRGQGTQVTVSS
SEQ ID NO: 1992 : P23ILPMP84G1 EVQLVESGGGMVQAGGSLRLSCTASGLTDNSYAMGWFRRAPGKEREFLT GLTLSGGSTYYADSVKGRFTTSRDSQKNTVSLQMNSLKPEDTAVYYCAANRFGY GSAAYTPDNYNYWAQGTQVTVSS
SEQ ID NO: 1996 : P23ILPMP84H1 EVQLVESGGGVVQAGESLRLSCAASGRSFSNFEMGWFRQAPGTEREFVAT INWRGSSTYYADSVKGRFTISRDNAENTVYLQMSSLKPEDTAVYYCAAGRLFPSS RSRDYDYWGQGTQVTVSS
SEQ ID NO: 2002 : P23ILPMP84F1 EVXLVESGGGVVQAGESLRLSCAASGRSFSDYGMGWFRQPPGTEREFVA AINRRGSSTYYADSVKGRFTISRDSAKNTVYLQMSSLKPEDTAVYFCAAGQLYPS SASRDYDYWGQGTQVTVSS
SEQ ID NO: 2004 : P23ILPMP84A2 EVQLVESGGGLVQAGGSRRVSCAASGLTFSDYSMAWFRQAPGKEREFVA AHAWLASRTDYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAAYYCAAGQRY LSRVSQGYEYWGQGTQVTVSS
SEQ ID NO: 2006 : PMP119A1 EVQLVESGGGLVQAGGSLRLSCAASGGTFSTYAMGWFRQAPGKEREFVA ASNWSGGSTPYADSVMGRFTISRDNAKNTVYLQMGSLKPEDTAVYYCAADVSG WAHKGAKEYEYWGQGTQVTVSS
SEQ ID NO: 2007 : PMP119C2 EVQLVESGGGLVQPGGSLRLSCVASGSIFTANDMAWYRQAPGKQREWVA TITRGDITLYAHSVKGRFTISRDYAANTVYLQMNSLKPEDTAVYYCNAPNNYYG DWGQGTQVTVXS
SEQ ID NO: 2023 : PMP121B7 EVXLVESGGGVVQAGESLRLSCAASGRSFSNYEMGWFRQAPGTEREFXG TISRRGSSTYYADSVKGRFTISRDNAKNTVYLQMSSLKPEDTAVYYCAAGQLFPS XHSRDYDYWGQGTQVTVSS
SEQ ID NO: 2024 : PMP121F1 EVQLVESGGGLVXPGGSLRLSCVASGFPFSKTWMYWFRQAPGKGLEQVS SIHTGFGVGVTYYADAVKGRFTISRDNAKNTLYLQMNSLKPEDTALYYCATDIQ GTTRGQGTQVTVSS

Figure 22 (continued)

SEQ ID NO: 2028 : PMP122H7 EVQLVESGGGVVQAGESLRLSCAASGRSFSNYEMGWFRQAPGTEREFVG SINLRGSSTYYADSVKGRFTISRDNAKNTVYLQMSGLKPDDTAVYYCAAGWLYP SSRSRDYDYWGQGTQVTVSS
SEQ ID NO: 2033 : PMP123C1 EVQLVESGGGLVQPGGSLRLSCAASGSFFSIKSMGWYRQAPGKQRELVAG ITSGGTNYADSVKGRFTISRDSAKNTVYLQMNSLKPEDTAVYYCNAVGERLAYT GVTEYDYWGQGTLVTVSS
SEQ ID NO: 2504 : P23ILP40-PMP20F2 EVQLVESGGGLVQPGGSLRLSCAASGFSLDYTAIGWFRQAPGKEREVVSC FTSVPGSTYHADSVKGRFTIASDNAKNTVYLQMNDLKPEDTAVYYCATDAQTY YSGSYCGRTPQEYPYWGQGTQVTVSS
SEQ ID NO: 2505 : P23ILP40-PMP22D10 EVQLVESGGGLVQAGASLRLSCAASGRTFRSYNMGWLRQAPGKEREFVA TISWNAGIPYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAASNSWS SSARFYDYWGQGTQVTVSS
SEQ ID NO: 2506 : P23ILP40-PMP23A11 EVQLVESGGGLVPPGGSLRLSCAASGFTFSSYAMSWVRRAPGRGLEWISSI SSGSDTTHVAGSVRGRFTISRDNAKNTLYLQMNSLKPDDTAVYYCVRAYDSIVPS PTQRTNYEYRGQGTQVTVSS
SEQ ID NO: 2507 : P23ILP40-PMP21B9 EVQLVESGGGLVQAGGSLRLSCAASGSIFSINGMGWFRQAPGKEREFVSGI NWSGSGNTYHADSVKGRATISRDNAKNTVYLQMNSLKPEDTAVYYCAASERTY YSSSYYYRRFYDYWGQGTQVTVSS
SEQ ID NO: 2508 : P23ILP40-PMP21H10 EVQLVESGGGLVQAGGSLRLSCAASGRTFSTYPMGYFRQAPGKERELVA AISRGGGSTYYEDSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAVQLVGD SVSSYTRHYGYWGPGAQVTVSS
SEQ ID NO: 2509 : P23ILP40-PMP22D6 EVQLVESGGGLVQAGGSLRLSCAASGRTFNNYLVGWFRQAPGKEREFVA AVRWEYGITEYADSVKGRFTISRDNAKNTVYLQMSSLRPEETAVYYCAAGTVRR SKFSNPIDYDYWGQGTQVTVSS

Figure 23

SEQ ID NO: 1942 : P23ILP40-PMP84G12 EVQLVESGGRLVQAGGSLRLSCAASGRTFDSNPMGWFRQAPGKKREFVA IISGNGGITNYANSVKGRFTISRDNAKNTIYLQMNSLKPEDTAVYYCAASGLYGS GSVYDLMYDYWGQGTQVTVSS
SEQ ID NO: 1946 : P23ILP40+PMP81E10 EVQLVESGGGLVQAGGSLRLSCVASGRTFNTYGMGWFRQAPGKEREFVA ANNWSGGATSYADSVKGRFTISRDNAKNTVFLQMNTLKPEDTAVYYCAAADRG GGWLVVRENDYDYWGQGTQVTVSS
SEQ ID NO: 1948 : P23ILP40+PMP84D3 EVQLVESGGGLVQPGGSLRLSCAASGFSISNNWMYWFRQAPGKGHEWVS TIKTGAGSTAYADFVKGRFTISRDNAKNTLYLQMNSLKPEDTALYYCARDWAGT VRGQGTQVTVSS
SEQ ID NO: 1950 : P23ILP40+PMP84E5 EVQLVESGGGLVQPGGSLRLSCAASGFAFSNYWMYWIRQAPGKGLEWVS TIKTSGSAAYADFVKGRFTISRDNAKNTLYLQMNNLKPEDTALYYCSRDYAGTV RGQGTQVTVSS
SEQ ID NO: 1952 : P12ILPMP80A3 EVQLVESGGGLVQAGESLKLSCAASGRPFSTYTMGWFRQAPGKEREIVAA SNWSGGSKYYSDSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCATRESGEL RIREYEYDYWGQGTQVTVSS
SEQ ID NO: 1953 : P12ILPMP80A10 EVQLVESGGGVVQAGESLRLSCAASGRSFSNYEMGWFRQAPGTEREFVG TINRRGSSTYYADSVKGRFTISRDNAKNTVFLQMSSLKPEDTAVYYCAAGWLYP SSSSRDYDYWGQGTQVTVSS
SEQ ID NO: 1954 : P12ILPMP80F10 EVQLVESGGGLVQPGGSLRLSCAASGFTLDDYAIGWFRQAPGKEREGVSC ISSSDGSTYYADSVKGRFTISRDNATNTVYLQMNSLKPEDTAVYRCAAVVDYYC PGYESGVFRYGMDYWGKGTLVTVSS
SEQ ID NO: 1956 : P12ILPMP80H10 EVQLVESGGGVVQAGESLRLSCAASGGSFSNYEMGWFRQAPGTEREFVG TINRRGSSTYYEDSVKGRFTISRDNAKNTVYLQMSSLKPEDTANYYCAAGWLYP SSRSRDYDYWGQGTQVTVSS
SEQ ID NO: 1957 : P12ILPMP80E10 EVQLVESGGGLVQAGGSLXLSCAASGRTFSDYGMGWFRQAPGKEREFVA VINWSGGSTGYAASVKGRFTISRDNYKNTVYLQMNSLKPDDTAVYYCAADTLH GGAVTTTPARYDYWGQGTQVTVSS
SEQ ID NO: 1959 : P12ILPMP80B10 EVQLVESGGGLVQPGGSLRLSCAASGFTLSGSWMYWVRQAPGKGLEWV STIKPNGSTASADSVKGRFTISRDNAKNTLYLQMNSLKPEDTALYYCARDFSGNQ RGQGTQVTVSS

Figure 23 (continued)

SEQ ID NO: 1962 : P23ILPMP81A1 EVQLVESGGGLVQTGGSLRLSCAASVINFRLADMDWYRQALGKQRELVA SISTGYRTNYADFVKGRFTISRDNAKNTVYLQMDSLKPEDTAVYYCAARDLRGL RVDYWGQGTQVTVSS
SEQ ID NO: 1963 : P23ILPMP81B1 EVQLVESGGGLVQPGGSLRLSCAASGRFFSTYSMGWFRQVPGKEREPVA AVNWNGISTYYADSVKGRFTISRDNAENTVYLQMNSLKPEDTAVYLCARKRFQY IFGSQQPESDFDSWGQGTQVTVSS
SEQ ID NO: 1964 : P23ILPMP81C1 EVQLVESGGGSVQAGGSLRLSCAASGQITFSDDAMGWFRQAPGKEREFVS AINWSGGSTSYTDSVRGRFTISRHNAKNTVYLQMNSLKPEDTAVYYCASRPGGG LWTQTHEYAYWGQGTQVTVSS
SEQ ID NO: 1965 : P23ILPMP81H10 EVQLVESGGGVVRAGESLRLSCAASGRSFSNYEMGWFRQAPGTEREFVG SINRRGSSTYYADSVKGRFTISRDNAKNTVYLQMSSLKPEDTAVYYCAAGWLYP SSRSRDYDYWGQGTQVTVSS
SEQ ID NO: 1967 : P23ILPMP81F10 EVQLVESGGGLVQPGGSLRLSCAASGFTFSTHWMYWVRQAPGKGLEWV ATSTFNILTGTENTYYSDSVKGRFTISRDNAKNTLYLQMNGLKPEDTALYYCARD SSGNLKGQGTQVTVSS
SEQ ID NO: 1969 : P23ILPMP84D5 EVQLVESGGGVVQAGESLRLSCAASGRSFSDYEMGWFRQAPGTEREFVA TINWRGSSTYYADSVKGRFTISRDSAKNTVYLQMSSLKPLDTAVYYCAAGRLFPS SRSRDYDYWGQGTQVTVSS
SEQ ID NO: 1970 : P23ILPMP84A12 EVQLVESGGGVVQAGESLRLSCAASGRSFSDYEMGWFRQAPGTEREFVA SINRRGSSTFYADSVKGRFTISRDNTKNTVYLQMSSLKPEDTAVYLCAAGWLFPS SRSRDYDYWGQGTQVTVSS
SEQ ID NO: 1973 : P23ILPMP84A6 EVQLVESGGGLVQAGGSLRLSCAASGRTFSTYATGWFRQAPGKEREFVA ATRGSNGLAYYGNSAKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCASSNSRC IGDGCYDEPHEYAYWGQGTQVTVSS
SEQ ID NO: 1981 : P23ILPMP84D12 EVQLVESGGGVVQAGESLRLSCAASGRIFSDYEMGWFRQAPGTEREFVA AISWRGSSTYYADSVKGRFTISRDNAKNTVYLQMSSLKPEDTAVYYCAAGRLFP SSRSRDYDYWGQGTQVTVSS
SEQ ID NO: 1982 : P23ILPMP84D2 EVQLVESGGGLVQPGGSLRLSCAASGFNFSNYRMYWVRQAPGKGLEWV SSIGAIGNVPAYADFVKGRFTISRDNAKNTLYLEMSSLKVEDTALYYCARDYQGV VRGKGTLVTVSS

Figure 23 (continued)

SEQ ID NO: 1984 : P23ILPMP84E1 EVQLVESGGGLVQPGGSLRLSCAASGFTFSGYWMYWLRQAPGKGLEWV STIKTTGGGAYAEFVKGRFTISRDNAKNTLYLQMNNLKPEDTALYYCARDFEGT VRGQGTQVTVSS
SEQ ID NO: 1985 : P23ILPMP84E10 EVQLVESGGGVVQAGESLRLSCAASGYNVKDYEMGWFRQAPGTEREFA AAINWRGSSTYYADSVKGRFTISRDNAKNTVYLQMSSLKPEDTAVYYCAAGRLY PSSRSRDYDYWGQGTQVTVSS
SEQ ID NO: 1987 : P23ILPMP84E8 EVQLVESGGGLVQAGVSLRLSCAASGRAFSNFDMGWFRQAPGREREFVA AINRSGSSTYVSASVKGRFTISRDNAKNTMSLQMNNLKPEDTAVYYVCATGLLFPS SAERNYDYWGQGTQVTVSS
SEQ ID NO: 1988 : P23ILPMP84F2 QVQLVESGGGLVQPGGSLRLSCAASGFTFSSSWMYWVRQAPGKGLEWV ATVKTNNSTVYADFVKGRFTISRDNAKNTLYLRMNSLKPEDTALYYCARDYAG RLRGQGTQVTVSS
SEQ ID NO: 1990 : P23ILPMP84F6 EVQLVESGGGAVQAGESLRLSCAASGRSFSNYEMGWFRQAPGTERAFVG TISRRGSSTYYADSVKGRFTISRDNAKNTVYLQMSSLKPEDTAVYYCAAGQLFPS SNSRDYDYWGQGTQVTVSS
SEQ ID NO: 1993 : P23ILPMP84G11 EVQLVESGGGLVQAGGSLRLSCAASGRTFSTYATGWFRQAPGKEREFVSA MRGSNGLAYYANSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCASSESRCI GDGCYDEPHEYAYWGQGTQVTVSS
SEQ ID NO: 1994 : P23ILPMP84G4 EVQLVESGGGVVQAGESLRLSCAASGRSFSNYEMGWFRQAPGTEREFVA AISRRRSSTYYADSVKGRFTISRDNAKNTVYLQMSSLKPEDTAVYYCAAGALFPS SRSRDYDYWGQGTQVTVSS
SEQ ID NO: 1995 : P23ILPMP84G6 EVQLVESGGGVVQAGESLRLSCAASGRSFSNYEMGWFRQAPGTEREFVST ISRRGSSTYYADSVKGRFTISRDNAKNTVYLQMSSLKPEDTAVYYCAAGQLFPSS RPRDYDYWGQGTQVTVSS
SEQ ID NO: 1997 : P23ILPMP84H2 EVQLVESGGGVVQAGESLRLSCAASGRSFSNYEMGWFRQAPGTEREFVG TINRRGSSTYYADSVKGRFTISRDNAKNTVFLQMSSLKPEDTAVYYCAAGWLFPS SLSRDYDFWGQGTQVTVSS
SEQ ID NO: 1998 : P23ILPMP84H3 EVQLVESGGGLVQPGGSLRLSCAASGFAFSNRWMYWVRQAPGKGLEWV STIKPNGSTAYADFVKGRFTFSKDNAKNTLYLQMNSLKPEDTALYYCSTDYAGT VRGQGTQVTVSS

Figure 23 (continued)

SEQ ID NO: 1999 : P23ILPMP84H6 EVQLVESGGGVVQAGESLRLSCAASGRSFSNYEMGWFRQAPGTEREFVG TISRRGSSTYYADSVKGRFTISRDNAKNTVYLQMSSLKPEDTAVYYCAAGQLFPS SHSRDYDYWGQGTQVTVSS
SEQ ID NO: 2000 : P23ILPMP84H8 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSSVMFWLRQAPGKGLEWVST IKPSGSTIYPNPAKGRFTISRDNAKNTLYLQMDNLAPEDTALYYCARDIGGAVRG QGTQVTVSS
SEQ ID NO: 2001 : P23ILPMP84H9 EVQLVESGGGVVQAGESLRLSCAASGRSLNNEEMGWFRQAPGTEREFVA TISRRGTGTYYADSVKGRFTISRDNAKNTVYLQMSSLKPEDTAVYYCAAGQLFPS SRSRDYDYWGQGTQVTVSS
SEQ ID NO: 2003 : P23ILPMP84D8 EMQLVESGGGLVQPGGSLRLSCAASGFSISNNWMYWFRQAPGKGHEWV STIKTGAGSTAYADFVKGRFTISRDNAKNTLYLQMNSLKPEDTALYYCARDWAG TVRGQGTQVTVSS
SEQ ID NO: 2005 : P23ILPMP84E7 EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWMYWVRQAPGKELEWVS TISNSGFTTRYADSVKGRFTISRDNAKNTLYLQMNSLKPEDTSLYYCARDLGGAL RGQGTQVTVSS
SEQ ID NO: 2030 : PMP122A8 EVXLVESGGGVVQAGESLRLSCSASGRSFSNYEMAWFRQAPGTEREFVAT INRRGSSTYYADSVKGRFTISRBNAKNTXVLQMSSLKPEDTXVYYCAAGWLFPX SRSRDYDYWGQGTQVTVSS
SEQ ID NO: 2510 : P23ILP40+21C4 EVQLVESGGGLVQAGGSLRLSCAASGRTFSGYDMGWFRQAPGKEREFVA QISRHNSNTYYADAVKGRFTISRDNAKNTVSLQMNSLKPEDTAVYYCAIGSLFPS SRERDYDYWGQGTQVTVSS
SEQ ID NO: 2511 : P23ILP40+22D7 EVQLVESGGGLVQAGGSLRLSCASSGRTFSIYARGWFRQAPGKEREFVAA IRSGLTTYSDSVKGRFTISRDIAKNTVFLQMNSLKSEDTAVYYCAAAVNYFTDFT DYSKRDSYDYWGQGTQVTVSS
SEQ ID NO: 2512 : P23ILP40+22E11 EVQLVESGGGLVQAGGSLRLSCAASGRTFSWSAVGWFRQAPGKEREFVA AIRWSGGSPYYADSVKDRFTISRDNAKNTVYLQMNSLRPEDTAVYLCGETSLFPT SRGSHYDTWGQGTQVTVSS
SEQ ID NO: 2513 : P23ILP40+22C7 EVQLVESGGGLVQAGGSLRLSCAASGRTFSSDAVGWFRQAPGLERVFVA AIRWSGGSAYYADSAKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCGATSLFP SSRGSHYDSWGQGTQVTVSS

Figure 23 (continued)

SEQ ID NO: 2514 : P23ILP40+23E3 EVQLVESGGELVQAGGSLRLSCAASGSIVSISAMAWYRQAPGKQRERVAT ITRGGTPDYADSAKDRFTISRDNAKNTVSLQMNNLKPEDTAVYYCKAALRTPTH DYNYYDYWGQGTQVTVSS
SEQ ID NO: 2515 : P23ILP40+23H3 EVQLVESGGGLVQAGDSLRLSCAASGRSFSNDAMGWFRQAPGKERSFVA AINWSGELTGYAGSVKGRFTISRDGVENMVFLQMNSLVPEDTGVYYCAAVEGR DYYRGAQYYDYWGQGTQVTVSS
SEQ ID NO: 2516 : P23ILPMP3G10 EVQLVESGGGVVQAGESLRLSCAASGYNVKDYEMGWFRQAPGMEREFA AAISWRGSSTYYADSVKGRFTISRDNAKNTVYLQMSSLKPEDTAVYYCAAGRLY PSSRSRDYDYWGQGTQVTVSS
SEQ ID NO: 2517 : P23ILPMP4F3 EVQLVESGGGVVQAGESLRLSCAASGYNVKDYEMGWFRQAPGMEREFA AAISWRGSSTYYADSVKGRFTISRDNAKNTVYLQMSSLKPEDTAVYYCAAGRLY PSSRSRDYDYWGQGTQVTVSS
SEQ ID NO: 2518 : P23ILPMP3A10 EVQLVESGGGVVQAGESLRLSCAASGYNFKDHDLGWFRQAPGMEREFV AAISWRGSSTYYADSVKGRFTISRDNAKNTVYLQMSSLKPEDTAVYYCAAGRLY PSSRSRDYDYWGQGTQVTVSS
SEQ ID NO: 2519 : P23ILPMP3C7 EVQPVESGGGVVQAGESLRLSCAASGRSFSDYEMGWFRQAPGTEREFVA TINRRGSSTYYADSVKGRFTISRDNAKNTVYLQMSSLKSEDTAVYYCAAGWLYP SSRSRDYDYWGQGTQVTVSS
SEQ ID NO: 2520 : P23ILPMP3G9 EVQLVESGGGVVQAGESLRLSCAASGRSFSNYEMGWFRQAPGTEREFVG SINRRGSSTYYADSVKGRFTISRDNAKNTVYLQMSSLKPEDTAVYYCAAGWLYP SSRSRDYDYWGQGTQVTVSS
SEQ ID NO: 2521 : P23ILPMP3D4 EVQLVESGGGVVQAGETLRLSCAASGRSFSNYEMGWFRQAPGTEREFVG TINRRGSSTYYTDSVKGRFSISRDNAKNTMYLQMSSLKPEDTAVYYCAAGWLFP SSRSRDYDYWGQGTQVTVSS
SEQ ID NO: 2522 : P23ILPMP3H5 EVQLVESGGGVVQAGESLRLSCAASGRSFSNYEMGWFRQAPGTEREFVG AINRRGSSTYYADSAKGRFTISRDNAKNTVFLQMSSLKPEDTAVYYCAAGWLFP SSRSRDYDYWGQGTQVTVSS
SEQ ID NO: 2523 : P23ILPMP3A11 EVQLVESGGGVVQAGESLRLSCAASGRTFSNYEMGWFRQAPGTEREFVA SISRRYSTYYPDSVKGRFTISRDNAKNTVYLQMSSLKPDDTAVYYCAAGQLFPSS RSRDYDYWGQGTQVTVSS

Figure 23 (continued)

SEQ ID NO: 2524 : P23ILPMP3A7 EVQLVESGGGVVQAGESLRLSCAASGRSFSNYEMGWFRQAPGTEREFVA AISRRRSSTYYADSVKGRFTISRDNAKNTVYLQMSSLKPEDTAVYYCAAGALFPS SRSRDYDYWGQGTQVTVSS
SEQ ID NO: 2525 : P23ILPMP3F11 EVQLVESGGGLVQAGGSLRLSCAASGSIFSINAMGWFRQAPGKERQFVAA INWSTGSTYYSDSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYFCASGYLFPSS RGSQYDYWGQGTQVTVSS
SEQ ID NO: 2526 : P23ILPMP3C1 EVQLVESGGGSVQAGGSLRLSCKVSGIMFSDKGMGWFRQAPGKERETVA ATNWSGGSTYYADSVKGRFTISRDNYKNTLHLQMASLKPEDTGIYYCAAAGDS WNSRRIEDYDYWGQGTPVTVSS
SEQ ID NO: 2527 : P23ILPMP3B8 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSSVMFWLRQAPGKGLEWLST IKPTGSTIYPGSGKGRFTISRDNAKNTLYLQINNLKPEDTALYYCARDIGGTVRGQ GTQVTVSS
SEQ ID NO: 2528 : P23ILPMP3E1 EVQLVESGGGLVQAGGSLRLSCAASGIIFSDNTMGWFRQAPGKEREFVAA IAGRGSRLNYADSVKGRFTISRDNTKNTVYLQMNSLKPEDTAIYYCAAKPYGRV YYTEGSNYDYWGQGTQVTVSS

Figure 24

SEQ ID NO: 1947 : P23ILP40+PMP122H9 EVQLVESGGGLVQAGGSLRLSCVASGRAFNTYGMGWFRQAPGKEREFVA ANNWSGGATSYADSVKSRFTISRDNYKNTVFLQMNTLKPEDTAVYYCAAANRG GGWLTVRENDYDYWGQGTQVTVSS
SEQ ID NO: 1949 : P23ILP40+PMP121A8 EVQLVESRGGLVQPGGSLRLSCAASGFTFSSSWMYWVRQAPGKGLEWVA TIKTGGSAAYADFVKGRFTISRDDAKNTLYLQMNSLKPEDTAQYYCARDYAGRL RGQGTQVTVSS
SEQ ID NO: 1951 : P23ILP40+PMP121H1 EVQLVESGGGLVQPGGSLRLSCAASGFAITSYYMYWVRQAPGKGLEWVS TITTTGGRAYADYVKGRFTISRDNAKNTLYLQMNSLKPEDTALYYCARDLGGAV RGQGTQVTVSS
SEQ ID NO: 1960 : P12ILPMP80C3 EVQLVESGGGLVQPGGSLRLSCAASGRTFSTYAMGWFRQAPGKEREFVA ASNWSGGSKHYADSVLGRFTISRDNYKNTVFLQMNSLKPEDTAVYFCAARGSGE LRLREYEYDYWGQGTQVTVSS
SEQ ID NO: 1961 : P12ILPMP80D3 EVQLVESGGGLVQAGGSLRLSCAASGGTFGSTFMGWFRQTPGKEREFVA AINWSGTFTWYSDSVKGRFSISRDNANNTVHLQMNKLKFEDTAVYYCATDFNG GERRVPASYDSWGQGTQVTVSS
SEQ ID NO: 1966 : P23ILPMP81E2 RGALVESGGGLVQAGGSLRLSCAASGRPFSSVAMGWFRQAPGKEREFVA AITGDSRSTYYSDSLKGRFTISRDNAKNTVYLQMNSLKPEDTAIYYCAATTYISGT YYYLTKQDMYAYWGQGTQVTVSS
SEQ ID NO: 2008 : PMP119F3-B EVQLVESGGGLVQPGGSLRLSCAASGFTLDYYHIGWFRQAPGKEREGVSC IDSSDGSTYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAAGPTWTQ RNDRSWIFYEYDYWGQGTQVTVSS
SEQ ID NO: 2009 : PMP119F8 EVXLVESGGGSVQAGGSLGLSCTASEGTFSRYTLAWFRQEPGKEREFVAA ISLSGTTAFYSNSVEGRFTVSRDNAKNTEYLQMNSLKSEDTAVYYCAARSRDEFY YADDARYVYWGQGTQVTVSS
SEQ ID NO: 2010 : PMP119H3 EVQLVESGGGLVRAGGSLRLSCAASGRAFSNYAMGWFRRAPGRERELVG AITWSGGGTYYADSVKGRFTISRDNAKSTVYLQMNSLKPEDTAVYSCAAPRYER MMSRLEVDYGYWGQGTQVTVSS
SEQ ID NO: 2011 : PMP120C7 EVQLVESGGGFVQPGGSLRLSCAASASIFSGYTMGWYRQAPGKERELVTS ISHRGGTNYADSVKGRFTISRENAKSTVYLQMNSLKPEDTGVYYCNRLINEASW GQGTQVTVSS

Figure 24 (continued)

SEQ ID NO: 2012 : PMP120A7 EVQLVESGGGFAQPGGSLRLSCAASASIFSGYTMAWYRQAPGKERELVTS ISHRGGTNYADSVKGRFTISRENAKSTVYLQMDSLKPEDTGVYYCNRLINEASW GQGTQVTVSS
SEQ ID NO: 2013 : PMP120F7 EVQLVESGGGFVQPGGSLRLSCAASASIFSGYTMGWYRQAPGKERELVTS ISHRGGTNYADSVKGRFTISRENAKSTVYLQMNSLKPEDTGVYFCNRLINEASWG QGTQVTVSS
SEQ ID NO: 2014 : PMP120H7 EVQLVESGGGLVQPGGSLRLTCAASGSIASNSAMGWYRQLPGKQRELIAH ITSRGHTTYADFVKGRFTISRDNVKNMVYLQMNSLKPEDTAVYYCNKILHSDYW GQGTQVTVSS
SEQ ID NO: 2015 : PMP120H8 EVQLVESGGGLVQPGGSLRLPCVASGSIFRGNTMGWYRQTPGKQRELVA SITSRGYTSYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCNRIVVESQW GQGTQVTVSS
SEQ ID NO: 2016 : PMP120H9 EVQLVESGGGLVQPGGSPRLSCVASGSIFRGNTMGWYRQTPGKQRELVAS ITSRGYTSYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCNRIVVESQW GQGTQVTVSS
SEQ ID NO: 2017 : PMP120A8 EVQLVESGGGFVQPGGSLXLSCAASASIFSGYTMGWYRQAPGKERELVTS ISHRGGTNYADSVKGRFTISRENAKSTVYLQMNSLKPEDTGVYYCNRLINEASW GQGTQVTVSS
SEQ ID NO: 2018 : PMP120D7 EVQLVESGGGFVQPGGSLRLSCAASASIFSGYTMGWYRQAPGKERELVTS ISHRGGTNYAESVKGRFTISRXNAKSTVYLEMNSLKPEDTGVYYCNRLINEASWG QGTQVTVSS
SEQ ID NO: 2019 : PMP120 E7 EVXLVESGGGFVQPGGSLRLSCAASASIFSGYTMGWYRQAPGKERELVTS ISHRGGTNYADSVKGRFTISRXNAKSTVYLQMNSLKPEDTGVYYCNRLINEASW GQGTQVTVSS
SEQ ID NO: 2020 : PMP120 E8 EVQLVESGGGFVQPGGSLXLSCAASASIFSGYTMAWYRQAPGKERELVTS ISHRGGTNYADSVKGRFTISRENAKSTVYLQMNSLKSEDTGVYYCNRLINEASW GQGTQVTVSS
SEQ ID NO: 2021 : PMP120F9 EVQLVESGGGFVQPGGSLRLSCAASASIFSGYTMGWYRQAPGKERELVTS ISHRGGTNYADSVKGRFTISRENAKSTVYLQMNSLKPEDTGVYYCNRLINEASW GQGXQVTVSS

Figure 24 (continued)

SEQ ID NO: 2022 : PMP121B3 EVQLVESGGGLVQAGGSLRLSCAASIRTFSSYNMAWFRQAPGKEREFVTA IIQSGGTTYYDDSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAARSAYAS GIYYYTREVSYNYWGQGTQVTVSS
SEQ ID NO: 2025 : PMP122C7 EVQLVESGGGLVQPGGSLRLSCAASGFTLDDYTIAWFRQAPGKEREGVSC ISSSALITFYADSVKGRFTISRBNAKNTVYLQMNSLKPDDTAVYYCAADRYYYCS GWPDESAYWGQGTQVTVSS
SEQ ID NO: 2026 : PMP122 E7 EVQLVESGGGLVQPGGSLRLSCAASGFTLDDYTIAWFRQAPGKEREGVSC ISSSALITFYADSVKGRFTISRDNAKNTVYLQMNSLKPDDTAVYYCAADRYYYCS GWPDESAYWGQGTQVTVSS
SEQ ID NO: 2027 : PMP122F7 EVQLVESGGGLVQPGGSLRISCAASGFTLDDYTIAWFRQAPGKEREGVSCI SSSALITFYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADRYYYCS GWPDESAYWGQGTQVTVSS
SEQ ID NO: 2029 : PMP122H8 EVQLVESGGGLVQPGGSLRLSCAASGFTLDDYTIAWFRQAPGKEREGVSC ISSSALITFYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADRYYYCS GWPDENAYWGQGTQVTVSS
SEQ ID NO: 2031 : PMP123A1 EVQLVESGGGLVQAGGSLRLSCAASGPLFENYVIGWFRQGPGKEREGVSC IRCTGGSTTYADSVKGRFTLSRDNAKNTLYLQMNSLTPDDAAVYYCAKPRAGM AVYEYDAWGQGTQVTVSS
SEQ ID NO: 2032 : PMP123B1 EVQLVESGGGLVQPGGSLRLSCTASGLTFSTYGMGWFRQAPGKNREFVA AIKRGGSAYYSHPVRGRFTISRDNGKNTVYLQMNSLKPEDTAVYYCAADQDPQE LLPFGLANEYDYWGQGTQVTVSS
SEQ ID NO: 2034 : PMP124B1 EVQLVESGGGLVQPGSSLRLSCAASGFTLDDYTIAWFRQAPGKEREGVSCI SSVDGSTNYGYPMKGRFTISTDNAKNMVYLQMNSLKPEDTAVYYCAAMKMCT RAFYGDPVDYWGKGTLVTVSS
SEQ ID NO: 2035 : PMP124C1 EVQLVESGGGLVQAGGSLRLACAASGLAFSRSAMGWFRQAPGKERENVA AISGGGLITDYTDSVKGRFTVSRDNAKNTVYLQMNNLKPEDTAVYYCAASLXGS LTEYDYWGRGTQVTVSS
SEQ ID NO: 2036 : PMP124F1 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYMMSWVRQAPGKGLEWVS FISSGGGISSYADSVEGRFTISRDNAKNTLYLHMNSLKPEDTAVYYCTKGRGDTR YDYRGQGTQVTVSS

Figure 24 (continued)

SEQ ID NO: 2037 : PMP124G1 EVQLVESGGGLVQAGGSLRLSCAASGRTFSSYVMGWFRQAPGKEREFVA AISSGGSITDYGDSVKGRFTISRDNAKNTVNLQMNSLKPEDTAVYYCAAQDGRGI LTRANHYDYWGQGTQVTVSS
SEQ ID NO: 2529 : P23ILPMP122G9 EVQLVESGGGLVQAGGSLRLSCAASGFTFSSYWMYWFRQAPGKGLEWV SSINSGSGNTYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAIYYCAAARTFY SRTYYPVNRDEYDYWGQGTQVTVSS

Figure 25

SEQ ID NO: 2491 : P23ILPMP31D4 EVQLVESGGGLVQAGGSLRLSCAASGRTFSIYAMGWFRQAPGKEREFVA AITWIGDSTYYADSVKGRFTIARDNAKNTVYLQMNSLKPEDTAVYYCAAEREAT MTLNFDSWGQGTQVTVSS
SEQ ID NO: 2492 : P23ILPMP31H8 EVQLVESGGGLVQAGGSLRLSCAASGRSISSYAMGWFRQAPGKEREFVAT ITWSGGSTYYADSVKGRFTISRDNAKNVVYLQMNNLKPEDTAVYYCAADLSSGL DVDFGSWGQGTQVTVSS
SEQ ID NO: 2493 : P23ILPMP32C10 EVQLVESGGGLVQAGGSLRLSCAASGRTFSINALGWFRQAPGKEREFVAA VNWSGGNTYYADSVKGRFTISKDNAKNTVYLQMNSLKPDDTAVYYCAADEYG GISVDFGSWGQGTRVTVSS
SEQ ID NO: 2494 : P23ILPMP33G3 EVQLVESGGGLVQAGGSLRLSCAASGQTFSIHAMGWFRQAPGKEREFVA HISWSGGSTYYADSVKGRFAISRDNAKNTVYLQMNSLKPEDTAVYYCAADDMR ELVTTFHYWGQGTQVTVSS
SEQ ID NO: 2495 : P23ILPMP32E2 EVQLVESGGGLVQAGGSLRLSCAASGGTFSSYAMGWFRQAPGKERDFVA AIDWSGSTTTYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADMSHS PIEIDFGSWGQGTQVTVSS
SEQ ID NO: 2496 : P23ILPMP33G7 EVQLVESGGGLVQAGGSLRLSCAASGGTFSSYAIGWFRQAPGKEREFVAA ITWIERSTYYADSVKGRFTISRDNAKNTVYLQMNSLEPEDTAVYYCGADDRGDL MSVDFRSWGQGTQVTVSS
SEQ ID NO: 2497 : P23ILPMP33D8 EVQLVESGGGLVQAGGSLRLSCAASGRTFSIYYMGWFRQAPGKEREFVA AITWIGGDTYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAVDDRTN MSVDFGSWGQGTQVTVSS
SEQ ID NO: 2498 : P23ILPMP32B10 EVQLVESGGGLVQAGGSLRLSCAASGRSFSDYAMGWFRQTPGKEREFVA AISWSDGSTYYANSVKGRFTTSRDNAKNTVYLQMNNLKPEDTAVYYCAARRLV YYSDPKYDYWGQGTQVTVSS
SEQ ID NO: 2499 : P23ILPMP33G4 EVQLVESGGGLVQAGGSLRLSCAASGRTFSVYAMGWFRQAPGKEREFVA AITWSGGETYYANSVKGRFTISRDNAKNTVYLQMSGLKPEDTAVYYCAADPSSD LVTVFGDSASWGQGTQVTVSS
SEQ ID NO: 2500 : P23ILPMP30B10 EVQLVESGGGLVQAGGSLRLSCAASDRTFSSYAMAWFRQAPGKEREFVA QIIWSGGSTYYADSVKGRFTISGDNAKNTVYLQMNRLKPEDTAVYYCAADSGRT DWTADLYDYWGQGTQVTVSS
SEQ ID NO: 2501 : P23ILPMP31F9 EVQLVESGGGSVQTGGSLRLSCAASGLTPSFSLYNMAWFRQAPGKEREFV ASITWSGTSTSYLDSVKGRFIISRDNAKNTVYLQMNILKPEDTAVYYCAARARFA GTSMTPGGYVYWGQGTQVTVSS

Figure 26

SEQ ID NO: 2038 : P27ILPMP82-A1 EVQLVESGGGLVQAGGSLRLSCAASGFTFDDYAIGWFRQAPGKEREGVSC ISSSDGSTYYADSVKGRFTISSDNAKNTVYLQMNSLKPEDTAVYYCATGLLDCPQ RYGSSWYKGIGYWGQGTQVTVSS
SEQ ID NO: 2039 : P27ILPMP82-A3 EVQLVESGGGLVQVGGSLRLSCAASEGTFNSYTMGWFRQAPGKEREFVA AISWIASVTEHSDSVKGRFAISRDDAKNTVYLEINTLKPEDTATYYCARRRAPYY HISRRTDEYDFWGRGTQVTVSS
SEQ ID NO: 2040 : P27ILPMP82-A10 EVQLVESGGGLVQAGDSLRLSCAASGRAFSTYTMGWFRQAPGKEREFVA VRTGKTGGTRYADSVKGRFTISGDNAKNTVYLQMNRLEPEDTAVYHCAASAIPV VVTTPEEYDYWGQGTQVTVSS
SEQ ID NO: 2041 : P27ILPMP82-A11 EVQLVESGGGLVQAGGSLRLSCAASGFTLDDYAIGWFRQAPGKEREGVS CISSSDGSTDYADSVKGRFTISSDNAKNTVYLQMNSLKPEDTAVYYCAAYYKPW KYYCSDYGSYEHDAWGQGTQVTVSS
SEQ ID NO: 2042 : P27ILPMP82-B1 EVQLVESGGGLVQAGGSLRLSCAASGLTFSTYTMGWFRQAPGKEREFVST ISGSGLIKDSVKDRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAARLSGWTSSRD KDYGYWGQGTQVTVSS
SEQ ID NO: 2043 : P27ILPMP82-B3 EVQLVESGGGLVQPGGSLTLSCAASGFTLDRYAIGWFRQAPGKQREGVA CISNLNSTDSKTYYADFVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCATPPY SDSYCLHREWVGLVPDDYWGQGTQVTVSS
SEQ ID NO: 2044 : P27ILPMP82-B10 EVQLVESGGGLVQAGGSLRLSCAASGRTFSSYTFGWFRRAPDKDREFVAQ ISWIGGRTAYADSVKGRFTISRDNAKSTVYLQMNSLNTEDTAVYYCAADRDVW VLSEHLYDYWGQGTQVTVSS
SEQ ID NO: 2045 : P27ILPMP82B11 EVQLVESGGGLVQAGGSLRLSCAASGGTVTNYGRAWFRQAPGKERDFVA GVNWSGSSTHYLDSVKGRFTISRDNAKNTVYLQMNNLKPEDTAVYYCAAAEGS TWYLESNLYNHWGQGTQVTVSS
SEQ ID NO: 2046 : P27ILPMP82-C1 EVQLVESGGGLVQVGGSLRLSCAASEHTFNSYTMGWFRQAPGKEREFVA AISWIASVTEYSDSVKGRFTISRDDAKKTVHLEINNLKPEDTATYYCARRRMPYY HISRRADEYDFWGRGTQVTVSS
SEQ ID NO: 2047 : P27ILPMP82-C3 EVQLVESGGGLVQAGGSLELSCVASGLTFDTYVTGWFRQAPGKEREFVA TISGSGLITSYEDSVKDRVTISRDNAKNTVYLQMNSLKPGDTAVYYCAARLSGWT SSRDYDYDYWGQGTQVTVSS

Figure 26 (continued)

SEQ ID NO: 2048 : P27ILPMP82-C10 EVQLVESGGGLVQAGDSLRLSCAASGRTLANYGMGWFRQAPGKEREFV AGVNWSGSSTYYLDSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAAAEG STWYLQPNLYNLWGQGTQVTVSS
SEQ ID NO: 2049 : P27ILPMP82-C11 EVQLVESGGGLVQAGGSLRLSCAASGRTFSTYTMAWFRQTPGKERDLVA GITGSGLRTYYADSVKGRFTISRDNAKNTVDLQMNSLKPEDTAVYYCAASLTGW IPSSLQSYNYRGQGTQVTVSS
SEQ ID NO: 2050 : P27ILPMP82-D1 EVQLVESGGGLVQVGGSLRLSCAASERTFNSYTMGWFRQAPGKEREFVA AISWIASVTDYSDSVKGRFTISRDDDKNTVYLEINNLKPEDTATYYCARRRMPYY HISRRTDEYDFWGRGTQVTVSS
SEQ ID NO: 2051 : P27ILPMP82-D3 EVQLVESGGGLVQAGGSLRLSCAASGLTFSTYTMGWFRQAPGKEREFVA TISGSGLIKDSVKDRFTVSRDNAKNTVYLQMDSLKPEDTAVYYCAARLSGWTSS RDYDYNYWGQGTQVTVSS
SEQ ID NO: 2052 : P27ILPMP82-D10 EVQLVESGGGLVQAGDSVRLSCAASGRTFSVDTNTMGWYRQAPGKEHEF VAAISWSGTTVYADSVKGRFTISKDNAKNTIYLQMNSLKPEDTAVYVCAAERGK YATTGNYDYWGQGTQVTVSS
SEQ ID NO: 2053 : P27ILPMP82-D11 EVQLVESGGGLVQAGGSLRLSCAASGIIFTNYAMAWFRQAPGKEREFVAA ISWRNSSTNYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTALYTCAARWRPQV DYVDHWSYTYWGQGAQVTVSS
SEQ ID NO: 2054 : P27ILPMP82-E1 EVQLVESGGDLVQPGGSLRLSCEASGRIFGFNGMGWYRQVQGKQRELVA RILSSISTYYVDSVKGRFTISRDNARNTVYLQMDSLKPEDTAIYYCNFEDYWGRG TQVTVSS
SEQ ID NO: 2055 : P27ILPMP82-E3 EVQLVESGGGLVQAGGSLRLSCVASGRTFRSQSMGWFRQAPGKEREIVA AISSDGISTFYTDSVKGRFTISRDNAKNTGYLQMNSLKPEDTAVYYCAATTYSSY TTSGLLYPYWGQGTQVTVSS
SEQ ID NO: 2056 : P27ILPMP82-E10 EVQLVESGGGLVQPGGSLRLSCAASGITLDDYATGWFRQAPGKEREGVSC ISGNHGSTYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAALRWGCT LYGDYEGPYDYWGQGTQVTVSS
SEQ ID NO: 2057 : P27ILPMP82-E11 EVQLVESGGGLVQPGGSLRLSCAASGFTLDDYPIGWFRQAPGKEREGVSC ISSSDGSTYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAAVPYRTCE GYDYIHYYPDDYWGQGTQVTVSS

Figure 26 (continued)

SEQ ID NO: 2058 : P27ILPMP82-F1 EVQLVESGGGLVQAGGSLRLSCAASGGTFSTYVMAWFRQAPGKEREFVT TISGSGLRTSYKDSVEDRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAARLSGW TSSRDYDYNYWGQGTQVTVSS
SEQ ID NO: 2059 : P27ILPMP82-F3 EVQLVESGGGLVQAGDSLRLSCTASGGTFITTYVMGWFRQAPGKEREFV AAIRRSGESGDTSYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYLCAAGT MRAYNYWGQGTQVTVSS
SEQ ID NO: 2060 : P27ILPMP82-F10 EVQLVESGGGLVQAGGSLSLSCAASGLTFSTYGMGWFRQAPGKEREFVA FISVSGIRTYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAAALTGWI EARAEKYNYWGQGTQVTVSS
SEQ ID NO: 2061 : P27ILPMP82-F11 EVQLVESGGGLVQAGGSLRLSCAASGFTLDDYAIGWFRQAPGKEREGVS CISSSDGSTYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADLLRH RMSGWGPYWFLYEYDYWGQGTQVTVSS
SEQ ID NO: 2062 : P27ILPMP82-G3 KVQLVESGGGLVQVGGSLRLSCAASERTFDSYAMAWFRQAPGKEREFAA AISWIASVIEYSDSVKGRFTISRDDAKNTVYLEINNLKPEDTATYYCARRRMPYY HISRRTDEYDFWGRGTQVTVSS
SEQ ID NO: 2063 : P27ILPMP82-G10 EVQLVESGGGLVQAGGSLRLSCAASGRTFSNYPMGWFRQAPGNEREFVA AISSSGLNTDYTDSVKGRFTISRDNAANTVYLQMNSLKPEDTAVYYCARSSSGW MRARDFTSWGRGTQVTVSS
SEQ ID NO: 2064 : P27ILPMP82-G11 EVQLVESGGGLVQAGGSLRLSCAASGFTLDDYAKGWFRQAPGKEREGVS CISSSDGSTYYADSVKGRFTISSDNAKNTVYLQMNSLKPEDTAVYYCAALPLPHC PPPPSLYYSGSFYPDDYWGQGTQVTVSS
SEQ ID NO: 2065 : P27ILPMP82-H3 EVQLVESGGGLVQAGGSLSLSCEASGRIFNLNGMGWYRQAQGKQRELVA RILSSISTYYTDSVKGRFTISRDNARNTVYLQMDSLKPEDTAVYYCNFGDYWGQG TQVTVSS
SEQ ID NO: 2066 : P27ILPMP82-H10 EVQLVESGGGLVQAGGSLRLSCAASGFTLDDYAIGWFRQAPGKEREGVS CISSSIGSTYYADSVKGRFTISSDNAKNTVYLEMNSLKPEDTAVYYCAYLRWGCS LYLTDYDYWGQGTQVTVSS
SEQ ID NO: 2067 : P27ILPMP82-H11 EVQLVESGGGLVQAGGSLRLSCAASGFTLDDYAIGWFRQALGKEREGVS CISSSDGFTYYADSVKGRFTISSDNAKNTVYLQMNNLKPEDTADYYCAPFSATCN GDSSWWSVSRYFGSWGPGTQVTVSS

Figure 26 (continued)

SEQ ID NO: 2068 : P27ILPMP82-G1 EVQLVESGGGLVQAGGSLRLSCAASGRTFSDYAMGWFRQAPGKERECVG AISKSGGSTIYADSVKGRFTISRDNAKNTLYLQMNSLKPEDSAVYYCAADRRHGD VVAARASSWGQGTQVTVSS
SEQ ID NO: 2069 : P27ILPMPA2 EVQLVESGGGLVPAGDSLRLACAASERSFSSYNTGWFRQAPGKEREFVAA TSGSTFSTYYTDSVKGRFTISRDNAKNTVYLQMDNLKPEDTAVYYCAASTSGNA WFTVYYSTLGEYDYWGQGTQVTVSS
SEQ ID NO: 2070 : P27ILPMP82A8 EVQLVESGGGLVQAGGSLRLSCAASGFTLDDYAIGWFRQAPGKEREGISCI SSTDSSTYYVDSVKGRFTISSDNAKNTVYLQMNSLKPEDTAVYYCAALRFGCSY YYTEYDYWGQGTQVTVSS
SEQ ID NO: 2071 : P27ILPMP82C8 EVQLVESGGGLVQPGGSLRLSCAASGFTLDDYAIGWFRQAPGKEREGVSF ISSSGGSTYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADRRAGD LVRYEYDYRGQGTQVTVSS
SEQ ID NO: 2072 : P27ILPMP82B5 EVQLVESGGGLVQPGGSLTLSCAASGFSLEHYAVGWFRQAPGKEREGVS CIDMDGSSHYADVVRGRFTISRBBAANTVTLQMTGLKPEDAXXYNCAIEWACTA KXGTSRXDWRQWXYVDWTQGTQVTVSS
SEQ ID NO: 2073 : P27ILPMP82D8 EVQLVESGGGLVQAGGSLRLSCAASGFTLDDYAIGWFRQAPGKEREGVS CIXSSDGSTYYADSVKGRFTMSSDNAKNTVYLQMNSLKPEDTAVYYCADCDTV DGIWYQEGSRGQGTQVTVSS
SEQ ID NO: 2074 : P27ILPMP82F5 EVQLVESGGGLVQPGGSLRLSCAASGFTLDYYAFGWFRQAPGKEREGVS CISMVNDSTYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTXVYYCAAQPTYC ETLLRVGEWPGGIIPYDYWGQGTQVTVSS
SEQ ID NO: 2075 : P27ILPMP82F7 EVQLVESGGGLVQPGGSLRLSCAASGFTLDEHTIGWFRQAPGKEREGVSCI SSSDGSTYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAAYYCAATMYNGV VATAQFMGDMSADWYNYWGQGTXVTVSS
SEQ ID NO: 2076 : P27ILPMP82H8 EVQLVESGGGLVQAGGSLXLSCAVSGFTLDDYAIGWFRQAPGKEREGVS YISSSDGSTYYADSVKGRFTISSDNAKNTVYLQMNSLKPEDTAVYYCAAITWDTV VRTAPFEYEPDYWGQGTQVTVSS

Figure 27

SEQ ID NO: 2077 : PMPIL12RB1-134-5A EVQLVESGGGLVQAGGSLRLSCAVSGIAFRYNSVAWSRQAPGSQRELVA RITNSARTNYADSVKGRFTISRDNDKNMVYLQMNSLKPEDTAVYYCGAGRSMT GDVAYWGQGTQVTVSS
SEQ ID NO: 2078 : PMPIL12RB1-134-5B EVQLVESGGGLVQAGGSLRLSCAASGITFDDDYAIGWFRQAPGKEREGVS LISSSDGSTYYADSVKGRFTITSDNAKNTVYLQMNSLKPEDTAVYYCAADPTSGL PSDDEYDYWGQGTQVTVSS
SEQ ID NO: 2079 : PMPIL12RB1-134-5C EVQLVESGGGLVQAGGSLRLSCAASGIAFRYNSVAWSRQAPGSQREVVA GITNSARTNYADSVKGRFTISRDNDKKMVYLQMNSLKPEDTAVYYCGAGRSMA GDVAYWGQGTQVTVSS
SEQ ID NO: 2080 : PMPIL12RB1-134-5E EVQLVESGGGLVQAGGSLRLSCAASGIAFRYNSVAWSRQAPGSQRELVAS ISNSARTKYADSVKGRFTISRDNEKKMLYLQMDSLKPEDTAVYYCGAGRSMAG DVAYWGQGTQVTVSS
SEQ ID NO: 2081 : PMPIL12RB1-134-5F EVQLVESGGGLVQPGGSLRLSCVASGRPLTGSTMAWFRQAPGKECEFVA RISGSGTINYADSLRGRFTISRDVPKNTVWLQMDSLKPDDTAVYYCAAVKVAGS YEYWGQGTQVTVSS
SEQ ID NO: 2082 : PMPIL12RB1-134-5G EVQLVESGGGSVQTGGSLTLSCTASGRTGSTDGVGWFRQAPGKEREFVSA IKWIGGSKYYSNSAEGRFTIAVDNAKNTVYLQMNSLNPEDTAVYYCAAGAIMFP SRPRDFDFWGQGTQVTVSS
SEQ ID NO: 2083 : PMPIL12RB1-134-8B EVQLVESGGGLVQAGGSLRLSCAASGRTFSSYAMGWFRQAPGKEREFVA HINWNGGNTYYADSVRGRFIISRDNAKNTLYLQMNRLKPEDTAVYYCAARPDR VIVKWDEYDYWGQGTQVTVSS
SEQ ID NO: 2084 : PMPIL12RB1-134-8D EVQLVESGGGLVQPGESLTLSCAASGFTFSSYWMYWVRQAPGRELEWVA RIQPGSSYTAYADSVKGRFTISRDLAKNTLYLQMNRLKSDDTAVYYCAKDWEM AAPSLGQGTQVTVSS
SEQ ID NO: 2085 : PMPIL12RB1-134-9B EVQLVESGGGLVQAGGSLRLSCAASGTFLSINRMGWYRQAPGKERELVA VIISGGSTNYADSVKGRFTISRENAELTVYLQMNSLKPEDTAVYYCNVWINTDGI YTYEYWGQGTQVTVSS
SEQ ID NO: 2086 : PMPIL12RB1-134-9C EVQLVESGGGSVQPGGSLRLSCAASGLIVGRPAMGWYRQAPGKQRELVA IIGSGGNTNYPESVKGRFTIARENANNTVYLQMNSLKPEDTAVYHCNLHGTRFW GQGTQVTVSS

Figure 27 (continued)

SEQ ID NO: 2087 : PMPIL12RB1-148-2D EVQLVESGGGLVQAGGSLRLSCAASGLTFSSPAMAWFRQVPGKEREFVA TIRRSSAWTDYADSVKGRFTISRDRPTNTAYLQMSSLKPEDTAVYYCAADKISRG IDPNWTYWGRGTQVTVSS
SEQ ID NO: 2088 : PMPIL12RB1-148-2F EVQLVESGGGLVQPGGSLRLSCAVSGISVRSSVVNWYRQAPGKQRELVAL IMGGAIRKYADDVKGRFTISSDSAKNTVYLQMNSLRPEDTAVYYCSALEYWGQG TQVTVSS
SEQ ID NO: 2089 : PMPIL12RB1-148-2G EVQLVESGGGLVQPGGSLRLSCAVSGISVRSSVVNWYRQAPGKQRELVAL IMGGAITKYADDVKGRFTISSDSARNTVYLQMNSLRPEDTAVYSCSALEYWGQG TQVTVSS
SEQ ID NO: 2090 : PMPIL12RB1-148-3C EVQLVESGGGLAQEGGSLRLSCAASGRPLTTYGMAWFRQAPGKEREFVA RIGAEPGATVYGDSVKGRFTISRDNAKNTVYLQMNTLKPEDTAVYYCAADAPPF GPYYRESVYDYWGQGTQVTVSS
SEQ ID NO: 2091 : PMPIL12RB1-148-3F EVQLVESGGGLVTAGGSLRLSCAASGFRFSVYDMGWFRQAPGKEREFVA VIVGSRTTDYADSVKGRFIIFRDNAKNTLYLQMNGLKPDDTAVYYCARRVGTYE TVLGYDKWGQGTQVTVSS
SEQ ID NO: 2092 : PMPIL12RB1-148-5D EVQLVESGGGLVQAGGSLRLSCAASGFTFDDYAIGWFRQAPGKEREGVSC ISSSDGSTYYADSVKGRFTISSDNAKNTVYLQMNSLKPEDTAVYYCAAPLLRGGC PITYYSGSYPHVYHAMDYWGKGTLVTVSS
SEQ ID NO: 2093 : PMPIL12RB1-148-7A EVQLVESGGGLVQPGGSLRLSCAASGFTFSRAWMYWVRQAPGETLEWVS RIQPGGGSTSYADSVKGRFTISRDNAKNTLYLQMNSLKSEDTAVYYCAKDWEM AAPSLGQGTLVTVSS
SEQ ID NO: 2094 : PMPIL12RB1-148-7F EVQLVESGGGLVQPGGSLRLSCKASRSIFSINTMDWHRQVPGKQRELVAA IVNGVWKNYADSVKGRFTISRDNAENTVYLQMNNLKPEDTAVYYCHAKRGVSD YWGQGTQVTVSS
SEQ ID NO: 2095 : PMPIL12RB1-134-11G EVXLVESGGGLVETGGSLRLSCAARGRIKSIADMGWYRQAPGKQRELVA TITFGGTTTYADSAKGRFTISRDNAENTVYLQMNSLKPEDTAVYFCNADRILYVS EGLYRTEVDSWGQGTQVTVSS
SEQ ID NO: 2096 : PMPIL12RB1-134-8A EVQLVESGGGLVQPGGSLRLSCAASGFTFSRAWMYWVRQAPGETLEWVS RIQPGGGSTSYADSVKGRFTISRDNAKNTLYLQMNSLKSEDTAVYYCAKDWEM AAPSLGQGTQVTVSS

Figure 27 (continued)

SEQ ID NO: 2097 : PMPIL12RB1-134-4C EVQLMESGGGVVQVGGSLRLSCAASGGTLYSYIVGWFSQAPGQDREFVG AIEYSGGITDYKDSVKGRFTISKDNPKNTVFLQMDSLKPEDTAVYYCGLTRVVGA RNPGDYAYWGQGTQVTVSS
SEQ ID NO: 2098 : PMPIL12RB1-134-8C EVQLVESGGGLAQTGGSLTLSCAASGRTPSIVAMGWFRQIPGKDREPVGEI ILSKGFTYYADSVKGRFTISRANAKNTITMSLQMHSLKSEDTAVYYCAARQNWS GNPTRPNEYEYWGQGTQVTVSS
SEQ ID NO: 2099 : PMPIL12RB1-148-10E EVQLVESGGGLVQTGGSLRLSCAASGRTSRLVAMGWFRQTPGKEREFVG EIILSKDFTYYADSVKGRFTISRANAKNTITMYLQMSSLKSEDTAVYYCAARQNW SGHPARTNEYEYWGQGTQVTVSS
SEQ ID NO: 2100 : PMPIL12RB1-148-11F EVQLVESGGGLVQTGGSLRLSCAASGRTPSIVAMGWFRQTPGKEREFVGE IILSKGFTYYADSVKGRFTISRANAKNTITMYLQMHSLKSEDSAVYYCAARQNWS GGPTRTNEYEYWGQGTQVTVSS
SEQ ID NO: 2101 : PMPIL12RB1-148-12D EVQLVESGGGLVQTGGSLRLSCAASGRTPSIVAMGWFRQTPGKERESVGE IILSKGFTYYADSVKGRFTISRANAKNTITMYLQMNSLKSEDTAVYYCAARQNWS GNPTRTNEYEYWGQGTQVTVSS
SEQ ID NO: 2102 : PMPIL12RB1-148-9C EVQLVESGGGLVQTGGSLXLSCAASGRTPRLVAMGWFRQTPGKEREFVG EIILSKGFTYYADSVKGRFTISRVNAKNTITMYLQMNSLKSEDTAVYYCAGRQN WSGSPARTNEYEYWGQGTQVTVSS
SEQ ID NO: 2103 : PMPIL12RB1-148-9F EVQLVESGGGLVQTGGSLRLSCAASGRTPSIIAMGWFRQTPGKEREFVGEI ILSKGFTYYADSVKGRFTISRANAKNTITMYLQMNSLKSEDTAVYYCAARQNWS GNPTRTNEYEYWGQGTQVTVSS

Figure 28

SEQ ID NO: 2104 : PMPIL12RB2-135-10B EVQLVESGGGLVQTGGSLRLSCTHSGRPLSMFAVGWFRQAPGEQRVLVA AISRSGGATYYPDSVKGRFAISRDNAKNTVNLQMNSLTPEDTAVYYCAAALGGV YNAIANDYKYWGQGTQVTVSS
SEQ ID NO: 2105 : PMPIL12RB2-135-10C EVQLVESGGGSVQAGGSLRLSCAASGRTFSDYAMGWFRQAPGKEREFVA GISRSGSTTGYAGSVKGRFSISRDNAKNAVYLQMNSLKPEDTAVYYCASKRSPYT GIYYSDLSQSEDWGQGTQVTVSS
SEQ ID NO: 2106 : PMPIL12RB2-135-12A EVQLVESGGGLVQAGGSLRLSCAASGFAFDDYEIGWFRQAPGKEREGVA CINNSDGSTYYIDSVKGRFTISKDSATNTVYLQMSSLKPEDTAVYYCAADSWCTV VAGKIHPFDSWGQGTQVTVSS
SEQ ID NO: 2107 : PMPIL12RB2-135-12B EVQLVESGGGLVQAGGSLRLSCAASGRTSSTYVMGWFRQAPGKEREFVA GISWSAGNTRYADSVKGRFTISRDIAKNTFDLQMNSLKPEDTAVYYCAADRRYG GSLDPSAWDFWGQGTQVTVSS
SEQ ID NO: 2108 : PMPIL12RB2-135-12C EVQLVESGGGSVQAGGSLRLSCAASGRTFSSYVMGWFRQAPGKEREFVA AVSWSAGNTRYANSVKGRFTISRDIAKNTFYLQMNSLKPEDTAVYYCVADRRYG GSLDPSAWDFWGQGTQVTVSS
SEQ ID NO: 2109 : PMPIL12RB2-135-1A EVQLVESGGGLVQPGGSLRLSCAVSGFTSDYYVIAWFRQTPGHEREGVSSI RKGDGATYYADSVKGRFSISRDNAKNMVYLQMNSLKPEDTAVYTCAARYDTLL GGGRPREFPYWGQGTQVTVSS
SEQ ID NO: 2110 : PMPIL12RB2-135-1C EVQLVESGGGLVQPGGSLRLSCAVSGFTSDYYVVAWFRQTPGHEREGVSS IRIGDYATYYADSVKGRFSISRDNAKNMVYLQMNSLKPEDTAVYTCAARYDSHL GGGRPREFPYWGQGTQVTVSS
SEQ ID NO: 2111 : PMPIL12RB2-135-1D EVQLVESGGGLVQPGGSLRLSCAVSGFTSDYYVIAWFRQTPGHEREGVSSI RITDNATYYADSVKGRFSISRDNAKNMVFLQMNSLKPEDTAVYTCAARYETLLG GGRPREFPYWGQGTQVTVSS
SEQ ID NO: 2112 : PMPIL12RB2-135-1E EVQLVESGGGLVQPGGSLILSCAVSGFTSDYYVIAWFRQTPGHEREGVSSI RIGDGATYYADSVKGRFSISRDNAKNMVYLQMNSLKPEDTAVYTCAARYDTLL GGGRPREFPYWGQGTQVTVSS
SEQ ID NO: 2113 : PMPIL12RB2-135-1F EVQLVESGGGLVQPGGSLRLSCAASGFSFSRNWMYWVRQAPGKGLEWV GDISMEGTNTYYRDSVQGRFTISRDNAKNILYLQMNSLKSEDTAVYYCARAKNE GFVPGGYDFDYRGQGTQVTVSS

Figure 28 (continued)

SEQ ID NO: 2114 : PMPIL12RB2-135-1H EVQLVESGGGLVQPGGSLRLSCAVSGFTSDYYVIAWFRQTPGHEREGLSSI RIGDSATFYADSVKGRFSISRDNAKNMVYLQMNSLKPEDTAVYTCAGRYDTLLG GGRPREFPYWGQGTQVTVSS
SEQ ID NO: 2115 : PMPIL12RB2-135-3A EVQLVESGGGLVQPGGSLRLSCAVSGFTSDFYVIAWFRQTPGHEREGVSSI RIGDNAAYYADSVKGRFSISRDYAKNMVYLQMNSLKAEDTAVYTCAGRYDSNL GGGRPREFPYWGRGTQVTVSS
SEQ ID NO: 2116 : PMPIL12RB2-135-3B EVQLVESGGGLVQPGGSLRLSCAASGRTIAAYKMAWFRQAPDKARERVA LITSFGLTVYADSVKGRFTISRDNAYNTVYLQMNHLKFEDTAVYYCAAGQQDSS NYNSWGQGTQVTVSS
SEQ ID NO: 2117 : PMPIL12RB2-135-3D EVQLVESRGGLVQPGGSLRLSCAVSGFTSDYYVIAWFRQTPGHEREGVSSI RKGDGATYYADSVKGRFSISRDNAKNMVYLQMNSLKPEDTAVYTCAARYDTLL GGGRPREFPYWGQGTQVTVSS
SEQ ID NO: 2118 : PMPIL12RB2-135-7B EVQLVESGGRLVQAGDSLRLSCAASGRTFTSYRMGWFRQAPGKEREFVS ALRWSSGNIDYTYYADSVKGRFSISGDYAKNTVYLQMNSLKAEDTAVYYCAAS TRWGVMESDTEYTSWGQGTQVTVSS
SEQ ID NO: 2119 : PMPIL12RB2-135-8A EVQLVESGGGLVQAGGSLTLSCAASGRTFSSYHMGWFRQAPGKEREYVA AISWSGHMTYYKDSAKGRFTISRDNAKNTVYLQMNNLKPEDTAVYYCAARNRD YWSDFDVPGRYAYWGQGTQVTVSS
SEQ ID NO: 2120 : PMPIL12RB2-135-8C EVQLVESGGRLVQAGDSLRLSCAASGRTFTNYRVGWFRQAPGKEREFVS ALRWSSSNIDYTYYADSVKGRFSISGDYAKNTVYLQMNSLKAEDTAVYYCAAST SWGVLESDTEYTSWGQGTQVTVSS
SEQ ID NO: 2121 : PMPIL12RB2-135-1B EVQLVESGGGLVQPGGSLRLSCAVSGFTSEYYVIAWFRQTPGHEREGVSSI RIRDNAAYYADSVKGRFSISRDNHKNMVYLQMNSLKPEDTAVYTCAGRYDTLL GGGRPREFPYWGQGTQVTXSX
SEQ ID NO: 2122 : PMPIL12RB2-135-3C EVXLVESGGALVQDGGSLRLSCAASGLTLSNYVAAWFRQAPGKEREYVG SIRWSSEQTYYANSVKGRFSISRDNAKNAVYLEMNTLKPEDTAVYYCALGTSFSA LPKLYNYWGQGTQVTVSS
SEQ ID NO: 2123 : PMPIL12RB2-135-7A EVXLVESGGRLVQAGDSLRLSCAASGRTFISYRMGWFRQAPGKEREFVA ALRWSSSNIDYTYYADSVKGRFSISGDYAKNTVYLQMNSLKAEDTAVYYCAAST RWGVMESDTEYTSWGQGTQVTVSS
SEQ ID NO: 2124 : PMPIL12RB2-136-4B EVQLVESGGGLVQSGGSLRLSCAASEGTFTIYPLGWFRQAPGKDRKFVAA LPWSAGIPQYSDSVKGRFTISRDNAKNTVYLQMNNLKPEDTAVYYCAXKGRDDS YQPXNYWGQGTQVTVSS

Figure 29

SEQ ID NO: 2125 : PMPIL23R-136-11C EVQLVESGGGSAQAGGSLRLSCAASGGTFSSYTMAWFRQAPEKEHEFVA VISGTGDSAYYADSAKGRFTISRDNAKHTVYLQMNVLKPEDTALYYCAGPCMVL GERCILMPHNYWGQGTQVTVSS
SEQ ID NO: 2126 : PMPIL23R-136-12A EVQLVESGGGLVQAGGSLKLSCAASGRSFSRYAMGWFRQAPGKEREFVA ATRWNGGSTYYVDYADSVKGRFTVSRDNVKNTMYLQMNSLKPEDTAGYYCAG KGTVYSGSRPISDEYDYDYWGQGTQVTVSS
SEQ ID NO: 2127 : PMPIL23R-136-12B EVPLVESGGGLVQSGGSLRLSCAASGSFDSDTVMAWYRQAPGKQRDFVA AVTGTGGTNYADSVKGRFSISRDNAKNTVYLQMNSLKPEDMGVYYCYMRILGG GRYWGQGTQVTVSS
SEQ ID NO: 2128 : PMPIL23R-136-12C EVQLVESGGGLVQAGGSLRLSCAASERTVSTYTSGWFRQAPGKERDLVA AIRWSDDFTYYADSVKGRFTISRDNAKNTVYLQMNSLKVEDTAVYYCAGHSFSA LIPPVSFWPSWGQGTQVTVSS
SEQ ID NO: 2129 : PMPIL23R-136-4C EVQLVESGGGLVQAGGSLRLSCAASGTIFRIENMYWFRQAPGNQREWVA RISRESGTSYADSVKDRFTISRDNAKNTVYLQMNSLKPGDTAVYYCTADVQTNS RGAQQIFRGQGTQVTVS
SEQ ID NO: 2130 : PMPIL23R-136-4D EVQLVESGGGLVQAGGSLRLSCAASGSIFRINNMYWFRQAHENQREWVA RITRESDTTYADSVKDRFTISRDNAKNTVYLQMNSLKPGDTAVYYCTADVQTNS RDAQQIFRGQGTRVTVSS
SEQ ID NO: 2131 : PMPIL23R-150-11A EVQLVESGGALVQPGESLRLSCVVSGDTSTYHAIGWFRQAPGKGREGVSC INRSDGTTAYADSVKGRFTISRDKAKNTVYLQMNALRPEDTAVYSCAADPMLYC DTDYEPQTTDFTSWGRGTQVTVSS
SEQ ID NO: 2132 : PMPIL23R-150-11F EVQLVESGGGSVQVGASLRLSCAARGRALSNYGVGWFRQAPGKEREFVA SVSWNGGNKNYRSSVKGRFTISRDNANDTVFLQMNSLKPEDTAVYYCSADVRP YGLGPRSDERVADWGQGTQVTVSS
SEQ ID NO: 2133 : PMPIL23R-150-11G EVQLVESGGGLVQAGGSLRVSCLASGNIVSRNVMAWYRQAPGKQRELV ASVDTGGSTLYADSVKGRFTISRDSAKSMVYLQMNSLKPEDTAVYYCNVPRYGY WGQGTQVTVSS
SEQ ID NO: 2134 : PMPIL23R-150-2C EVQLVESGGGLVQSGGSLRLSCAASEGTFTIYPLGWFRQAPGKDRKFVAA LPWSAGIPQYSDSVKGRFTISRDNAKNTVYLQMNNLKPEDTAVYYCAAKGRDDS YQPWNYWGQGTQVTVSS

Figure 29 (continued)

SEQ ID NO: 2135 : PMPIL23R-150-2D EVQLVESGGGLVQPGGSLTLSCVASGRTFSTDVMGWFRQAPGKEREFVA AHRTSGISTVYAASVKGRFTISRDNAKNTVYLGMKSLKPEDTAVYYCAAGSDAS GGYDYWGQGTQVTVSS
SEQ ID NO: 2136 : PMPIL23R-150-2G EVQLVESGGGLVQPGGSLTLSCVASGRTFSTDVMGWFRQAPGKEREFVA AHRRNGISTVYAASVKGRFTISRDNAKNTVYLGMKSLKPEDTAVYYCAAGSDAS GGYDYWGQGTQVTVSS
SEQ ID NO: 2137 : PMPIL23R-150-7H EVQLVESGGGLVQAGGSLRLSCAASGRTFSSYAMGWFRQAPGKDREFVA AISWIGESTYYADSVKGRFTISRDNAKNTVYLRMNSLKPEDTAVYYCAADLYYT AYVAAADEYDYWGQGTQVTVSS
SEQ ID NO: 2138 : PMPIL23R-150-9H EVQLVESGGGLVQAGGSLKLSCAASGRSFSRYAMGWFRQAPGKEREFVA ATRWNGGSTYYADYADSVKGRFTVSRDNAKNTMYLQMNSLKPEDTAVYYCAG KGTVYSGSSPISDEYGYDYWGQGTQVTVSS
SEQ ID NO: 2139 : PMPIL23R-150-1B EVQLVESGGGLMQAGDSLRLSCAASGRTSYIYTMAWFRQAPGKEREFVA AIRWSDTTTYYADSVKGRFTASRDNAKNTMYLQMNSLKPMDTAVYYCAVKRD SSTYYRVRNYDYWGQGTQVTVSS
SEQ ID NO: 2140 : PMPIL23R-150-2B EVQLVESGGGLVQAGGSLRLSCAAAERTFSDYAVGWFRQAPGKEREFVS AVSRFGTITNYADSVQGRFTISRDNAKNTVYLQMTGLKFEDTAVYYCAAARTVY VGHLYYIDNEYAYWGQGTQVTVSS
SEQ ID NO: 2141 : PMPIL23R-136-4B EVQLVESGGGLVQSGGSLRLSCAASEGTFTIYPLGWFRQAPGKDRKFVAA LPWSAGIPQYSDSVKGRFTISRDNAKNTVYLQMNNLKPEDTAVYYCAXKGRDDS YQPXNYWGQGTQVTVSS

Figure 30

SEQ ID NO: 2142 : 23IL121A2-35GS-119G7 (P23IL0004)
EVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVA
AIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGIPY
STSDRVIKGVNDYDYWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSG
GGGSGGGGSEVQLVESGGGLVQAGGSLTLSCAVSGLTFNNYAMGWFRQVPGKE
REFVAAISRSGLRTFYSDSVKGRFTISRDSAKSTVYVQMNNLKPEDTAVYFCAAD
RRTYYSEGPSLTDTLRYDYWGQGTQVTVSS

SEQ ID NO: 2143 : 23IL121A2-35GS-81G2 (P23IL0005)
EVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVA
AIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGIPY
STSDRVIKGVNDYDYWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSG
GGGSGGGGSEVQLVESGGGLVQPGGSLRLSCIASGLPFSTKSMGWFRQAPGKER
EFVARISPGGTSRYYGDFVKGRFAISRDNAKNTTWLQMNSLKAEDTAVYYCASG
ERSTYIGSNYYYRTNEYDYWGTGTQVTVSS

SEQ ID NO: 2144 : 23IL121A2-35GS-81A12 (P23IL0003)
EVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVA
AIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGIPY
STSDRVIKGVNDYDYWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSG
GGGSGGGGSEVQLVESGGGLVQAGGSLRLSCAASGRTLSSYAMGWFRQAPGKE
REFVARISQGGTAIYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAK
DPSPYYYRGSAYLLSGSYDSWGQGTQVTVSS

SEQ ID NO: 2145 : 23IL121A2-35GS-124H5 (P23IL0001)
EVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVA
AIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGIPY
STSDRVIKGVNDYDYWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSG
GGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMYWVRQAPGKG
LERVAPLNPGGTITLYADFVKSRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAAP
SGTLYTRNKSGYIYWGQGTQVTVSS

SEQ ID NO: 2146 : 23IL121A2-35GS-124H2 (P23IL0002)
EVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVA
AIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGIPY
STSDRVIKGVNDYDYWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSG
GGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFYLDDYAIAWFRQAPGKER
EGVSGIDSGDGSTYYADSVKGRFTISSDNAKNTVYLQMNSLRPEDTAVYYCARV
RTGWGLNAPDYAMDYWGKGTLVTVSS

SEQ ID NO: 2147 : P 23IL121A2-35GS-124H5 (P23IL0007)
EVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVA
AIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGIPY
STSDRVIKGVNDYDYWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSG
GGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMYWVRQAPGKG
LERVAPLNPGGTITLYADFVKSRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAAP
SGTLYTRNKSGYIYWGQGTQVTVSS

Figure 30 (continued)

SEQ ID NO: 2148 : P 23IL121A2-35GS-124H2 (P23IL0006)
EVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVA
AIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGIPY
STSDRVIKGVNDYDYWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSG
GGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFYLDDYAIAWFRQAPGKER
EGVSGIDSGDGSTYYADSVKGRFTISSDNAKNTVYLQMNSLRPEDTAVYYCARV
RTGWGLNAPDYAMDYWGKGTLVTVSS

SEQ ID NO: 2149 : P 23IL121A2-35GS-124C4 (P23IL0009)
EVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVA
AIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGIPY
STSDRVIKGVNDYDYWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSG
GGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTLDDYAIAWFRQAPGKER
EGVSGIDSGDGSAYYADSVKGRFTISSDNAKNTVYLQMNSLRPEDTAVYYCARV
RTGWGLNAPDYAMDYWGKGTLVTVSS

SEQ ID NO: 2150 : P 23IL121A2-35GS-119C9 (P23IL0008)
EVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVA
AIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGIPY
STSDRVIKGVNDYDYWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSG
GGGSGGGGSEVQLVESGGGLVQAGGSLTLSCAASVRTFSTSAMGWFRQAPGKE
REFVAAINWNAGSTYHADSVKGRFTISGDNAKNSVFLQMNGLKPEDTAVYYCA
AQASGRVTYFDYAYRRGSNYDYWGQGTQVTVSS

SEQ ID NO: 2151 : P 23IL119A3-35GS-119B2 (P23IL0012)
EVQLVESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAWHRQAPG
MQRELVATINSGSRTNYADSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQ
TSGSGSPNFWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGG
GSEVQLVESGGGLVQAGGSLRLSCAAPGRTFSEYAMGWFRQNPGNEREFVAAIS
RGGGFTDYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADGRSSFGI
AKRSRYEYDSWGQGTQVTVSS

SEQ ID NO: 2152 : P 23IL119A3-35GS-119C9 (P23IL0017)
EVQLVESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAWHRQAPG
MQRELVATINSGSRTNYADSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQ
TSGSGSPNFWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGG
GSEVQLVESGGGLVQAGGSLTLSCAASVRTFSTSAMGWFRQAPGKEREFVAAIN
WNAGSTYHADSVKGRFTISGDNAKNSVFLQMNGLKPEDTAVYYCAAQASGRVT
YFDYAYRRGSNYDYWGQGTQVTVSS

SEQ ID NO: 2153 : P 23IL119A3-35GS-119G7 (P23IL0013)
EVQLVESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAWHRQAPG
MQRELVATINSGSRTNYADSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQ
TSGSGSPNFWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGG
GSEVQLVESGGGLVQAGGSLTLSCAVSGLTFNNYAMGWFRQVPGKEREFVAAIS
RSGLRTFYSDSVKGRFTISRDSAKSTVYVQMNNLKPEDTAVYFCAADRRTYYSE
GPSLTDTLRYDYWGQGTQVTVSS

Figure 30 (continued)

SEQ ID NO: 2154 : P 23IL119A3-35GS-123F1 (P23IL0014) EVQLVESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAWHRQAPG MQRELVATINSGSRTNYADSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQ TSGSGSPNFWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGG GSEVQLVESGGGLVQAGGSLRLSCAASGRTSSSYSMGWFRQAPGKEREFVAYIS GGGLTIYYAHSVKGRFTISRDNAKNTVYLQMNSLNSADTAVYSCAAPKRDLYLG SRYPVPESYDYWGQGTQVTVSS
SEQ ID NO: 2155 : P 23IL119A3-35GS-124H2 (P23IL0015) EVQLVESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAWHRQAPG MQRELVATINSGSRTNYADSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQ TSGSGSPNFWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGG GSEVQLVESGGGLVQPGGSLRLSCAASGFYLDDYAIAWFRQAPGKEREGVSGIDS GDGSTYYADSVKGRFTISSDNAKNTVYLQMNSLRPEDTAVYYCARVRTGWGLN APDYAMDYWGKGTLVTVSS
SEQ ID NO: 2156 : P 23IL119A3-35GS-124H5 (P23IL0016) EVQLVESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAWHRQAPG MQRELVATINSGSRTNYADSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQ TSGSGSPNFWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGG GSEVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMYWVRQAPGKGLERVAPL NPGGTITLYADFVKSRFTISRDNAKNTVYLQMNSLKPEDTAVYYVCAAPSGTLYTR NKSGYIYWGQGTQVTVSS
SEQ ID NO: 2157 : P 23IL119A3-35GS-81A12 (P23IL0010) EVQLVESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAWHRQAPG MQRELVATINSGSRTNYADSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQ TSGSGSPNFWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGG GSEVQLVESGGGLVQAGGSLRLSCAASGRTLSSYAMGWFRQAPGKEREFVARIS QGGTAIYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAKDPSPYYRG SAYLLSGSYDSWGQGTQVTVSS
SEQ ID NO: 2158 : P 23IL119A3-35GS-81G2 (P23IL0014) EVQLVESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAWHRQAPG MQRELVATINSGSRTNYADSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQ TSGSGSPNFWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGG GSEVQLVESGGGLVQPGGSLRLSCIASGLPFSTKSMGWFRQAPGKEREFVARISP GGTSRYYGDFVKGRFAISRDNAKNTTWLQMNSLKAEDTAVYYCASGERSTYIGS NYYRTNEYDYWGTGTQVTVSS
SEQ ID NO: 2159 : P 23IL119A3-35GS-124C4 (P23IL0018) EVQLVESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAWHRQAPG MQRELVATINSGSRTNYADSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQ TSGSGSPNFWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGG GSEVQLVESGGGLVQPGGSLRLSCAASGFTLDDYAIAWFRQAPGKEREGVSGIDS GDGSAYYADSVKGRFTISSDNAKNTVYLQMNSLRPEDTAVYYCARVRTGWGLN APDYAMDYWGKGTLVTVSS

Figure 30 (continued)

SEQ ID NO: 2160 : P23IL121A2-35GS-121A2 (P23IL0028) EVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVA AIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGIPY STSDRVIKGVNDYDYWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSG GGGSGGGGSEVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKER EFVAAIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRK GIPYSTSDRVIKGVNDYDYWGQGTQVTVSS
SEQ ID NO: 2161 : P23IL119G7-35GS-121A2 (P23IL0022) EVQLVESGGGLVQAGGSLTLSCAVSGLTFNNYAMGWFRQVPGKEREFVA AISRSGLRTFYSDSVKGRFTISRDSAKSTVYVQMNNLKPEDTAVYFCAADRRTYY SEGPSLTDTLRYDYWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGG GSGGGGSEVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREF VAAIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGI PYSTSDRVIKGVNDYDYWGQGTQVTVSS
SEQ ID NO: 2162 : P23IL123F1-35GS-121A2 (P23IL0023) EVQLVESGGGLVQAGGSLRLSCAASGRTSSSYSMGWFRQAPGKEREFVA YISGGGLTIYYAHSVKGRFTISRDNAKNTVYLQMNSLNSADTAVYSCAAPKRDL YLGSRYPVPESYDYWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGG GSGGGGSEVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREF VAAIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGI PYSTSDRVIKGVNDYDYWGQGTQVTVSS
SEQ ID NO: 2163 : P23IL119B2-35GS-121A2 (P23IL0021) EVQLVESGGGLVQAGGSLRLSCAAPGRTFSEYAMGWFRQNPGNEREFVA AISRGGGFTDYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADGRSS FGIAKRSRYEYDSWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGG SGGGGSEVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFV AAIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGIP YSTSDRVIKGVNDYDYWGQGTQVTVSS
SEQ ID NO: 2164 : P23IL81G2-35GS-121A2 (P23IL0020) EVQLVESGGGLVQPGGSLRLSCIASGLPFSTKSMGWFRQAPGKEREFVARI SPGGTSRYYGDFVKGRFAISRDNAKNTTWLQMNSLKAEDTAVYYCASGERSTYI GSNYYRTNEYDYWGTGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGG SGGGGSEVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFV AAIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGIP YSTSDRVIKGVNDYDYWGQGTQVTVSS
SEQ ID NO: 2165 : P 23IL81A12-35GS-121A2 (P23IL0019) EVQLVESGGGLVQAGGSLRLSCAASGRTLSSYAMGWFRQAPGKEREFVA RISQGGTAIYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAKDPSPY YRGSAYLLSGSYDSWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGG GSGGGGSEVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREF VAAIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGI PYSTSDRVIKGVNDYDYWGQGTQVTVSS

Figure 30 (continued)

SEQ ID NO: 2166 : P 23IL124H5-35GS-121A2 (P23IL0025) EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMYWVRQAPGKGLERV APLNPGGTITLYADFVKSRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAAPSGTL YTRNKSGYIYWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSG GGGSEVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVAA IRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGIPYS TSDRVIKGVNDYDYWGQGTQVTVSS
SEQ ID NO: 2167 : P 23IL124H2-35GS-121A2 (P23IL0024) EVQLVESGGGLVQPGGSLRLSCAASGFYLDDYAIAWFRQAPGKEREGVS GIDSGDGSTYYADSVKGRFTISSDNAKNTVYLQMNSLRPEDTAVYYCARVRTGW GLNAPDYAMDYWGKGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGS GGGGSEVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVA AIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGIPY STSDRVIKGVNDYDYWGQGTQVTVSS
SEQ ID NO: 2168 : P 23IL124C4-35GS-121A2 (P23IL0027) EVQLVESGGGLVQPGGSLRLSCAASGFTLDDYAIAWFRQAPGKEREGVSG IDSGDGSAYYADSVKGRFTISSDNAKNTVYLQMNSLRPEDTAVYYCARVRTGW GLNAPDYAMDYWGKGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGS GGGGSEVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVA AIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGIPY STSDRVIKGVNDYDYWGQGTQVTVSS
SEQ ID NO: 2169 : P 23IL119C9-35GS-121A2 (P23IL0026) EVQLVESGGGLVQAGGSLTLSCAASVRTFSTSAMGWFRQAPGKEREFVA AINWNAGSTYHADSVKGRFTISGDNAKNSVFLQMNGLKPEDTAVYYCAAQASG RVTYFDYAYRRGSNYDYWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGG SGGGGSGGGGSEVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPG KEREFVAAIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCA LRKGIPYSTSDRVIKGVNDYDYWGQGTQVTVSS
SEQ ID NO: 2530 : P 23IL0029 ; P 23IL121A2-9GS-119G7 EVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVA AIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGIPY STSDRVIKGVNDYDYWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGGSL RLSCIASGLPFSTKSMGWFRQAPGKEREFVARISPGGTSRYYGDFVKGRFAISRDN AKNTTWLQMNSLKAEDTAVYYCASGERSTYIGSNYYRTNEYDYWGTGTLVTVS S
SEQ ID NO: 2531 : P 23IL0030 : P 23IL121A2-9GS-119G7 EVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVA AIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGIPY STSDRVIKGVNDYDYWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQAGGSL TLSCAVSGLTFNNYAMGWFRQVPGKEREFVAAISRSGLRTFYSDSVKGRFTISRD SAKSTVYVQMNNLKPEDTAVYFCAADRRTYYSEGPSLTDTLRYDYWGQGTQVT VSS

Figure 30 (continued)

SEQ ID NO: 2532 : P23IL0031 : P 23IL121A2-9GS-124C4 EVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVA AIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGIPY STSDRVIKGVNDYDYWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGGSL RLSCAASGFTLDDYAIAWFRQAPGKEREGVSGIDSGDGSAYYADSVKGRFTISSD NAKNTVYLQMNSLRPEDTAVYYCARVRTGWGLNAPDYAMDYWGKGTQVTVS S
SEQ ID NO: 2533 : P23IL0032 : P 23IL119A3-9GS-81G2 EVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVA AIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGIPY STSDRVIKGVNDYDYWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSL RLSCAASGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRD NAKTTLYLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEVQ LVESGGGLVQPGGSLRLSCIASGLPFSTKSMGWFRQAPGKEREFVARISPGGTSRY YGDFVKGRFAISRDNAKNTTWLQMNSLKAEDTAVYYCASGERSTYIGSNYYRTN EYDYWGTGTQVTVSS
SEQ ID NO: 2534 : P23IL0033 : P 23IL121A2-20GS-124C4 EVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVA AIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGIPY STSDRVIKGVNDYDYWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSEVQLVES GGGLVQPGGSLRLSCAASGFTLDDYAIAWFRQAPGKEREGVSGIDSGDGSAYYA DSVKGRFTISSDNAKNTVYLQMNSLRPEDTAVYYCARVRTGWGLNAPDYAMDY WGKGTQVTVSS
SEQ ID NO: 2535 : P23IL0034 : P 23IL121A2-9GS-ALB1-9GS-81G2 EVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVA AIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGIPY STSDRVIKGVNDYDYWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSL RLSCAASGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRD NAKTTLYLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEVQ LVESGGGLVQPGGSLRLSCIASGLPFSTKSMGWFRQAPGKEREFVARISPGGTSRY YGDFVKGRFAISRDNAKNTTWLQMNSLKAEDTAVYYCASGERSTYIGSNYYRTN EYDYWGTGTQVTVSS
SEQ ID NO: 2536 : P23IL0035 : P 23IL121A2-9GS-ALB1-9GS-119G7 EVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVA AIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGIPY STSDRVIKGVNDYDYWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSL RLSCAASGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRD NAKTTLYLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEVQ LVESGGGLVQAGGSLTLSCAVSGLTFNNYAMGWFRQVPGKEREFVAAISRSGLR TFYSDSVKGRFTISRDSAKSTVYVQMNNLKPEDTAVYFCAADRRTYYSEGPSLTD TLRYDYWGQGTQVTVSS

Figure 30 (continued)

SEQ ID NO: 2537 : P23IL0036 : P 23IL119A3-9GS-ALB1-9GS-81G2 EVQLVESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAWHRQAPG MQRELVATINSGSRTNYADSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQ TSGSGSPNFWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCAAS GFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLY LQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEVQLVESGGG LVQPGGSLRLSCIASGLPFSTKSMGWFRQAPGKEREFVARISPGGTSRYYGDFVK GRFAISRDNAKNTTWLQMNSLKAEDTAVYYCASGERSTYIGSNYYRTNEYDYW GTGTQVTVSS
SEQ ID NO: 2538 : P23IL0037: P 23IL121A2-9GS-ALB1-9GS-124C4 EVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVA AIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGIPY STSDRVIKGVNDYDYWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSL RLSCAASGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRD NAKTTLYLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEVQ LVESGGGLVQPGGSLRLSCAASGFTLDDYAIAWFRQAPGKEREGVSGIDSGDGSA YYADSVKGRFTISSDNAKNTVYLQMNSLRPEDTAVYYCARVRTGWGLNAPDYA MDYWGKGTQVTVSS
SEQ ID NO: 2539 : P23IL0038 : P 23IL119A3-35GS-81G2-GGGC-PEG40 EVQLVESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAWHRQAPG MQRELVATINSGSRTNYADSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQ TSGSGSPNFWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGG GSEVQLVESGGGLVQPGGSLRLSCIASGLPFSTKSMGWFRQAPGKEREFVARISP GGTSRYYGDFVKGRFAISRDNAKNTTWLQMNSLKAEDTAVYYCASGERSTYIGS NYYRTNEYDYWGTGTQVTVSSGGGC
SEQ ID NO: 2540 : P23IL0039 : P 23IL121A2-35GS-124C4- GGGC-PEG40 EVQLVESGGGLVQAGGSLRLSCAASGSIFNFNYMGWFRQAPGKEREFVA AIRWSGSSTYYADSVKGRFTISRDDAKNTVALQMNSLKPEDTAIYYCALRKGIPY STSDRVIKGVNDYDYWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSG GGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTLDDYAIAWFRQAPGKER EGVSGIDSGDGSAYYADSVKGRFTISSDNAKNTVYLQMNSLRPEDTAVYYCARV RTGWGLNAPDYAMDYWGKGTLVTVSSGGGC

Figure 30 (continued)

SEQ ID NO: 2541 : P23IL0041 : P 23IL119A3-35GS-81G2-HSA

EVQLVESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAWHRQAPG
MQRELVATINSGSRTNYADSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQ
TSGSGSPNFWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGG
GSEVQLVESGGGLVQPGGSLRLSCIASGLPFSTKSMGWFRQAPGKEREFVARISP
GGTSRYYGDFVKGRFAISRDNAKNTTWLQMNSLKAEDTAVYYCASGERSTYIGS
NYYRTNEYDYWGTGTQVTVSSDAHKSEVAHRFKDLGEENFKALVLIAFAQYLQ
QCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGE
MADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYL
YEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSA
KQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHG
DLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPS
LAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLE
KCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYT
KKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEK
TPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQ
IKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKL
VAASQAALGL

SEQ ID NO: 2542 : P23IL0042 : P 23IL119A3-35GS-81G2-9GS -ALB1

EVQLVESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAWHRQAPG
MQRELVATINSGSRTNYADSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQ
TSGSGSPNFWGQGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGG
GSEVQLVESGGGLVQPGGSLRLSCIASGLPFSTKSMGWFRQAPGKEREFVARISP
GGTSRYYGDFVKGRFAISRDNAKNTTWLQMNSLKAEDTAVYYCASGERSTYIGS
NYYRTNEYDYWGTGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCA
ASGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTT
LYLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSS

SEQ ID NO: 2543 : P23IL0043 : P 23IL119A3(H37Y)-9GS-ALB1-9GS-81A12

EVQLVESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG
MQRELVATINSGSRTNYADSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQ
TSGSGSPNFWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCAAS
GFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLY
LQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEVQLVESGGG
LVQAGGSLRLSCAASGRTLSSYAMGWFRQAPGKEREFVARISQGGTAIYYADSV
KGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAKDPSPYYRGSAYLLSGSYDSW
GQGTQVTVSS

SEQ ID NO: 2544 : P23IL0044= P23IL0049 : P 23IL119A3(H37Y-M43K)-9GS-ALB1-9GS-81A12

EVQLVESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG
KQRELVATINSGSRTNYADSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQ
TSGSGSPNFWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCAAS
GFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLY
LQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEVQLVESGGG
LVQAGGSLRLSCAASGRTLSSYAMGWFRQAPGKEREFVARISQGGTAIYYADSV
KGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAKDPSPYYRGSAYLLSGSYDSW
GQGTQVTVSS

Figure 30 (continued)

SEQ ID NO: 2545 : P23IL0045 : P 23IL124C4-35GS-119A3 EVQLVESGGGLVQPGGSLRLSCAASGFTLDDYAIAWFRQAPGKEREGVSG IDSGDGSAYYADSVKGRFTISSDNAKNTVYLQMNSLRPEDTAVYYCARVRTGW GLNAPDYAMDYWGKGTQVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGS GGGGSEVQLVESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAWHRQAP GMQRELVATINSGSRTNYADSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYC QTSGSGSPNFWGQGTQVTVSS
SEQ ID NO: 2546 : P23IL0046 : P 23IL119A3-9GS-ALB1-9GS-81A12 EVQLVESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAWHRQAPG MQRELVATINSGSRTNYADSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQ TSGSGSPNFWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCAAS GFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLY LQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEVQLVESGGG LVQAGGSLRLSCAASGRTLSSYAMGWFRQAPGKEREFVARISQGGTAIYYADSV KGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAKDPSPYYRGSAYLLSGSYDSW GQGTQVTVSS
SEQ ID NO: 2547 : P23IL0047 : P 23IL119A3(M43K)-9GS-ALB1-9GS-81A12 EVQLVESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAWHRQAPG MQRELVATINSGSRTNYADSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQ TSGSGSPNFWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCAAS GFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLY LQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEVQLVESGGG LVQAGGSLRLSCAASGRTLSSYAMGWFRQAPGKEREFVARISQGGTAIYYADSV KGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAKDPSPYYRGSAYLLSGSYDSW GQGTQVTVSS
SEQ ID NO: 2548 : P23IL0050 : P 23IL 37D5-9GS-ALB1 EVQLVESGGGLVQPGGSLRLSCAASGFTLDYLAIGWFRQAPGKEREGVSC VSSSGQYTYYADSVKGRFTISRDNAESTVYLQMNSLKPEDTAVYYCATDPECYR VRGYYNGEYDYWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSC AASGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKT TLYLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSS
SEQ ID NO: 2549 : P23IL0051 : P 23IL 37D5-9GS-ALB1-9GS-124C4 EVQLVESGGGLVQPGGSLRLSCAASGFTLDYLAIGWFRQAPGKEREGVSC VSSSGQYTYYADSVKGRFTISRDNAESTVYLQMNSLKPEDTAVYYCATDPECYR VRGYYNGEYDYWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSC AASGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKT TLYLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEVQLVESG GGLVQPGGSLRLSCAASGFTLDDYAIAWFRQAPGKEREGVSGIDSGDGSAYYAD SVKGRFTISSDNAKNTVYLQMNSLRPEDTAVYYCARVRTGWGLNAPDYAMDY WGKGTQVTVSS

Figure 30 (continued)

SEQ ID NO: 2550 : P23IL0052 : P 23IL 37D5-9GS-ALB1-9GS-20B11
EVQLVESGGGLVQPGGSLRLSCAASGFTLDYLAIGWFRQAPGKEREGVSC
VSSSGQYTYYADSVKGRFTISRDNAESTVYLQMNSLKPEDTAVYYCATDPECYR
VRGYYNGEYDYWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSC
AASGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKT
TLYLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEVQLVESG
GGLVQAGGSLRLSCAVSGDTFSVYGMGWFRQAPGMEREFVAGISWNAGITAYT
DTLKGRFTISRDRAKNTMYLQMNSLQPEDTAVYYCAADVTRHYIATRSKVDAS
MYDYWGQGTQVTVSS

SEQ ID NO: 2551 : P23IL0053 : P 23IL 37D5-9GS-ALB1-15GS-124C4
EVQLVESGGGLVQPGGSLRLSCAASGFTLDYLAIGWFRQAPGKEREGVSC
VSSSGQYTYYADSVKGRFTISRDNAESTVYLQMNSLKPEDTAVYYCATDPECYR
VRGYYNGEYDYWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSC
AASGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKT
TLYLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGGSGGGGSE
VQLVESGGGLVQPGGSLRLSCAASGFTLDDYAIAWFRQAPGKEREGVSGIDSGD
GSAYYADSVKGRFTISSDNAKNTVYLQMNSLRPEDTAVYYCARVRTGWGLNAP
DYAMDYWGKGTQVTVSS

SEQ ID NO: 2552 : P23IL0054 : P 23IL 124C4-15GS-ALB1-9GS-37D5
EVQLVESGGGLVQPGGSLRLSCAASGFTLDDYAIAWFRQAPGKEREGVSG
IDSGDGSAYYADSVKGRFTISSDNAKNTVYLQMNSLRPEDTAVYYCARVRTGW
GLNAPDYAMDYWGKGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQPG
NSLRLSCAASGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTIS
RDNAKTTLYLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSE
VQLVESGGGLVQPGGSLRLSCAASGFTLDYLAIGWFRQAPGKEREGVSCVSSSGQ
YTYYADSVKGRFTISRDNAESTVYLQMNSLKPEDTAVYYCATDPECYRVRGYYN
GEYDYWGQGTQVTVSS

SEQ ID NO: 2553 : P23IL0055 : P 23IL 32E2-9GS-ALB1-9GS-124C4
EVQLVESGGGLVQAGGSLRLSCAASGGTFSSYAMGWFRQAPGKERDFVA
AIDWSGSTTTYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADMSHS
PIEIDFGSWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCAASGF
TFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQ
MNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEVQLVESGGGLV
QPGGSLRLSCAASGFTLDDYAIAWFRQAPGKEREGVSGIDSGDGSAYYADSVKG
RFTISSDNAKNTVYLQMNSLRPEDTAVYYCARVRTGWGLNAPDYAMDYWGKG
TQVTVSS

SEQ ID NO: 2554 : P23IL0056 : P 23IL 124C4-9GS-ALB1-9GS-32E2
EVQLVESGGGLVQPGGSLRLSCAASGFTLDDYAIAWFRQAPGKEREGVSG
IDSGDGSAYYADSVKGRFTISSDNAKNTVYLQMNSLRPEDTAVYYCARVRTGW
GLNAPDYAMDYWGKGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSC
AASGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKT
TLYLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEVQLVESG
GGLVQAGGSLRLSCAASGGTFSSYAMGWFRQAPGKERDFVAAIDWSGSTTTYA
DSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAADMSHSPIEIDFGSWGQG
TQVTVSS

Figure 30 (continued)

SEQ ID NO: 2555 : 23IL0069 : P 23IL 37D5-15GS-ALB1-15GS-20B11 EVQLVESGGGLVQPGGSLRLSCAASGFTLDYLAIGWFRQAPGKEREGVSC VSSSGQYTYYADSVKGRFTISRDNAESTVYLQMNSLKPEDTAVYYCATDPECYR VRGYYNGEYDYWGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQPG NSLRLSCAASGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTIS RDNAKTTLYLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGGS GGGGSEVQLVESGGGLVQAGGSLRLSCAVSGDTFSVYGMGWFRQAPGMEREFV AGISWNAGITAYTDTLKGRFTISRDRAKNTMYLQMNSLQPEDTAVYYCAADVTR HYIATRSKVDASMYDYWGQGTQVTVSS
SEQ ID NO: 2556 : 23IL0070 : P 23IL 37D5-15GS-ALB1-15GS-124C4 EVQLVESGGGLVQPGGSLRLSCAASGFTLDYLAIGWFRQAPGKEREGVSC VSSSGQYTYYADSVKGRFTISRDNAESTVYLQMNSLKPEDTAVYYCATDPECYR VRGYYNGEYDYWGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQPG NSLRLSCAASGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTIS RDNAKTTLYLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGGS GGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTLDDYAIAWFRQAPGKEREGVS GIDSGDGSAYYADSVKGRFTISSDNAKNTVYLQMNSLRPEDTAVYYCARVRTG WGLNAPDYAMDYWGKGTQVTVSS
SEQ ID NO: 2557 : 23IL0071 : P 23IL 20B11-9GS-ALB1-9GS-37D5 EVQLVESGGGLVQAGGSLRLSCAVSGDTFSVYGMGWFRQAPGMEREFV AGISWNAGITAYTDTLKGRFTISRDRAKNTMYLQMNSLQPEDTAVYYCAADVTR HYIATRSKVDASMYDYWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNS LRLSCAASGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISR DNAKTTLYLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEV QLVESGGGLVQPGGSLRLSCAASGFTLDYLAIGWFRQAPGKEREGVSCVSSSGQY TYYADSVKGRFTISRDNAESTVYLQMNSLKPEDTAVYYCATDPECYRVRGYYNG EYDYWGQGTQVTVSS
SEQ ID NO: 2558 : 23IL0072 : P 23IL124C4-15GS-ALB1-15GS-37D5 EVQLVESGGGLVQPGGSLRLSCAASGFTLDDYAIAWFRQAPGKEREGVSG IDSGDGSAYYADSVKGRFTISSDNAKNTVYLQMNSLRPEDTAVYYCARVRTGW GLNAPDYAMDYWGKGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQPG NSLRLSCAASGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTIS RDNAKTTLYLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGGS GGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTLDYLAIGWFRQAPGKEREGVS CVSSSGQYTYYADSVKGRFTISRDNAESTVYLQMNSLKPEDTAVYYCATDPECY RVRGYYNGEYDYWGQGTQVTVSS

Figure 31

SEQ ID NO: 2559 : P23IL119A3(H37Y) VQLVESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPGM QRELVATINSGSRTNYADSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQT SGSGSPNFWGQGTQVTVSS
SEQ ID NO: 2560 : P23IL119A3(M43K) EVQLVESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAWHRQAPG KQRELVATINSGSRTNYADSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQ TSGSGSPNFWGQGTQVTVSS
SEQ ID NO: 2561 : P23IL119A3(H37Y-M43K) EVQLVESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG KQRELVATINSGSRTNYADSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQ TSGSGSPNFWGQGTQVTVSS
SEQ ID NO: 2562 : P23IL 119A3-BASIC EVQLVESGGGLVQPGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG MQRELVATINSGSRTNYADSVKGRFTISRDNAQKTLYLQMNNLRPEDTAVYYCQ TSGSGSPNFWGQGTLVTVSS
SEQ ID NO: 2563 : P23IL 119A3V1 EVQLVESGGGLVQPGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG KQRELVATINSGSRTNYADSVKGRFTISRDNAQKTLYLQMNNLRPEDTAVYYCQ TSGSGSPNFWGQGTLVTVSS
SEQ ID NO: 2564 : P23IL 119A3V2 EVQLVESGGGLVQPGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG MGRELVATINSGSRTNYADSVKGRFTISRDNAQKTLYLQMNNLRPEDTAVYYCQ TSGSGSPNFWGQGTLVTVSS
SEQ ID NO: 2565 : P23IL 119A3V3 EVQLVESGGGLVQPGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG MQRELVSTINSGSRTNYADSVKGRFTISRDNAQKTLYLQMNNLRPEDTAVYYCQ TSGSGSPNFWGQGTLVTVSS
SEQ ID NO: 2566 : P23IL 119A3V4 EVQLVESGGGLVQPGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG MQRELVATINSGSRTYYADSVKGRFTISRDNAQKTLYLQMNNLRPEDTAVYYCQ TSGSGSPNFWGQGTLVTVSS
SEQ ID NO: 2567 : P23IL 119A3V5 EVQLVESGGGLVQPGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG MQRELVATINSGSRTNYADSVKGRFTISRDNSQKTLYLQMNNLRPEDTAVYYCQ TSGSGSPNFWGQGTLVTVSS
SEQ ID NO: 2568 : P23IL 119A3V6 EVQLVESGGGLVQPGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG MQRELVATINSGSRTNYADSVKGRFTISRDNAKKTLYLQMNNLRPEDTAVYYCQ TSGSGSPNFWGQGTLVTVSS

Figure 31 (continued)

SEQ ID NO: 2569 : P23IL 119A3V7 EVQLVESGGGLVQPGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG MQRELVATINSGSRTNYADSVKGRFTISRDNAQNTLYLQMNNLRPEDTAVYYCQ TSGSGSPNFWGQGTLVTVSS
SEQ ID NO: 2570 : P23IL 119A3V8 EVQLVESGGGLVQPGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG MQRELVATINSGSRTNYADSVKGRFTISRDNAQKTLYLQMNNLRPEDTAVYYCA TSGSGSPNFWGQGTLVTVSS
SEQ ID NO: 2571 : P23IL 119A3V9 EVQLVESGGGLVQPGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG MQRELVATINSGSRTNYADSVKGRFTISRDNAQKTLYLQMNSLRPEDTAVYYCQ TSGSGSPNFWGQGTLVTVSS
SEQ ID NO: 2572 : P23IL119A3V10 EVQLLESGGGLVQPGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG KGRELVATINSGSRTNYADSVKGRFTISRDNSKKTLYLQMNSLRPEDTAVYYCQT SGSGSPNFWGQGTLVTVSS
SEQ ID NO: 2573 : P23IL119A3V11 EVQLLESGGGLVQPGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG KGRELVATINSGSRTNYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCQT SGSGSPNFWGQGTLVTVSS
SEQ ID NO: 2574 : P23IL119A3V12 EVQLLESGGGLVQPGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG KGRELVSTINSGSRTNYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCQT SGSGSPNFWGQGTLVTVSS
SEQ ID NO: 2575 : P23IL119A3V13 EVQLLESGGGLVQPGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG KGRELVATINSGSRTYYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCQT SGSGSPNFWGQGTLVTVSS
SEQ ID NO: 2576 : P23IL119A3V14 EVQLLESGGGLVQPGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG KGRELVSTINSGSRTYYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCQT SGSGSPNFWGQGTLVTVSS
SEQ ID NO: 2577 : P23IL119A3V15 EVQLLESGGGLVQPGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG KGRELVSTINSGSRTNYADSVKGRFTISRDNSKKTLYLQMNSLRPEDTAVYYCQT SGSGSPNFWGQGTLVTVSS
SEQ ID NO: 2578 : P23IL119A3V16 EVQLLESGGGLVQPGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG KGRELVATINSGSRTYYADSVKGRFTISRDNSKKTLYLQMNSLRPEDTAVYYCQT SGSGSPNFWGQGTLVTVSS

Figure 31 (continued)

SEQ ID NO: 2579 : P23IL119A3V17 EVQLLESGGGLVQPGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG KGRELVSTINSGSRTYYADSVKGRFTISRDNSKKTLYLQMNSLRPEDTAVYYCQT SGSGSPNFWGQGTLVTVSS
SEQ ID NO: 2580 : P23IL 81A12-BASIC EVQLVESGGGLVQPGGSLRLSCAASGRTLSSYAMGWFRQAPGKEREFVA RISQGGTAIYYADSVKGRFTISRDNAKNTLYLQMNSLRPEDTAVYYCAKDPSPYY RGSAYLLSGSYDSWGQGTLVTVSS
SEQ ID NO: 2581 : P23IL 81A12V1 EVQLVESGGGLVQPGGSLRLSCAASGRTLSSYAMGWFRQAPGKGREFVA RISQGGTAIYYADSVKGRFTISRDNAKNTLYLQMNSLRPEDTAVYYCAKDPSPYY RGSAYLLSGSYDSWGQGTLVTVSS
SEQ ID NO: 2582 : P23IL 81A12V2 EVQLVESGGGLVQPGGSLRLSCAASGRTLSSYAMGWFRQAPGKEREFVS RISQGGTAIYYADSVKGRFTISRDNAKNTLYLQMNSLRPEDTAVYYCAKDPSPYY RGSAYLLSGSYDSWGQGTLVTVSS
SEQ ID NO: 2583 : P23IL 81A12V3 EVQLVESGGGLVQPGGSLRLSCAASGRTLSSYAMGWFRQAPGKEREFVA RISQGGTAIYYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAKDPSPYY RGSAYLLSGSYDSWGQGTLVTVSS
SEQ ID NO: 2584 : P23IL81A12V4 EVQLLESGGGLVQPGGSLRLSCAASGRTLSSYAMGWFRQAPGKGREFVS RISQGGTAIYYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAKDPSPYY RGSAYLLSGSYDSWGQGTLVTVSS
SEQ ID NO: 2585 : P23IL81A12V5 EVQLLESGGGLVQPGGSLRLSCAASGRTLSSYAMGWFRQAPGKGREFVA RISQGGTAIYYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAKDPSPYY RGSAYLLSGSYDSWGQGTLVTVSS
SEQ ID NO: 2586 : P23IL 81G2-BASIC EVQLVESGGGLVQPGGSLRLSCIASGLPFSTKSMGWFRQAPGKGREFVARI SPGGTSRYYGDFVKGRFAISRDNAKNTTWLQMNSLKAEDTAVYYCASGERSTYI GSNYYRTNEYDYWGTGTLVTVSS
SEQ ID NO: 2587 : P23IL 81G2V1 EVQLVESGGGLVQPGGSLRLSCAASGLPFSTKSMGWFRQAPGKGREFVA RISPGGTSRYYGDFVKGRFAISRDNAKNTTWLQMNSLKAEDTAVYYCASGERST YIGSNYYRTNEYDYWGTGTLVTVSS
SEQ ID NO: 2588 : P23IL 81G2V2 EVQLVESGGGLVQPGGSLRLSCIASGLPFSTKSMGWFRQAPGKGREFVSRI SPGGTSRYYGDFVKGRFAISRDNAKNTTWLQMNSLKAEDTAVYYCASGERSTYI GSNYYRTNEYDYWGTGTLVTVSS

Figure 31 (continued)

SEQ ID NO: 2589 : P23IL 81G2V3 EVQLVESGGGLVQPGGSLRLSCIASGLPFSTKSMGWFRQAPGKGREFVARI SPGGTSRYYADFVKGRFAISRDNAKNTTWLQMNSLKAEDTAVYYCASGERSTYI GSNYYRTNEYDYWGTGTLVTVSS
SEQ ID NO: 2590 : P23IL 81G2V4 EVQLVESGGGLVQPGGSLRLSCIASGLPFSTKSMGWFRQAPGKGREFVARI SPGGTSRYYGDSVKGRFAISRDNAKNTTWLQMNSLKAEDTAVYYCASGERSTYI GSNYYRTNEYDYWGTGTLVTVSS
SEQ ID NO: 2591 : P23IL 81G2V5 EVQLVESGGGLVQPGGSLRLSCIASGLPFSTKSMGWFRQAPGKGREFVARI SPGGTSRYYGDFVKGRFTISRDNAKNTTWLQMNSLKAEDTAVYYCASGERSTYI GSNYYRTNEYDYWGTGTLVTVSS
SEQ ID NO: 2592 : P23IL 81G2V6 EVQLVESGGGLVQPGGSLRLSCIASGLPFSTKSMGWFRQAPGKGREFVARI SPGGTSRYYGDFVKGRFAISRDNSKNTTWLQMNSLKAEDTAVYYCASGERSTYI GSNYYRTNEYDYWGTGTLVTVSS
SEQ ID NO: 2593 : P23IL 81G2V7 EVQLVESGGGLVQPGGSLRLSCIASGLPFSTKSMGWFRQAPGKGREFVARI SPGGTSRYYGDFVKGRFAISRDNAKNTLWLQMNSLKAEDTAVYYCASGERSTYI GSNYYRTNEYDYWGTGTLVTVSS
SEQ ID NO: 2594 : P23IL 81G2V8 EVQLVESGGGLVQPGGSLRLSCIASGLPFSTKSMGWFRQAPGKGREFVARI SPGGTSRYYGDFVKGRFAISRDNAKNTTYLQMNSLKAEDTAVYYCASGERSTYI GSNYYRTNEYDYWGTGTLVTVSS
SEQ ID NO: 2595 : P23IL 81G2V9 EVQLVESGGGLVQPGGSLRLSCIASGLPFSTKSMGWFRQAPGKGREFVARI SPGGTSRYYGDFVKGRFAISRDNAKNTTWLQMNSLRAEDTAVYYCASGERSTYI GSNYYRTNEYDYWGTGTLVTVSS
SEQ ID NO: 2596 : P23IL 81G2V10 EVQLVESGGGLVQPGGSLRLSCIASGLPFSTKSMGWFRQAPGKGREFVARI SPGGTSRYYGDFVKGRFAISRDNAKNTTWLQMNSLKAEDTAVYYCASGERSTYI GSNYYRTNEYDYWGQGTLVTVSS
SEQ ID NO: 2597 : P23IL81G2V11 EVQLLESGGGLVQPGGSLRLSCAASGLPFSTKSMGWFRQAPGKGREFVSR ISPGGTSRYYGDFVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASGERSTYI GSNYYRTNEYDYWGQGTLVTVSS
SEQ ID NO: 2598 : P23IL37D5V1 (=23ILPMP46F4) EVQLLESGGGLVQPGGSLRLSCAASGFTLDYLAIGWFRQAPGKGREGVSC VSSSGQYTYYADSVKGRFTISRDNSESTVYLQMNSLRPEDTAVYYCATDPECYR VRGYYNGEYDYWGQGTLVTVSS

Figure 31 (continued)

SEQ ID NO: 2599 : P23IL37D5V3 (=23ILPMP46E1) EVQLLESGGGLVQPGGSLRLSCAASGFTLDYLAIGWFRQAPGKGREGVSC VSSSGQYTYYADSVKGRFTISRDNAENTVYLQMNSLRPEDTAVYYCATDPECYR VRGYYNGEYDYWGQGTLVTVSS
SEQ ID NO: 2600 : P23IL37D5V6 (=23ILPMP46C1) EVQLLESGGGLVQPGGSLRLSCAASGFTLDYLAIGWFRQAPGKGREGVSC VSSSGQYTYYADSVKGRFTISRDNSENTVYLQMNSLRPEDTAVYYCATDPECYR VRGYYNGEYDYWGQGTLVTVSS
SEQ ID NO: 2601 : P23IL37D5V16 EVQLLESGGGLVQPGGSLRLSCAASGFTLDYLAIGWFRQAPGKGREGVSC VSSSGQYTYYADSVKGRFTISRDNSKNTVYLQMNSLRPEDTAVYYCATDPECYR VRGYYNGEYDYWGQGTLVTVSS
SEQ ID NO: 2602 : P23IL37D5V17 EVQLLESGGGLVQPGGSLRLSCAASGFTLDYLAIGWFRQAPGKGREGVSC VSSSGQYTYYADSVKGRFTISRDNSKNTLYLQMNSLRPEDTAVYYCATDPECYR VRGYYNGEYDYWGQGTLVTVSS
SEQ ID NO: 2603 : P23IL124C4-BASIC EVQLVESGGGLVQPGGSLRLSCAASGFTLDDYAIAWFRQAPGKGREGVS GIDSGDGSAYYADSVKGRFTISSDNAKNTLYLQMNSLRPEDTAVYYCARVRTGW GLNAPDYAMDYWGKGTLVTVSS
SEQ ID NO: 2604 : P23IL124C4V1 EVQLVESGGGLVQPGGSLRLSCAASGFTLDDYAIAWFRQAPGKGREGVS GIDSGDGSAYYADSVKGRFTISRDNAKNTLYLQMNSLRPEDTAVYYCARVRTG WGLNAPDYAMDYWGKGTLVTVSS
SEQ ID NO: 2605 : P23IL124C4V2 EVQLVESGGGLVQPGGSLRLSCAASGFTLDDYAIAWFRQAPGKGREGVS GIDSGDGSAYYADSVKGRFTISSDNSKNTLYLQMNSLRPEDTAVYYCARVRTGW GLNAPDYAMDYWGKGTLVTVSS
SEQ ID NO: 2606 : P23IL124C4V3 EVQLVESGGGLVQPGGSLRLSCAASGFTLDDYAIAWFRQAPGKGREGVS GIDSGDGSAYYADSVKGRFTISSDNAKNTLYLQMNSLRPEDTAVYYCARVRTGW GLNAPDYAMDYWGQGTLVTVSS
SEQ ID NO: 2607 : P23IL20B11-BASIC EVQLLESGGGLVQPGGSLRLSCAVSGDTFSVYGMGWFRQAPGMGREFVA GISWNAGITAYTDTLKGRFTISRDRAKNTMYLQMNSLQPEDTAVYYCAADVTRH YIATRSKVDASMYDYWGQGTLVTVSS
SEQ ID NO: 2608 : P23IL20B11V1 EVQLLESGGGLVQPGGSLRLSCAASGDTFSVYGMGWFRQAPGMGREFVA GISWNAGITAYTDTLKGRFTISRDRAKNTMYLQMNSLQPEDTAVYYCAADVTRH YIATRSKVDASMYDYWGQGTLVTVSS

Figure 31 (continued)

SEQ ID NO: 2609 : P23IL20B11V2 EVQLLESGGGLVQPGGSLRLSCAVSGDTFSVYGMGWFRQAPGKGREFVA GISWNAGITAYTDTLKGRFTISRDRAKNTMYLQMNSLQPEDTAVYYCAADVTRH YIATRSKVDASMYDYWGQGTLVTVSS
SEQ ID NO: 2610 : P23IL20B11V3 EVQLLESGGGLVQPGGSLRLSCAVSGDTFSVYGMGWFRQAPGMGREFVS GISWNAGITAYTDTLKGRFTISRDRAKNTMYLQMNSLQPEDTAVYYCAADVTRH YIATRSKVDASMYDYWGQGTLVTVSS
SEQ ID NO: 2611 : P23IL20B11V4 EVQLLESGGGLVQPGGSLRLSCAVSGDTFSVYGMGWFRQAPGMGREFVA GISWNAGITAYTDTLKGRFTISRDNAKNTMYLQMNSLQPEDTAVYYCAADVTRH YIATRSKVDASMYDYWGQGTLVTVSS
SEQ ID NO: 2612 : P23IL20B11V5 EVQLLESGGGLVQPGGSLRLSCAVSGDTFSVYGMGWFRQAPGMGREFVA GISWNAGITAYTDTLKGRFTISRDRSKNTMYLQMNSLQPEDTAVYYCAADVTRH YIATRSKVDASMYDYWGQGTLVTVSS
SEQ ID NO: 2613 : P23IL20B11V6 EVQLLESGGGLVQPGGSLRLSCAVSGDTFSVYGMGWFRQAPGMGREFVA GISWNAGITAYTDTLKGRFTISRDRAKNTLYLQMNSLQPEDTAVYYCAADVTRH YIATRSKVDASMYDYWGQGTLVTVSS
SEQ ID NO: 2614 : P23IL124C4V7 EVQLLESGGGLVQPGGSLRLSCAVSGDTFSVYGMGWFRQAPGMGREFVA GISWNAGITAYTDTLKGRFTISRDRAKNTMYLQMNSLRPEDTAVYYCAADVTRH YIATRSKVDASMYDYWGQGTLVTVSS

Figure 32

SEQ ID NO: 2615 : P23IL0057 = P23IL 119A3V10-9GS-ALB8-9GS-81A12V4 EVQLLESGGGLVQPGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG KGRELVATINSGSRTNYADSVKGRFTISRDNSKKTLYLQMNSLRPEDTAVYYCQT SGSGSPNFWGQGTLVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCAASG FTFSSFGMSWVRQAPGKGLEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYL QMNSLRPEDTAVYYCTIGGSLSRSSQGTLVTVSSGGGGSGGGSEVQLLESGGGLV QPGGSLRLSCAASGRTLSSYAMGWFRQAPGKGREFVSRISQGGTAIYYADSVKG RFTISRDNSKNTLYLQMNSLRPEDTAVYYCAKDPSPYYRGSAYLLSGSYDSWGQ GTLVTVSS
SEQ ID NO: 2616 : P23IL0058 = P23IL0064 = P23IL 119A3V16-9GS-ALB8-9GS-81A12V4 EVQLLESGGGLVQPGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG KGRELVATINSGSRTYYADSVKGRFTISRDNSKKTLYLQMNSLRPEDTAVYYCQT SGSGSPNFWGQGTLVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCAASG FTFSSFGMSWVRQAPGKGLEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYL QMNSLRPEDTAVYYCTIGGSLSRSSQGTLVTVSSGGGGSGGGSEVQLLESGGGLV QPGGSLRLSCAASGRTLSSYAMGWFRQAPGKGREFVSRISQGGTAIYYADSVKG RFTISRDNSKNTLYLQMNSLRPEDTAVYYCAKDPSPYYRGSAYLLSGSYDSWGQ GTLVTVSS
SEQ ID NO: 2617 : P23IL0059 = P23IL 119A3V10-9GS-ALB1-9GS-81A12V4 EVQLLESGGGLVQPGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG KGRELVATINSGSRTNYADSVKGRFTISRDNSKKTLYLQMNSLRPEDTAVYYCQT SGSGSPNFWGQGTLVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCAASG FTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYL QMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEVQLLESGGGL VQPGGSLRLSCAASGRTLSSYAMGWFRQAPGKGREFVSRISQGGTAIYYADSVK GRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAKDPSPYYRGSAYLLSGSYDSWG QGTLVTVSS
SEQ ID NO: 2618 : P23IL0060= P23IL 119A3V16-9GS-ALB1-9GS-81A12V4 EVQLLESGGGLVQPGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG KGRELVATINSGSRTYYADSVKGRFTISRDNSKKTLYLQMNSLRPEDTAVYYCQT SGSGSPNFWGQGTLVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCAASG FTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYL QMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEVQLLESGGGL VQPGGSLRLSCAASGRTLSSYAMGWFRQAPGKGREFVSRISQGGTAIYYADSVK GRFTISRDNSKNTLYLQMNSLRPEDTAVYYCAKDPSPYYRGSAYLLSGSYDSWG QGTLVTVSS
SEQ ID NO: 2619 : P23IL0061 : P23IL 119A3V10-35GS -81G2V11-GGGC EVQLLESGGGLVQPGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG KGRELVATINSGSRTNYADSVKGRFTISRDNSKKTLYLQMNSLRPEDTAVYYCQT SGSGSPNFWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGG SEVQLLESGGGLVQPGGSLRLSCAASGLPFSTKSMGWFRQAPGKGREFVSRISPG GTSRYYGDFVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASGERSTYIGSNY YRTNEYDYWGQGTLVTVSSGGGC

Figure 32 (continued)

SEQ ID NO: 2620 : P23IL0062 = P23IL0065 : P23IL 119A3V16-35GS - 81G2V11-GGGC

EVQLLESGGGLVQPGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG
KGRELVATINSGSRTYYADSVKGRFTISRDNSKKTLYLQMNSLRPEDTAVYYCQT
SGSGSPNFWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGG
SEVQLLESGGGLVQPGGSLRLSCAASGLPFSTKSMGWFRQAPGKGREFVSRISPG
GTSRYYGDFVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASGERSTYIGSNY
YRTNEYDYWGQGTLVTVSSGGGC

SEQ ID NO: 2621 : P23IL0065 : P23IL 119A3V16-35GS-81G2V11-HSA

EVQLLESGGGLVQPGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG
KGRELVATINSGSRTYYADSVKGRFTISRDNSKKTLYLQMNSLRPEDTAVYYCQT
SGSGSPNFWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGG
SEVQLLESGGGLVQPGGSLRLSCAASGLPFSTKSMGWFRQAPGKGREFVSRISPG
GTSRYYGDFVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASGERSTYIGSNY
YRTNEYDYWGQGTLVTVSSDAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCP
FEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMAD
CCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIA
RRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQR
LKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGDLL
ECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLA
ADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEK
CCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTK
KVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKT
PVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQI
KKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLV
AASQAALGL

SEQ ID NO: 2622 : 23IL0075 : P23IL 119A3V16-9GS-ALB8-9GS-81A12V5

EVQLLESGGGLVQPGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG
KGRELVATINSGSRTYYADSVKGRFTISRDNSKKTLYLQMNSLRPEDTAVYYCQT
SGSGSPNFWGQGTLVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCAASG
FTFSSFGMSWVRQAPGKGLEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYL
QMNSLRPEDTAVYYCTIGGSLSRSSQGTLVTVSSGGGGSGGGSEVQLLESGGGLV
QPGGSLRLSCAASGRTLSSYAMGWFRQAPGKGREFVARISQGGTAIYYADSVKG
RFTISRDNSKNTLYLQMNSLRPEDTAVYYCAKDPSPYYRGSAYLLSGSYDSWGQ
GTLVTVSS

Figure 33

SEQ ID NO: 2623 : P23IL0200 : P23IL 3B8-9GS-ALB1-15GS-119A3 (H37YM43K)

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSSVMFWLRQAPGKGLEWLST IKPTGSTIYPGSGKGRFTISRDNAKNTLYLQINNLKPEDTALYYCARDIGGTVRGQ GTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCAASGFTFRSFGMSWV RQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLKPEDTA VYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGG SLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPGKQRELVATINSGSRTNYADSV KGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQTSGSGSPNFWGQGTQVTVSS

SEQ ID NO: 2624 : P23IL0201 : P23IL 3C1-9GS-ALB1-15GS-119A3(H37Y-M43K)

EVQLVESGGGSVQAGGSLRLSCKVSGIMFSDKGMGWFRQAPGKERETVA ATNWSGGSTYYADSVKGRFTISRDNYKNTLHLQMASLKPEDTGIYYCAAAGDS WNSRRIEDYDYWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSC AASGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKT TLYLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGGSGGGGSE VQLVESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPGKQREL VATINSGSRTNYADSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQTSGSG SPNFWGQGTQVTVSS

SEQ ID NO: 2625 : P23IL0202 : P23IL 23E3-9GS-ALB1-15GS-119A3(H37Y-M43K)

EVQLVESGGELVQAGGSLRLSCAASGSIVSISAMAWYRQAPGKQRERVAT ITRGGTPDYADSAKDRFTISRDNAKNTVSLQMNNLKPEDTAVYYCKAALRTPTH DYNYYDYWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCAASG FTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYL QMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGGSGGGGSEVQLV ESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPGKQRELVATIN SGSRTNYADSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQTSGSGSPNFW GQGTQVTVSS

SEQ ID NO: 2626 : P23IL0203 : P23IL 119A3(H37Y-M43K)-15GS-ALB1-9GS-3B8

EVQLVESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPG KQRELVATINSGSRTNYADSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQ TSGSGSPNFWGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGNSLR LSCAASGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDN AKTTLYLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEVQL VESGGGLVQPGGSLRLSCAASGFTFSSSVMFWLRQAPGKGLEWLSTIKPTGSTIYP GSGKGRFTISRDNAKNTLYLQINNLKPEDTALYYCARDIGGTVRGQGTQVTVSS

Figure 33 (continued)

SEQ ID NO: 2627 : P23IL0204 : P23IL 119A3(H37Y-M43K)- 15GS-ALB1-9GS-3C1

EVQLVESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPGKQRELVATINSGSRTNYADSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQTSGSGSPNFWGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGNSLRLSCAASGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEVQLVESGGGSVQAGGSLRLSCKVSGIMFSDKGMGWFRQAPGKERETVAATNWSGGSTYYADSVKGRFTISRDNYKNTLHLQMASLKPEDTGIYYCAAAGDSWNSRRIEDYDYWGQGTQVTVSS

SEQ ID NO: 2628 : P23IL0205 : P23IL 119A3(H37Y-M43K)-15GS-ALB1-9GS-23E3

EVQLVESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAWYRQAPGKQRELVATINSGSRTNYADSVKGRFTISRDNAQKTVYLQMNNLKPEDTAVYYCQTSGSGSPNFWGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGNSLRLSCAASGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEVQLVESGGELVQAGGSLRLSCAASGSIVSISAMAWYRQAPGKQRERVATITRGGTPDYADSAKDRFTISRDNAKNTVSLQMNNLKPEDTAVYYCKAALRTPTHDYNYYDYWGQGTQVTVSS

SEQ ID NO: 2629 : P23IL0206 : P23IL 37D5-9GS-ALB1-15GS-22D7

EVQLVESGGGLVQPGGSLRLSCAASGFTLDYLAIGWFRQAPGKEREGVSCVSSSGQYTYYADSVKGRFTISRDNAESTVYLQMNSLKPEDTAVYYCATDPECYRVRGYYNGEYDYWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCAASGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGSLRLSCASSGRTFSIYARGWFRQAPGKEREFVAAIRSGLTTYSDSVKGRFTISRDIAKNTVFLQMNSLKSEDTAVYYCAAAVNYFTDFTDYSKRDSYDYWGQGTQVTVSS

SEQ ID NO: 2643 : P23IL 3C1-15GS-ALB1-15GS-81A12

EVQLVESGGGSVQAGGSLRLSCKVSGIMFSDKGMGWFRQAPGKERETVAATNWSGGSTYYADSVKGRFTISRDNYKNTLHLQMASLKPEDTGIYYCAAAGDSWNSRRIEDYDYWGQGTPVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGNSLRLSCAASGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGSLRLSCAASGRTLSSYAMGWFRQAPGKEREFVARISQGGTAIYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAKDPSPYYRGSAYLLSGSYDSWGQGTQVTVSS

SEQ ID NO: 2644 : P23IL81A12-15GS-ALB1-15GS-80D10

EVQLVESGGGLVQAGGSLRLSCAASGRTLSSYAMGWFRQAPGKEREFVARISQGGTAIYYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAKDPSPYYRGSAYLLSGSYDSWGQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGNSLRLSCAASGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGGSLRLSCAASGRTFEGNPMGWFRQASGKKREFVASIDWSGGITSYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAASARFGSGSYYDLMYDYWGQGTQVTVSS

Figure 34

SEQ ID NO: 2630 : P23IL400 : P23IL 3B8-9GS-ALB1-9GS-3C1

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSSVMFWLRQAPGKGLEWLST
IKPTGSTIYPGSGKGRFTISRDNAKNTLYLQINNLKPEDTALYYCARDIGGTVRGQ
GTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCAASGFTFRSFGMSWV
RQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLKPEDTA
VYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEVQLVESGGGSVQAGGSLRLSCK
VSGIMFSDKGMGWFRQAPGKERETVAATNWSGGSTYYADSVKGRFTISRDNYK
NTLHLQMASLKPEDTGIYYCAAAGDSWNSRRIEDYDYWGQGTQVTVSS

SEQ ID NO: 2631 : P 23IL401: P23IL 3C1-9GS -ALB1-9GS -3B8

EVQLVESGGGSVQAGGSLRLSCKVSGIMFSDKGMGWFRQAPGKERETVA
ATNWSGGSTYYADSVKGRFTISRDNYKNTLHLQMASLKPEDTGIYYCAAAGDS
WNSRRIEDYDYWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSC
AASGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKT
TLYLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEVQLVESG
GGLVQPGGSLRLSCAASGFTFSSSVMFWLRQAPGKGLEWLSTIKPTGSTIYPGSG
KGRFTISRDNAKNTLYLQINNLKPEDTALYYCARDIGGTVRGQGTQVTVSS

SEQ ID NO: 2632 : P 23IL402: P23IL 3C1-9GS -ALB1-9GS -3G10

EVQLVESGGGSVQAGGSLRLSCKVSGIMFSDKGMGWFRQAPGKERETVA
ATNWSGGSTYYADSVKGRFTISRDNYKNTLHLQMASLKPEDTGIYYCAAAGDS
WNSRRIEDYDYWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSC
AASGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKT
TLYLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEVQLVESG
GGVVQAGESLRLSCAASGYNVKDYEMGWFRQAPGMEREFAAAISWRGSSTYYA
DSVKGRFTISRDNAKNTVYLQMSSLKPEDTAVYYCAAGRLYPSSRSRDYDYWG
QGTQVTVSS

SEQ ID NO: 2633 : P 23IL403 : P23IL 3G10-9GS -ALB1-9GS -3C1

EVQLVESGGGVVQAGESLRLSCAASGYNVKDYEMGWFRQAPGMEREFA
AAISWRGSSTYYADSVKGRFTISRDNAKNTVYLQMSSLKPEDTAVYYCAAGRLY
PSSRSRDYDYWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCAA
SGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTL
YLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEVQLVESGG
GSVQAGGSLRLSCKVSGIMFSDKGMGWFRQAPGKERETVAATNWSGGSTYYAD
SVKGRFTISRDNYKNTLHLQMASLKPEDTGIYYCAAAGDSWNSRRIEDYDYWGQ
GTQVTVSS

SEQ ID NO: 2634 : P 23IL404 : P23IL 3B8-9GS -ALB1-15GS -80D10

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSSVMFWLRQAPGKGLEWLST
IKPTGSTIYPGSGKGRFTISRDNAKNTLYLQINNLKPEDTALYYCARDIGGTVRGQ
GTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCAASGFTFRSFGMSWV
RQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLKPEDTA
VYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQAGG
SLRLSCAASGRTFEGNPMGWFRQASGKKREFVASIDWSGGITSYADSVKGRFTIS
RDNAKNTVYLQMNSLKPEDTAVYYCAASARFGSGSYYDLMYDYWGQGTQVTV
SS

Figure 34 (continued)

SEQ ID NO: 2635 : P 23IL405 : P23IL 3B8-9GS -ALB1-15GS -84G12
EVQLVESGGGLVQPGGSLRLSCAASGFTFSSSVMFWLRQAPGKGLEWLST
IKPTGSTIYPGSGKGRFTISRDNAKNTLYLQINNLKPEDTALYYCARDIGGTVRGQ
GTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCAASGFTFRSFGMSWV
RQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLKPEDTA
VYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGGSGGGGSEVQLVESGGRLVQAGG
SLRLSCAASGRTFDSNPMGWFRQAPGKKREFVAIISGNGGITNYANSVKGRFTISR
DNAKNTIYLQMNSLKPEDTAVYYCAASGLYGSGSVYDLMYDYWGQGTQVTVS
S

SEQ ID NO: 2636 : P 23IL406 :P23IL 23E3-9GS -ALB1-15GS -84G1
EVQLVESGGELVQAGGSLRLSCAASGSIVSISAMAWYRQAPGKQRERVAT
ITRGGTPDYADSAKDRFTISRDNAKNTVSLQMNNLKPEDTAVYYCKAALRTPTH
DYNYYDYWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCAASG
FTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYL
QMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGGSGGGGSEVQLV
ESGGGMVQAGGSLRLSCTASGLTDNSYAMGWFRRAPGKEREFLTGLTLSGGSTY
YADSVKGRFTTSRDSQKNTVSLQMNSLKPEDTAVYYCAANRFGYGSAAYTPDN
YNYWAQGTQVTVSS

SEQ ID NO: 2637 : P 23IL407 : P23IL 23E3-9GS -ALB1-15GS -81A1
EVQLVESGGELVQAGGSLRLSCAASGSIVSISAMAWYRQAPGKQRERVAT
ITRGGTPDYADSAKDRFTISRDNAKNTVSLQMNNLKPEDTAVYYCKAALRTPTH
DYNYYDYWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCAASG
FTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYL
QMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGGSGGGGSEVQLV
ESGGGLVQTGGSLRLSCAASVINFRLADMDWYRQALGKQRELVASISTGYRTNY
ADFVKGRFTISRDNAKNTVYLQMDSLKPEDTAVYYCAARDLRGLRVDYWGQGT
QVTVSS

SEQ ID NO: 2638 : P 23IL408 : P23IL 22D7-9GS -ALB1-15GS -80D10
EVQLVESGGGLVQAGGSLRLSCASSGRTFSIYARGWFRQAPGKEREFVAA
IRSGLTTYSDSVKGRFTISRDIAKNTVFLQMNSLKSEDTAVYYCAAAVNYFTDFT
DYSKRDSYDYWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCA
ASGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTT
LYLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGGSGGGGSEV
QLVESGGGLVQAGGSLRLSCAASGRTFEGNPMGWFRQASGKKREFVASIDWSG
GITSYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAASARFGSGSYYD
LMYDYWGQGTQVTVSS

SEQ ID NO: 2639 : P 23IL409 :P23IL 22E11-9GS -ALB1-15GS -80D10
EVQLVESGGGLVQAGGSLRLSCAASGRTFSWSAVGWFRQAPGKEREFVA
AIRWSGGSPYYADSVKDRFTISRDNAKNTVYLQMNSLRPEDTAVYLCGETSLFPT
SRGSHYDTWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCAAS
GFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLY
LQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGGSGGGGSEVQL
VESGGGLVQAGGSLRLSCAASGRTFEGNPMGWFRQASGKKREFVASIDWSGGIT
SYADSVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAASARFGSGSYYDLM
YDYWGQGTQVTVSS

Figure 34 (continued)

SEQ ID NO: 2640 : P 23IL410 : P23IL 22D7-9GS -ALB1-9GS-22D10 EVQLVESGGGLVQAGGSLRLSCASSGRTFSIYARGWFRQAPGKEREFVAA IRSGLTTYSDSVKGRFTISRDIAKNTVFLQMNSLKSEDTAVYYCAAAVNYFTDFT DYSKRDSYDYWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCA ASGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTT LYLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEVQLVESG GGLVQAGASLRLSCAASGRTFRSYNMGWLRQAPGKEREFVATISWNAGIPYYAD SVKGRFTISRDNAKNTVYLQMNSLKPEDTAVYYCAASNSWSSSARFYDYWGQG TQVTVSS
SEQ ID NO: 2641 : P 23IL411 :P23IL 22D7-9GS-ALB1-15GS -84G12 EVQLVESGGGLVQAGGSLRLSCASSGRTFSIYARGWFRQAPGKEREFVAA IRSGLTTYSDSVKGRFTISRDIAKNTVFLQMNSLKSEDTAVYYCAAAVNYFTDFT DYSKRDSYDYWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCA ASGFTFRSFGMSWVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTT LYLQMNSLKPEDTAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGGSGGGGSEV QLVESGGRLVQAGGSLRLSCAASGRTFDSNPMGWFRQAPGKKREFVAIISGNGGI TNYANSVKGRFTISRDNAKNTIYLQMNSLKPEDTAVYYCAASGLYGSGSVYDLM YDYWGQGTQVTVSS

Figure 35

SEQ ID NO: 2645 : P12IL120C7-9GS-ALB1-9GS-122H8

EVQLVESGGGFVQPGGSLRLSCAASASIFSGYTMGWYRQAPGKERELVTS
ISHRGGTNYADSVKGRFTISRENAKSTVYLQMNSLKPEDTGVYYCNRLINEASW
GQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCAASGFTFRSFGMS
WVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLKPED
TAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGGSLRLS
CAASGFTLDDYTIAWFRQAPGKEREGVSCISSSALITFYADSVKGRFTISRDNAKN
TVYLQMNSLKPEDTAVYYCAADRYYYCSGWPDENAYWGQGTQVTVSS

SEQ ID NO: 2646 : P12IL120C7-9GS-ALB1-9GS-122G9

EVQLVESGGGFVQPGGSLRLSCAASASIFSGYTMGWYRQAPGKERELVTS
ISHRGGTNYADSVKGRFTISRENAKSTVYLQMNSLKPEDTGVYYCNRLINEASW
GQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCAASGFTFRSFGMS
WVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLKPED
TAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEVQLVESGGGFVQPGGSLRLS
CAASASIFSGYTMGWYRQAPGKERELVTSISHRGGTNYADSVKGRFTISRENAKS
TVYLQMNSLKPEDTGVYYCNRLINEASWGQGTQVTVSS

Figure 36

SEQ ID NO: 2647 : P12IL120C7-9GS-ALB1-9GS-3C1

EVQLVESGGGFVQPGGSLRLSCAASASIFSGYTMGWYRQAPGKERELVTS
ISHRGGTNYADSVKGRFTISRENAKSTVYLQMNSLKPEDTGVYYCNRLINEASW
GQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCAASGFTFRSFGMS
WVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLKPED
TAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEVQLVESGGGSVQAGGSLRLS
CKVSGIMFSDKGMGWFRQAPGKERETVAATNWSGGSTYYADSVKGRFTISRDN
YKNTLHLQMASLKPEDTGIYYCAAAGDSWNSRRIEDYDYWGQGTPVTVSS

SEQ ID NO: 2648 : P12IL120C7-9GS-ALB1-9GS-3B8

EVQLVESGGGFVQPGGSLRLSCAASASIFSGYTMGWYRQAPGKERELVTS
ISHRGGTNYADSVKGRFTISRENAKSTVYLQMNSLKPEDTGVYYCNRLINEASW
GQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGNSLRLSCAASGFTFRSFGMS
WVRQAPGKEPEWVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLKPED
TAVYYCTIGGSLSRSSQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGGSLRLS
CAASGFTFSSSVMFWLRQAPGKGLEWLSTIKPTGSTIYPGSGKGRFTISRDNAKNT
LYLQINNLKPEDTALYYCARDIGGTVRGQGTQVTVSS

Figure 37

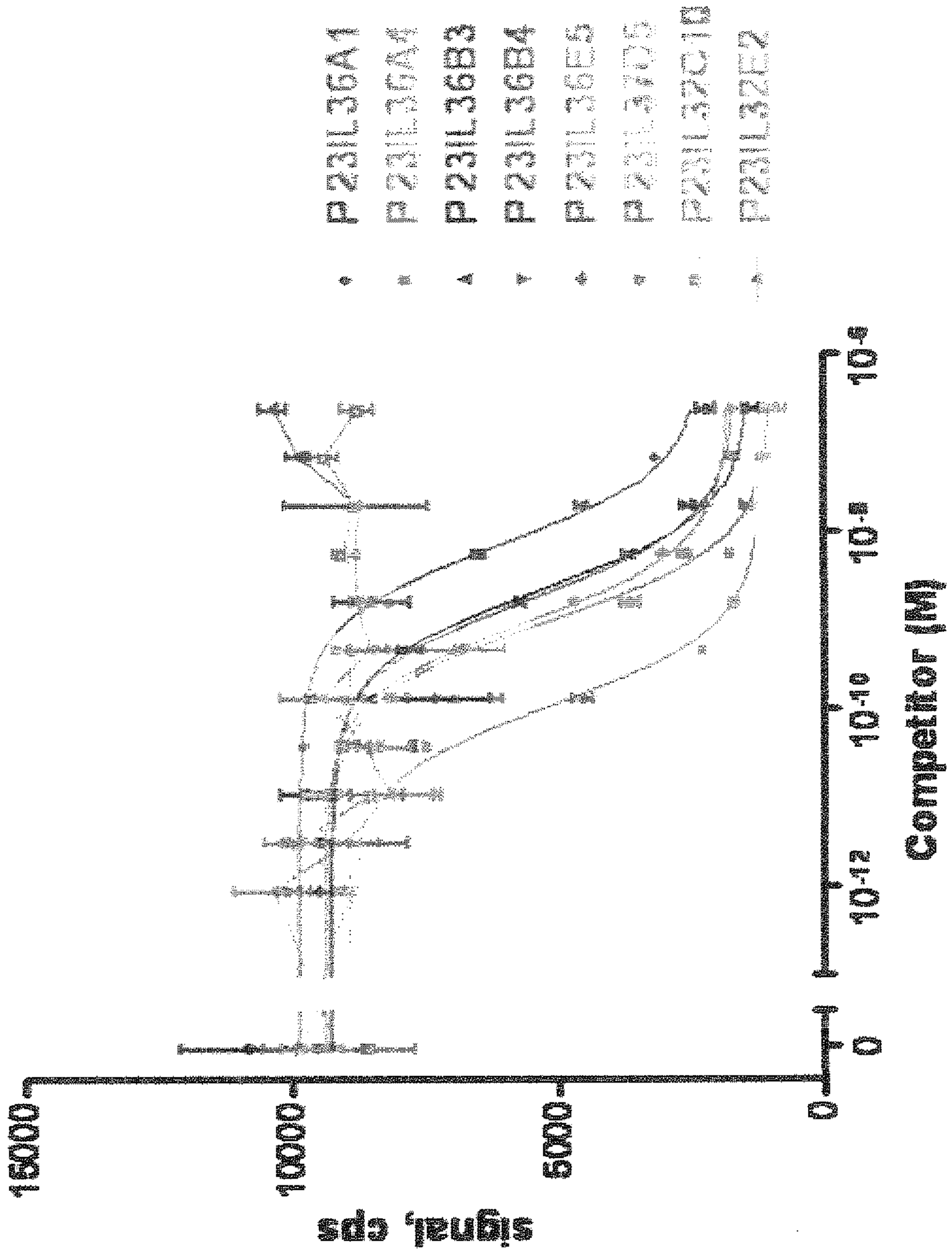
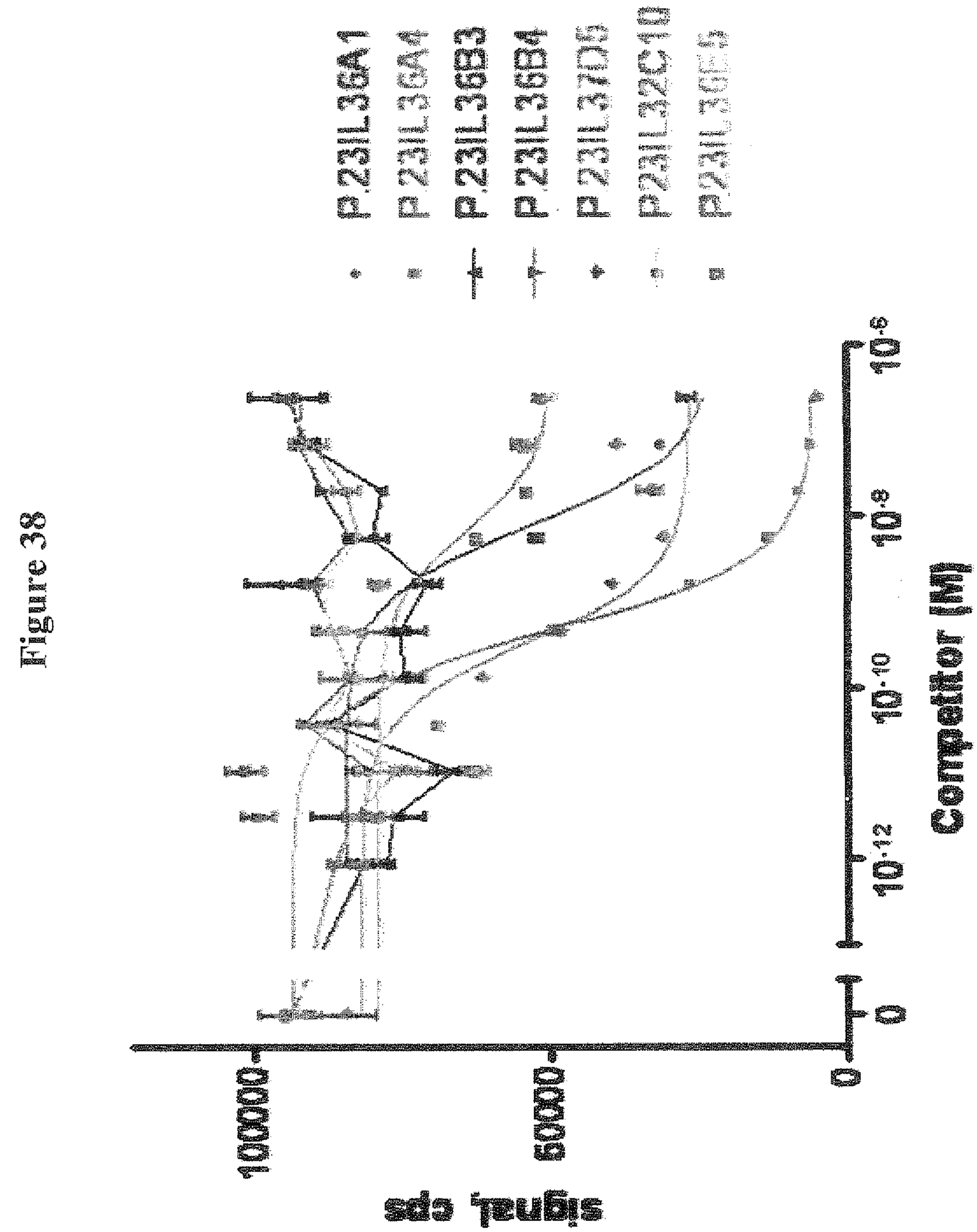

p23A4
p23A4
p23B3
p23B4
p23E5
p23C5
p23C10
p23F7
signal, cps
16000
10000
5000
0
0
10^{-12}
10^{-10}
10^{-8}
Competitor (M)

Figure 38


EP2311368A1
EP2311368A4
EP2311368B1
EP2311368B4
EP2311368D0
EP2311368T3
EP4411368T3
10-6
10-8
10-10
10-12
0
competitor (M)
0
50000
100000
signal cps

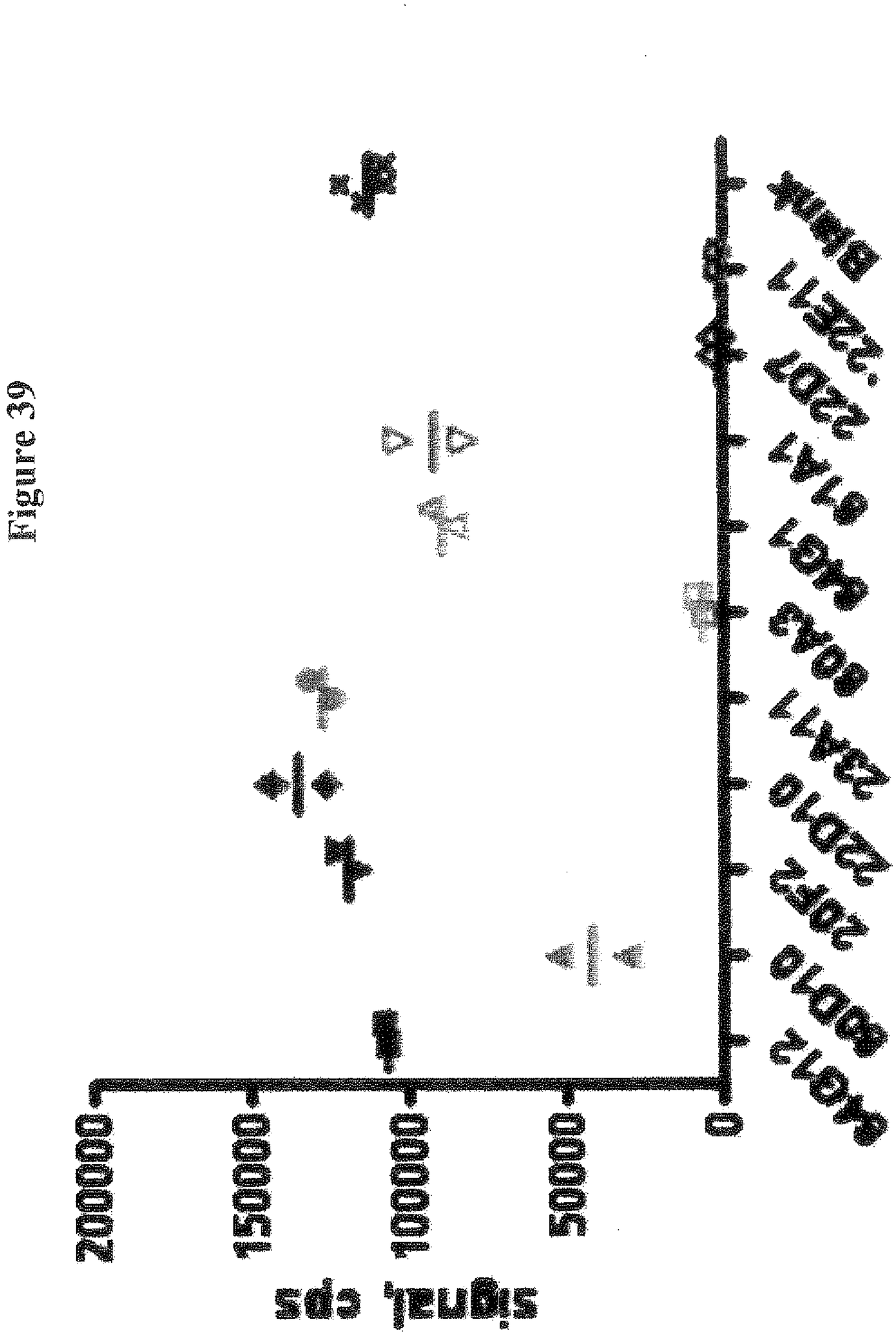

signal, cps
200000
150000
100000
50000
0
Footprint
Page 114 of 132

Figure 39

Figure 40

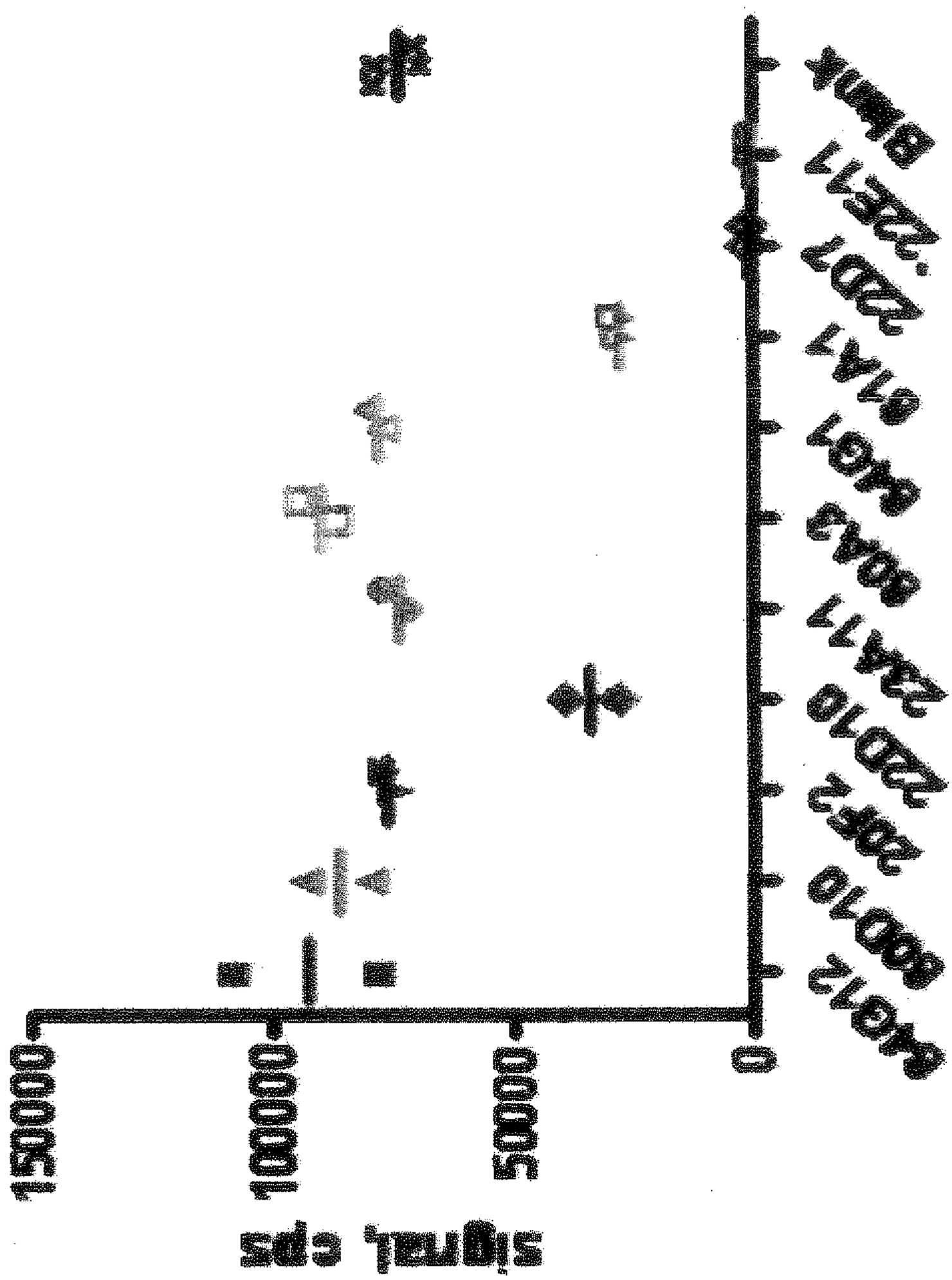


Figure 41

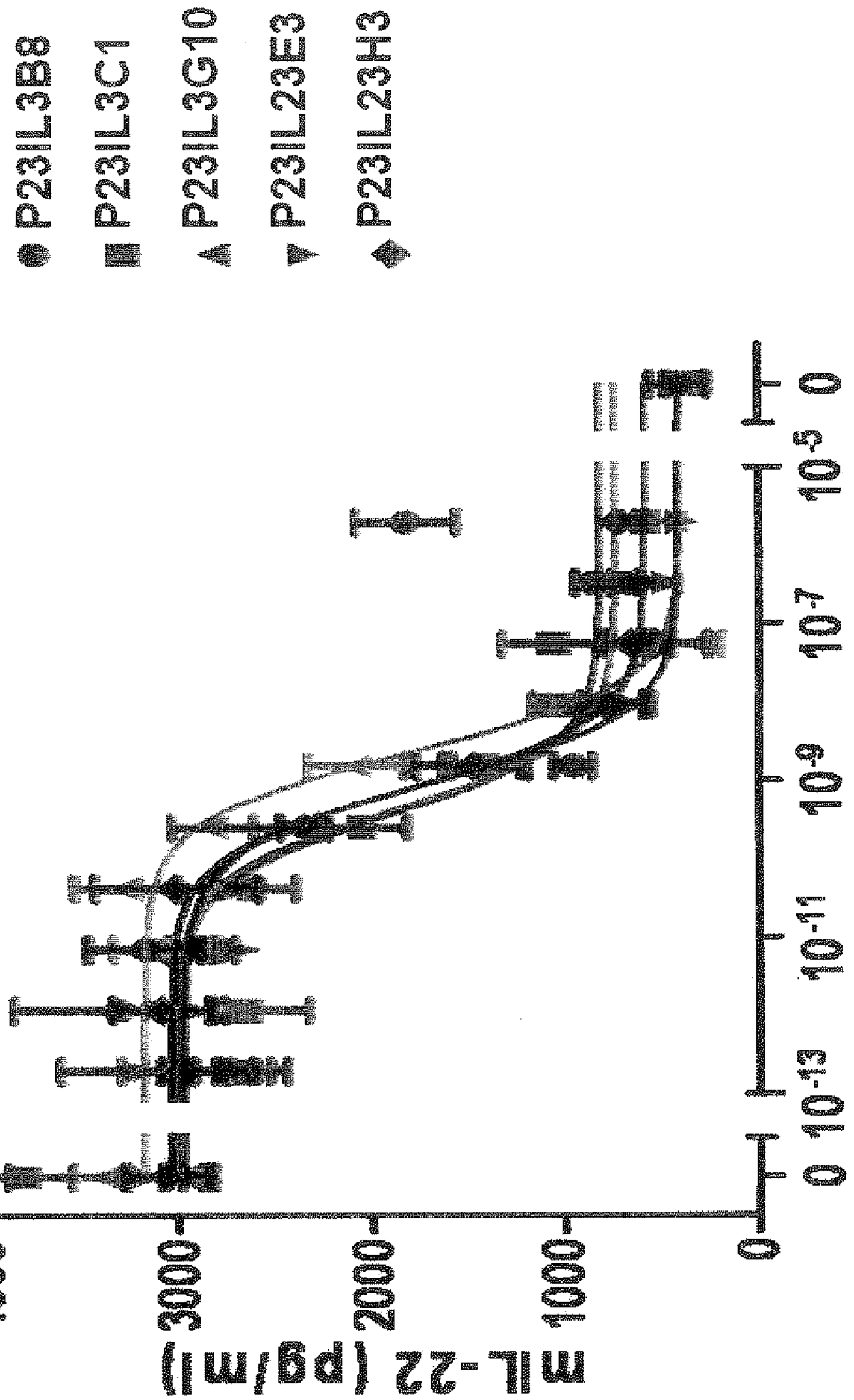
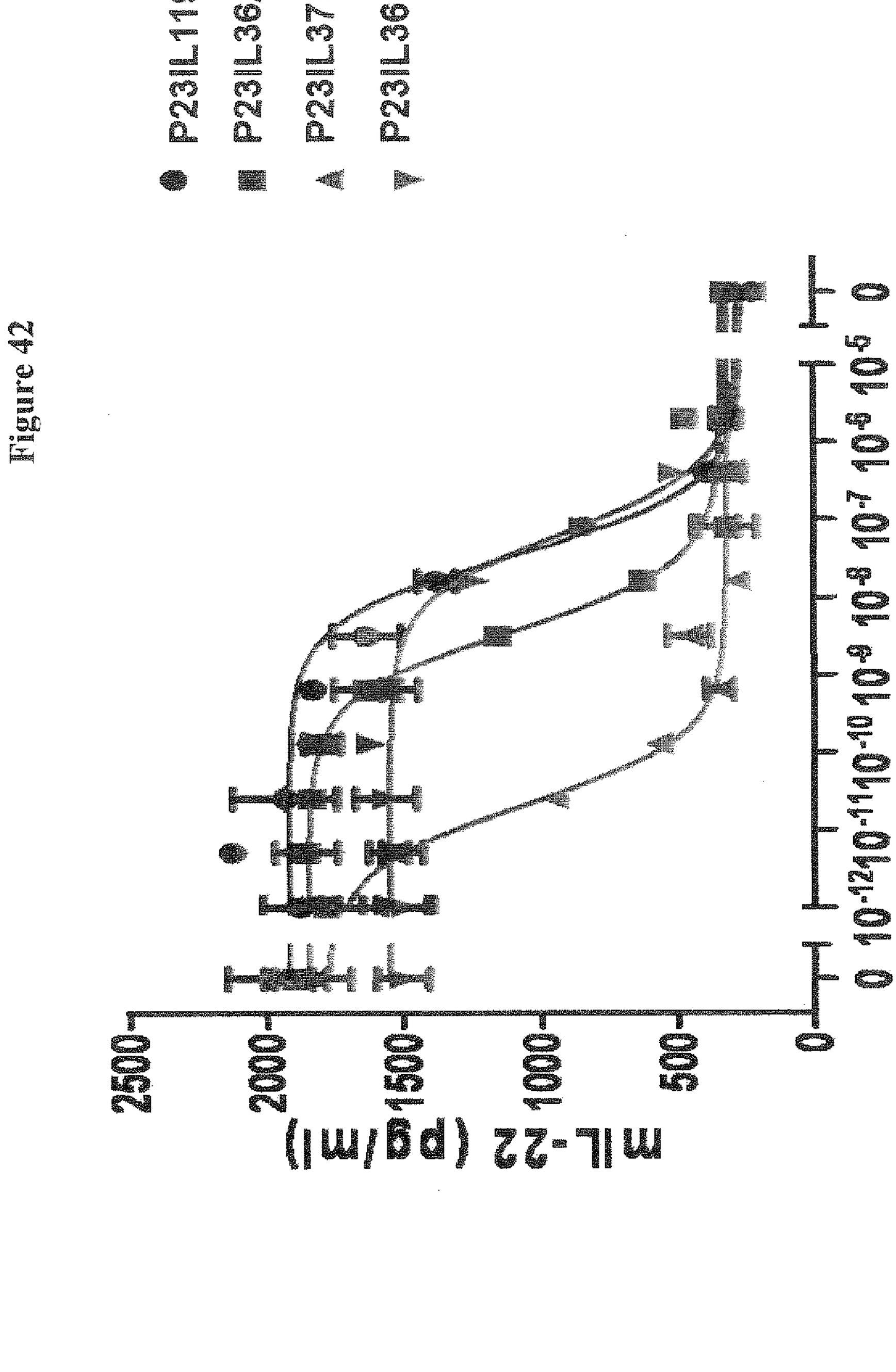

P23IL3B8
P23IL3C1
P23IL3G10
P23IL23E3
P23IL23H3
mIL-22 (pg/ml)
4000
3000
2000
1000
0
nb (M)
10-5
10-7
10-9
10-11
10-13
0

Figure 42


gA3
A4
D5
B4
P23IL11
P23IL36
P23IL37
P23IL36
nb (M)
0
10-12
10-11
10-10
10-9
10-8
10-7
10-6
10-5
0
500
1000
1500
2000
2500
mIL-22 (pg/ml)

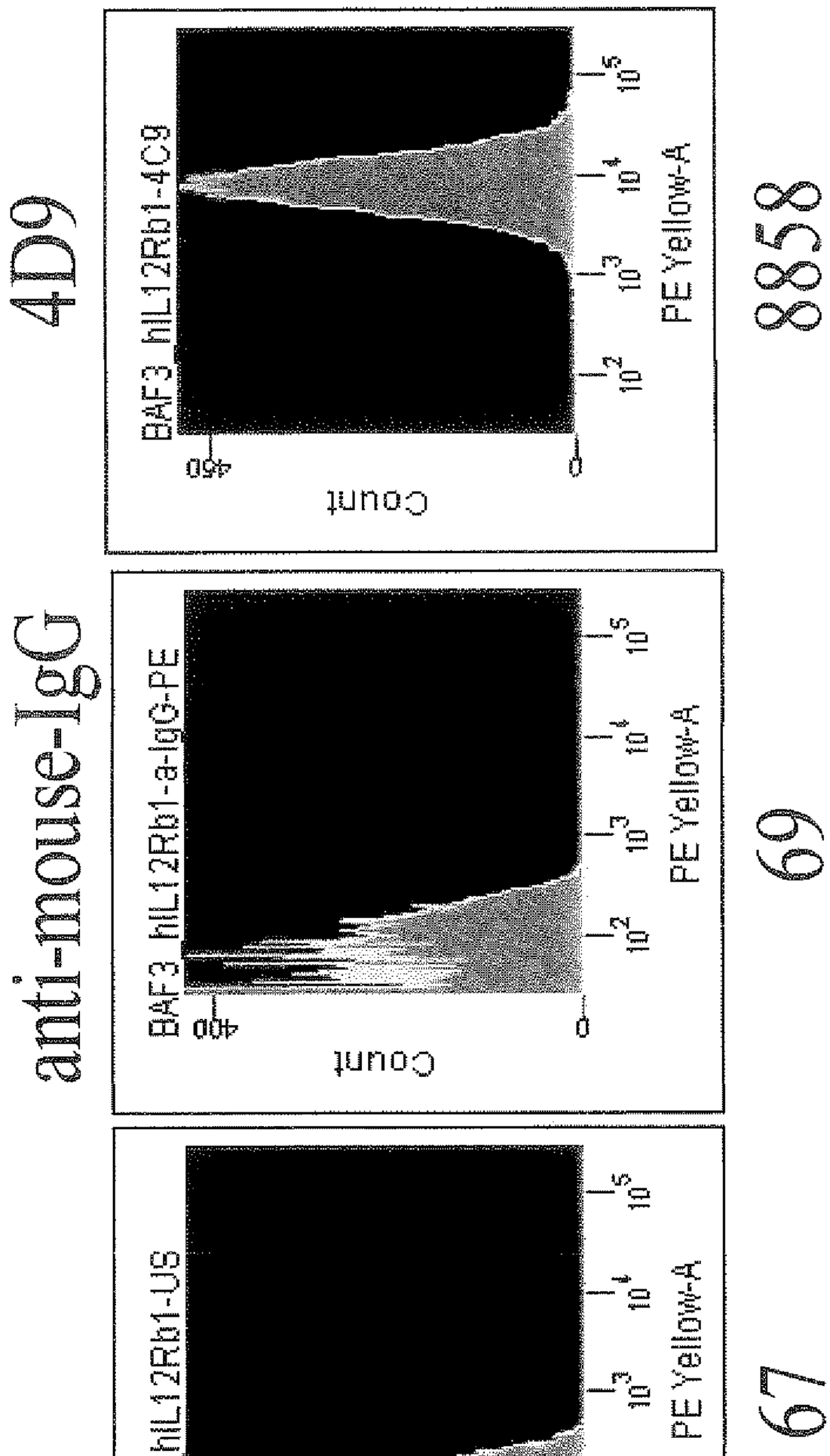

4D9
BAF3_hIL12Rb1-4C9
Count
PE Yellow-A
8858
anti-mouse-IgG
BAF3_hIL12Rb1-a-IgG-PE
69
Unstained
BAF3_hIL12Rb1-US
67
SSC-A (x 1.000)
FSC-A (x 1.000)
MCF

Figure 43

Figure 44

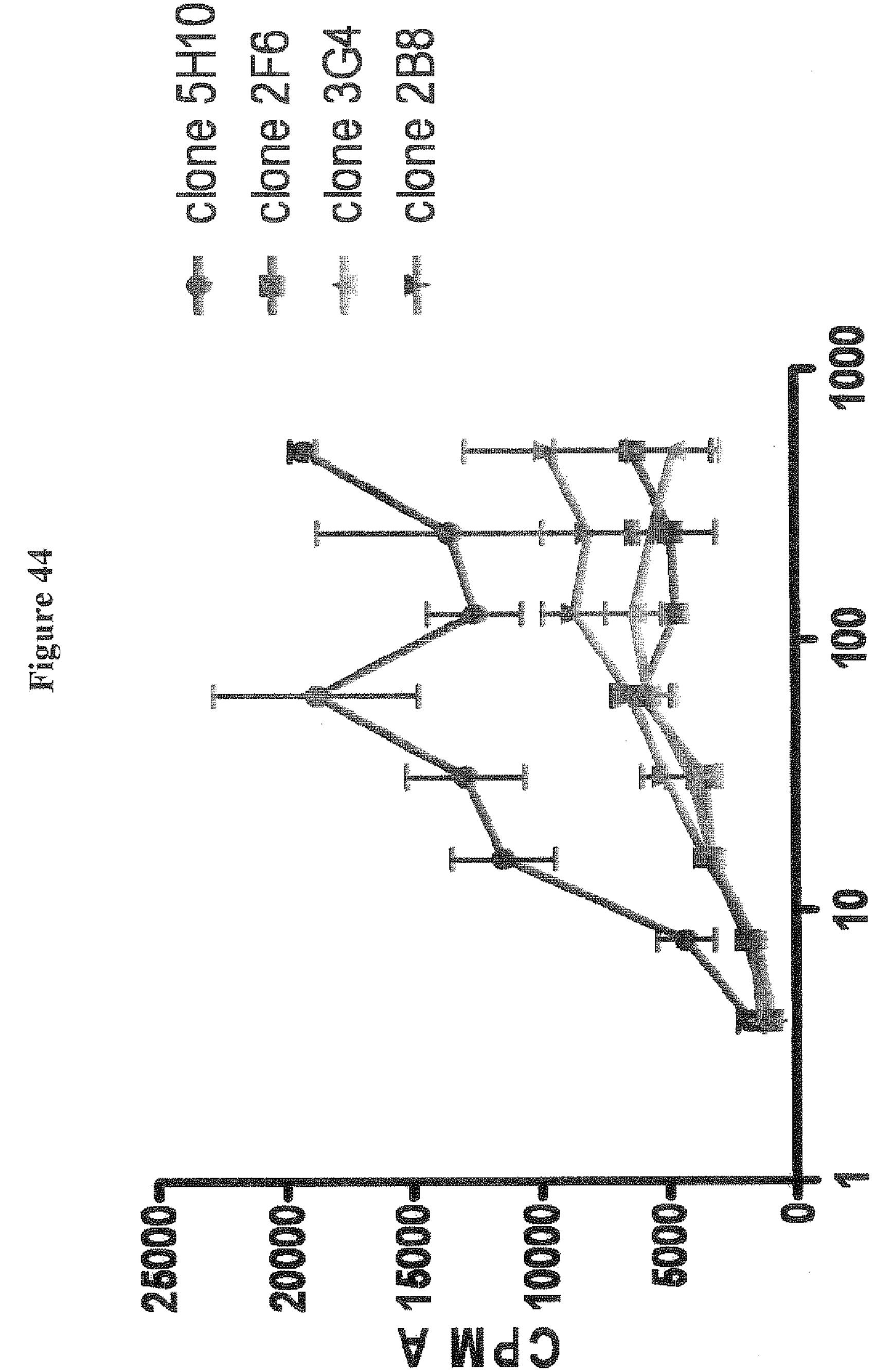
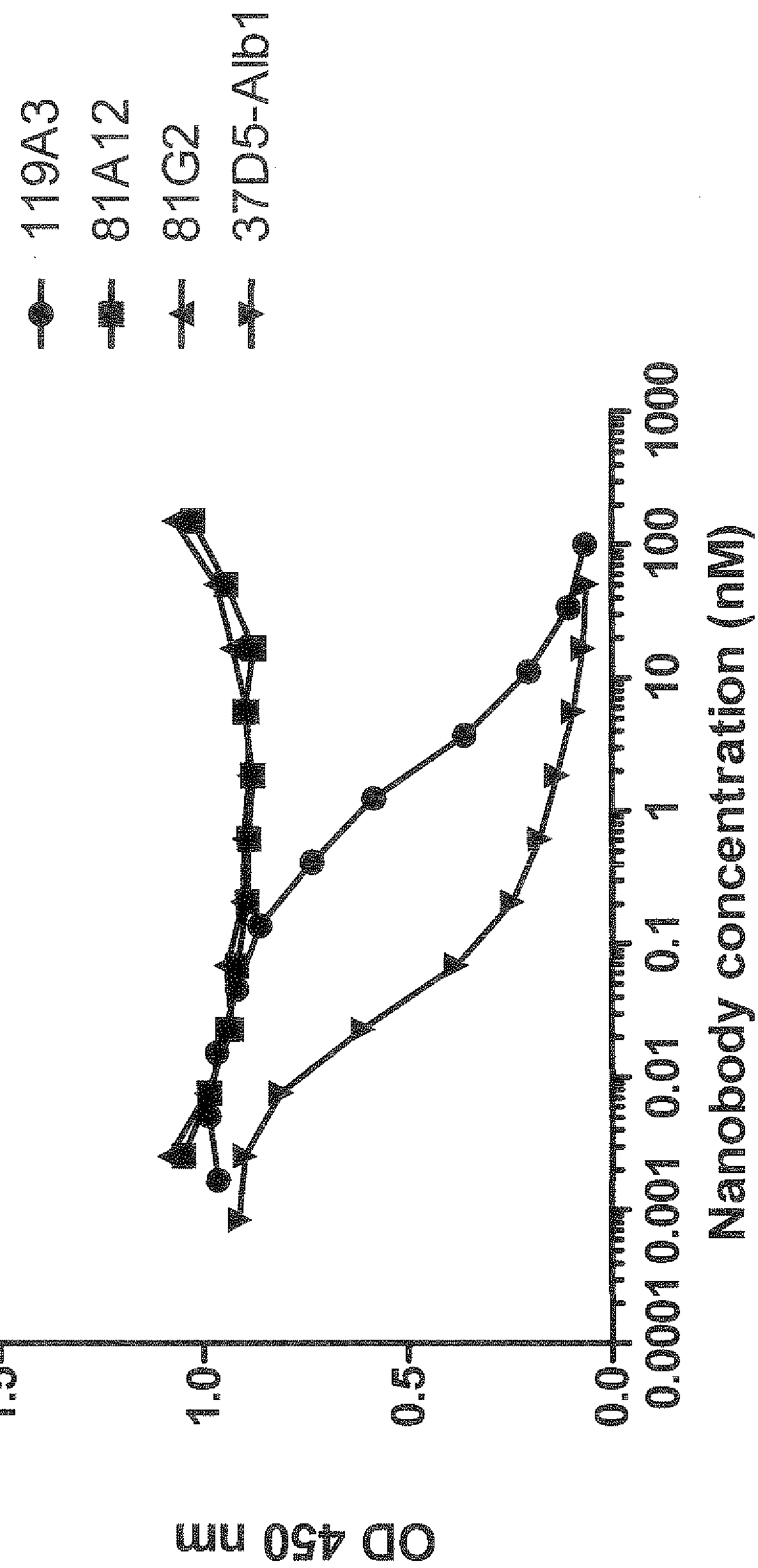

ne 5H10 clo
ne 2F6 clo
ne 3G4 clo
ne 2B8 clo
CPM A
25000
20000
15000
10000
5000
0
1
10
100
1000
Concentration hIL-23 (ng/ml)

Figure 45


119A3
81A12
81G2
37D5-Alb1
OD 450 nm
1.5
1.0
0.5
0.0
0.0001 0.001 0.01 0.1
1 10 100 1000
Nanobody concentration (nM)

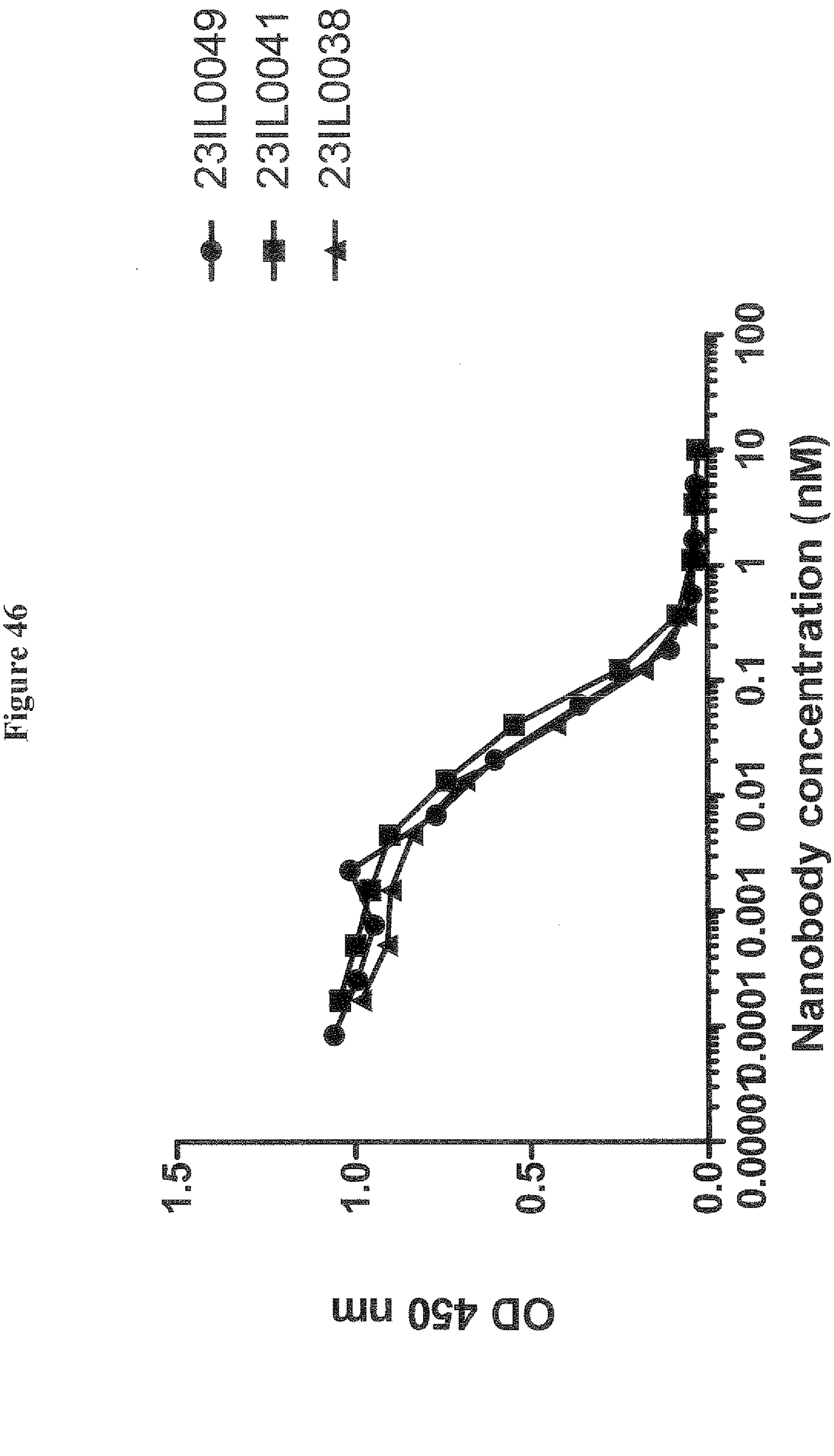
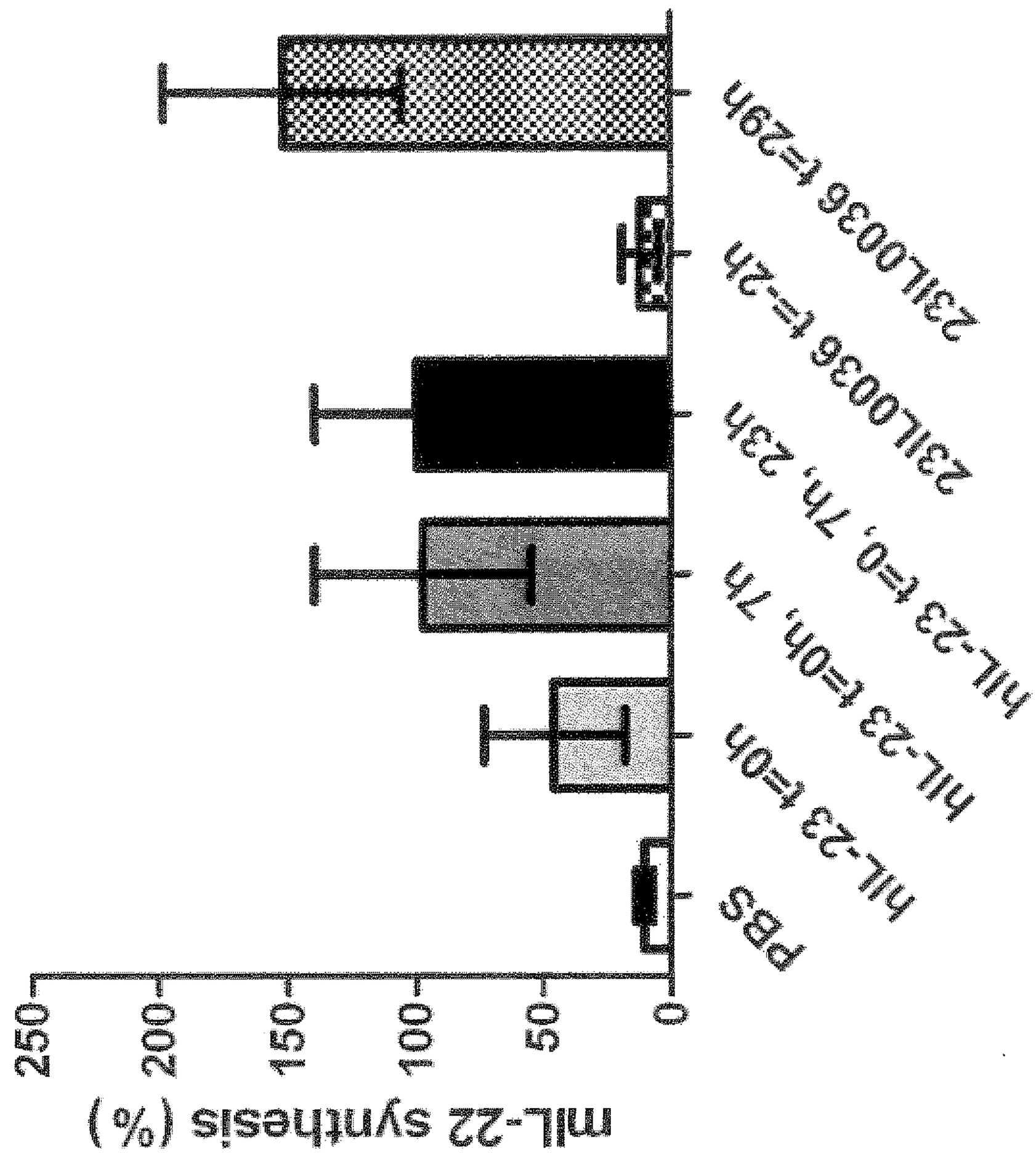

23IL0049
23IL0041
23IL0038
Nanobody concentration (nM)
0.00001
0.0001
0.001
0.01
0.1
1
10
100
OD 450 nm
-1.5
-1.0
-0.5
0.0
0.5

Figure 46

Figure 47


mIL-22 synthesis (%)
250
200
150
100
50
0
PBS
mIL-22
mIL-23 (t=0h, 7h)
mIL-23 (t=0h, 7h, 23h)
23L0038 (t=0h, 7h)
23L0038 (t=0h, 7h, 23h)

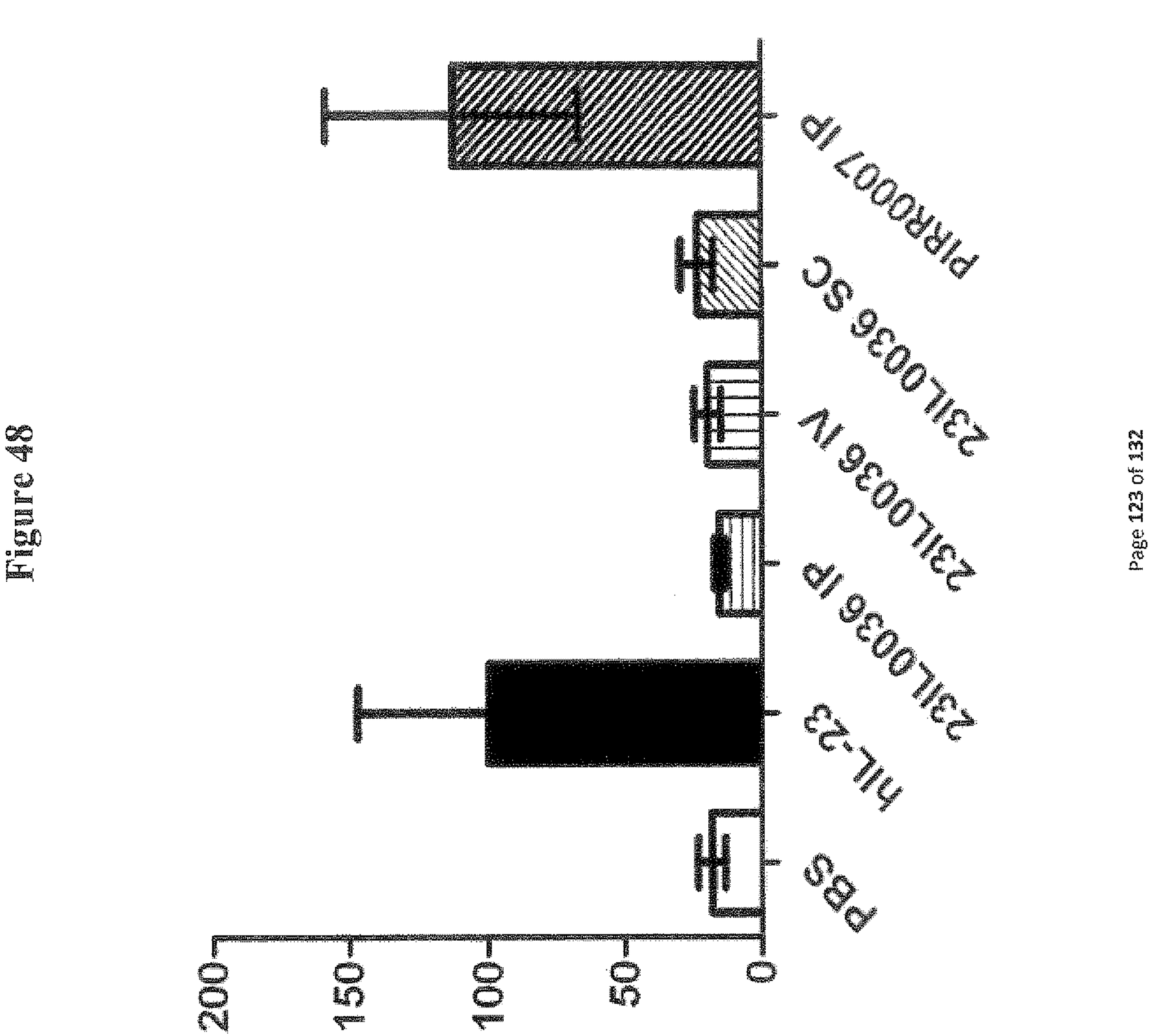

mIL-22 synthesis (%)
0
50
100
150
200
pBS
mIL-23
23IL0036 IP
23IL0036 SC
23IL0036 IV
PIRR0007 IP

Figure 48

Figure 49B

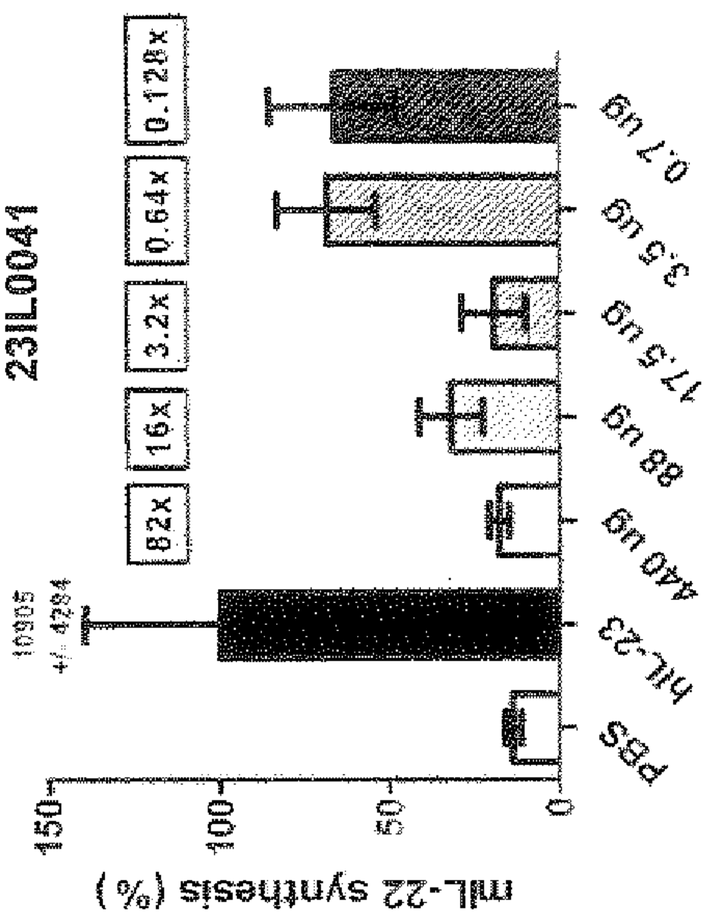


Figure 49D

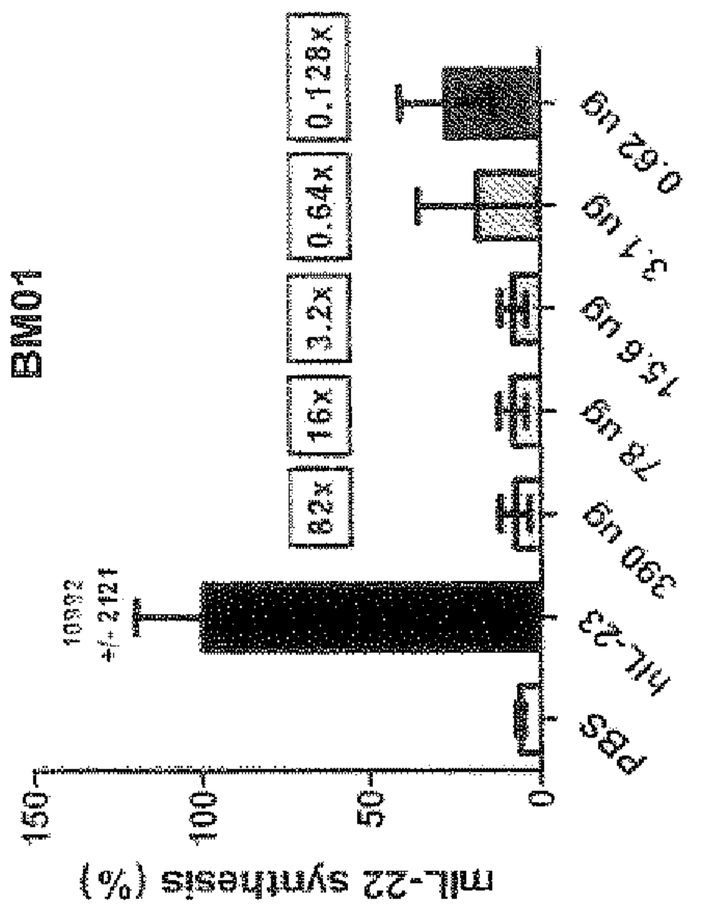


Figure 49A

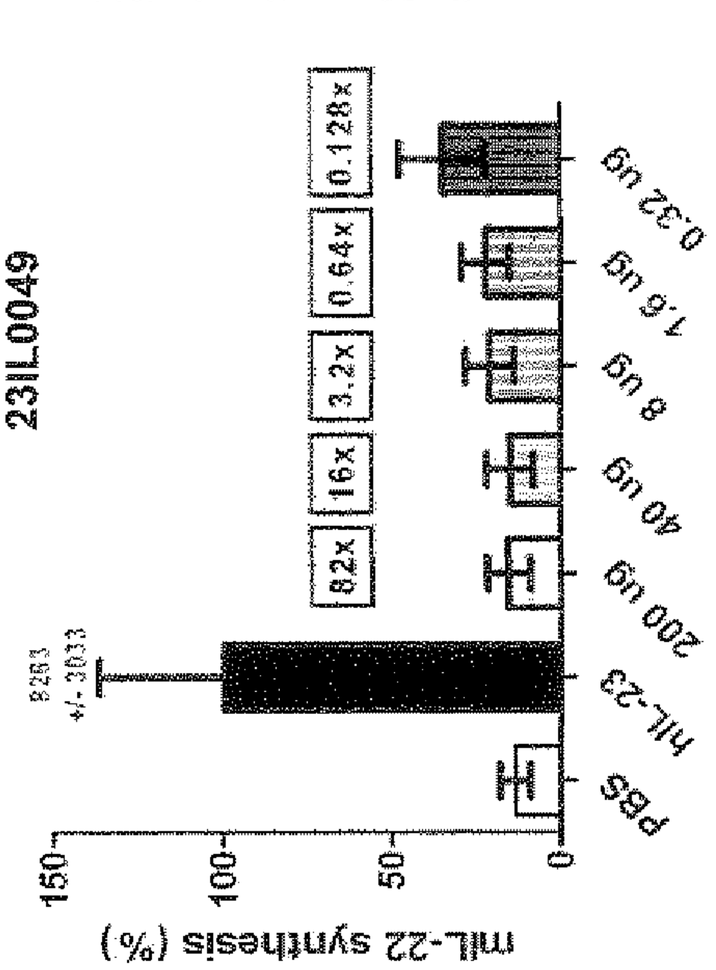


Figure 49C

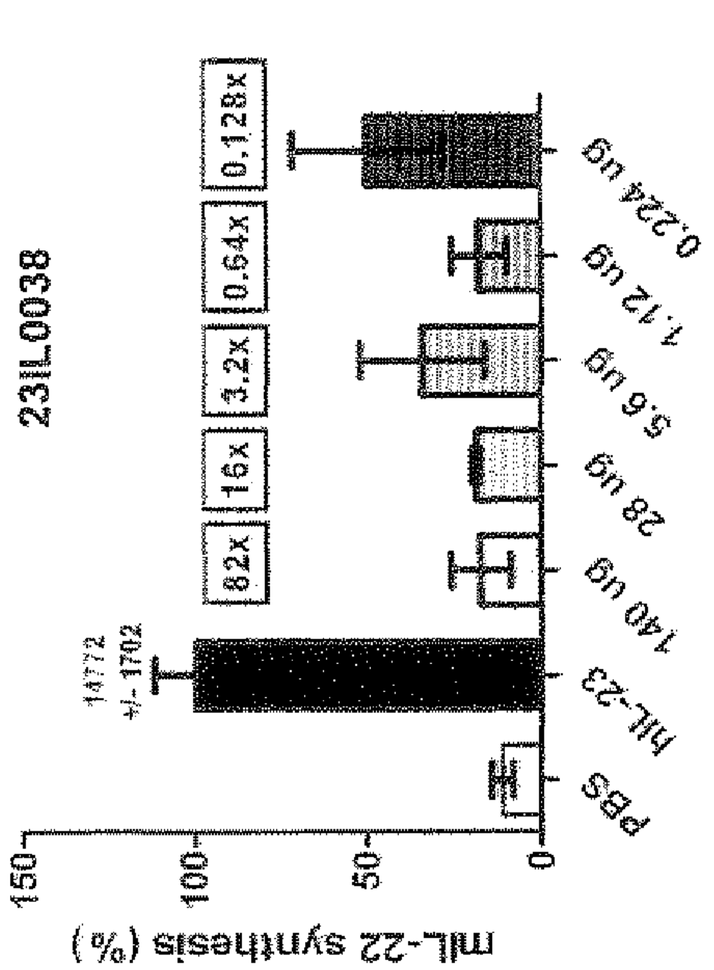


Figure 50

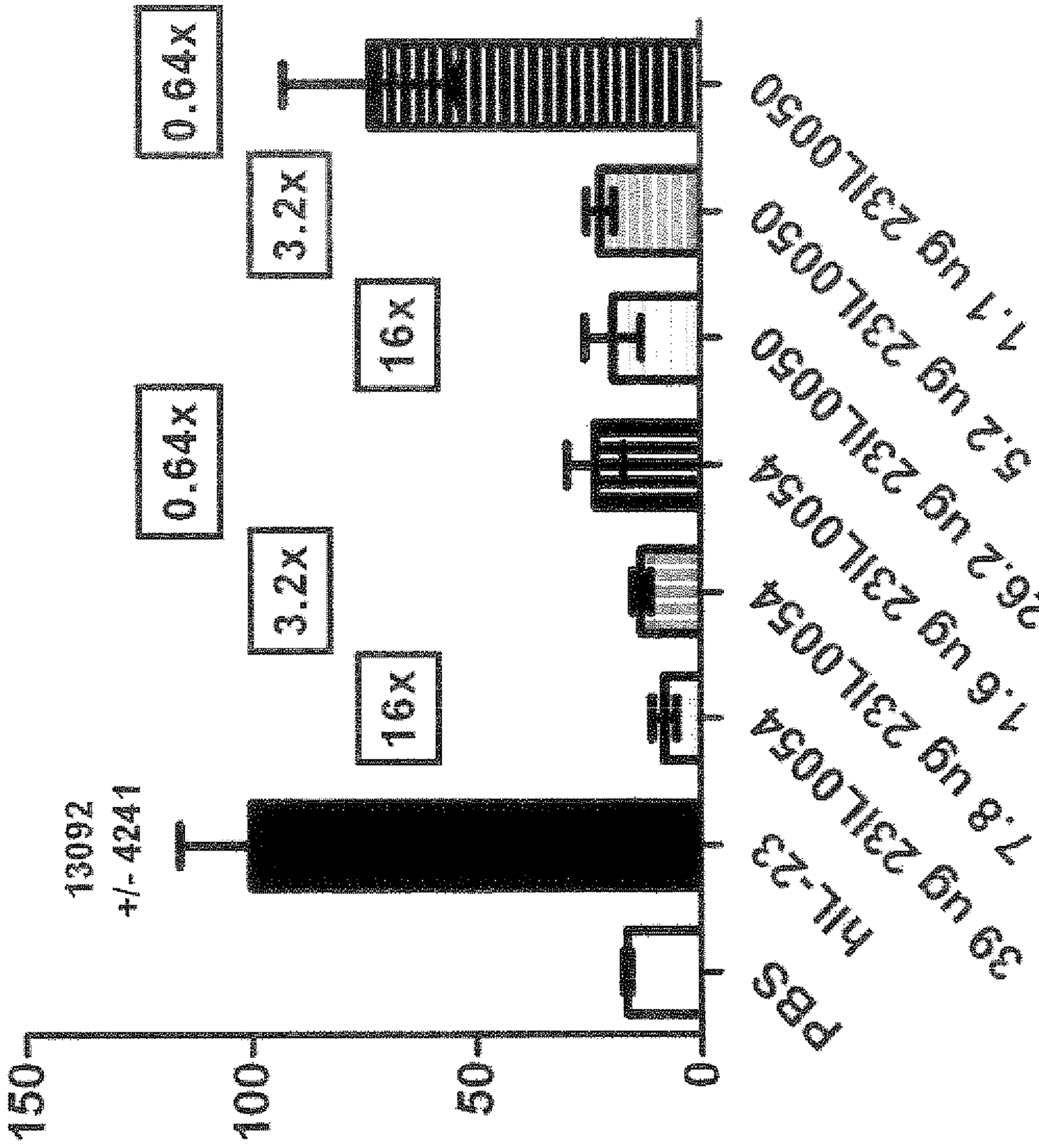

mIL-22 synthesis (%)
150
100
50
0
13092
+/- 4241
0.64x
3.2x
16x
0.64x
3.2x
16x
0.64x
3.2x
16x
pBS
hIL-23
39 ug 23IL0050
7.8 ug 23IL0050
1.6 ug 23IL0050
0.32 ug 23IL0050
0.064 ug 23IL0050
7.8 ug 23IL0054
1.6 ug 23IL0054
0.32 ug 23IL0054
0.064 ug 23IL0054

Figure 51A

```
Kabat#:          1        10        20        30                  40        50        60        70        80        90        100       110
                 |--------|---------|---------|-----abcdefghi----|---------|--a------|---------|---------|--abc-----|---------|---------|---
119A3       : EVQLVESGGGLVQAGGSLRLSCAASGRIFSLPASGNIFNLLTIAW RQAPG E V TIN-SGSRT YADSVKGRFTISRDN TVYLQMN LK EDTAVYYC SGSGSPNFWGQGTQVTVSS
119A3v16    : ....L........P.....................|.....|.....-...|.....|.....|.....|.....|..L....|.R.....|.....|.....|.....L.....
VH3-23/JH5  : ....L........P...........FT..SY---------AMS.|.....|...|..A.SG..GS.....|.....|.....|.....L....|.R.....|---------.....L.....
```

Figure 51B

```
Kabat#:          1        10        20        30        40        50        60        70        80        90        100                 110
                 |--------|---------|---------|---------|---------|--a------|---------|---------|--abc-----|---------|abcdefghijk---------|---
81A12       : EVQLVESGGGLVQAGGSLRLSCAASGRTLSSYAMGW RQAPGK E V RISQGGTAIYYADSVKGRFTISRDN KNTVYLQMNSLK EDTAVYYCAKDPSPYYRGSAYLLSGSYDSWGQGTQVTVSS
81A12v4     : ....L........P.....................|.....|.....|.....|.....|...L....|.R.....|.....|.....|.....|.....|.....L.....
VH3-23/JH5  : ....L........P...........F.F....S.|.....|...|..A..GS.GST.....|.....|...L....|.R.....|.....|---------.....|.....L.....
```

Figure 51C

```
Kabat#:          1        10        20        30        40        50        60        70        80        90        100                 110
                 |--------|---------|---------|---------|---------|--a------|---------|---------|--abc-----|---------|abcdefghijk---------|---
81G2        : EVQLVESGGGLVQPGGSLRLSCTASGLPFSTKSMGW RQAPGKE E V RISPGGTSRYY D VKGRF ISRDN KNT LQMNSL AEDTAVYYCA GERSTYIGSNYYRTNEYDYWG GTQVTVSS
81G2v11     : ....L.....................|.....|.....G...|.....|.....|.....|.....|.....|.....|.....|.....|.....|.....|.....L.....
VH3-23/JH5  : ....L.....................|...FT..SYA.S.|.....G...|..A..GS.G.T..S.....|.....|.....|.....|.....|---------.....L.....
```

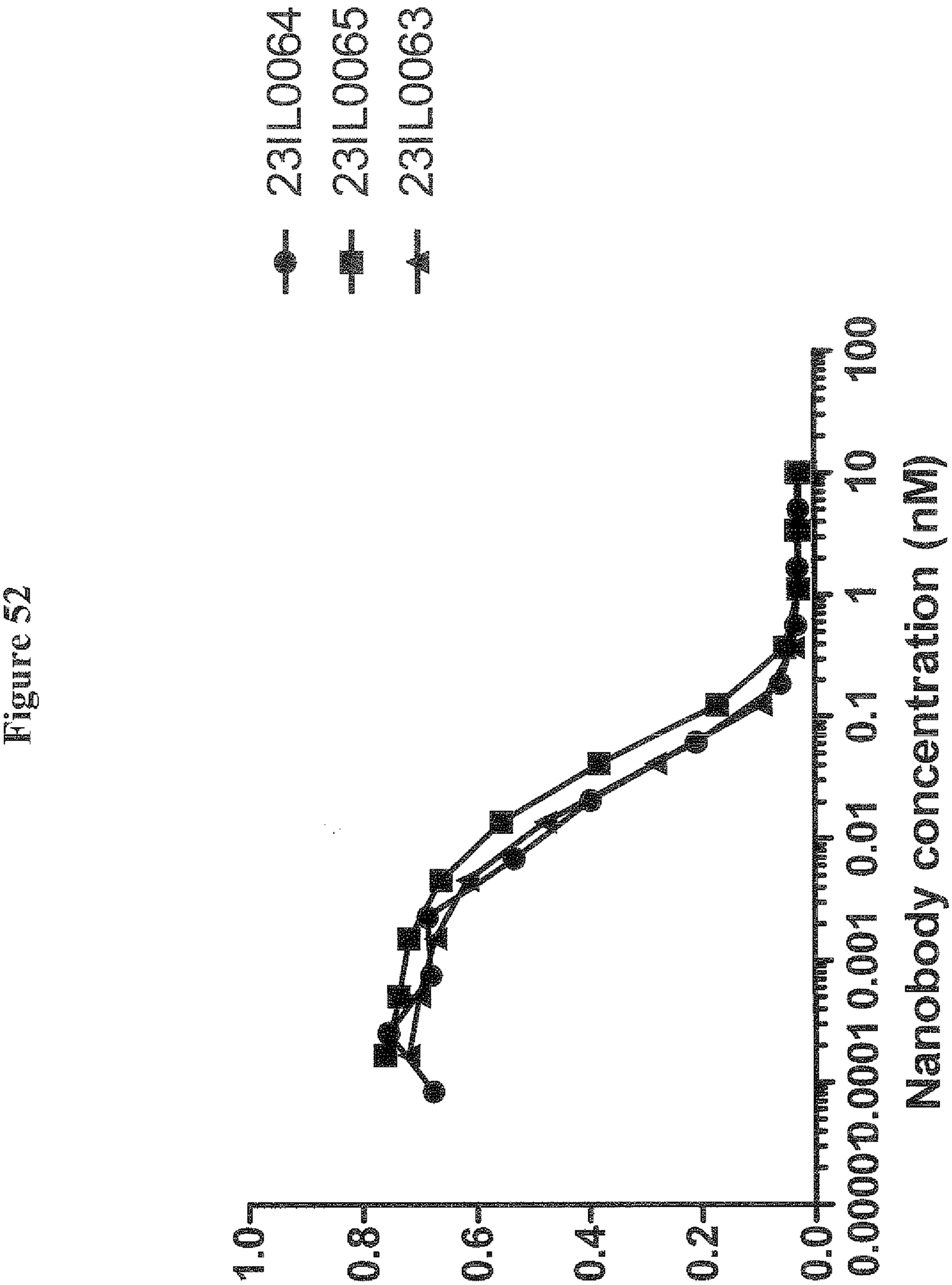
Figure 51D

```
Kabat#:          1        10        20        30        40        50        60        70        80        90        100                 110
                 |--------|---------|---------|---------|---------|--a------|---------|---------|--abc------|---------|abcdefghi---------|---
37D5        : EVQLVESGGGLVQPGGSLRLSCAASGFTLDYLAIGW RQAPGKE E VSCVSSSGQYTYYADSVKGRFTISRDN  T YLQMNSLK EDTAVYYCA DPECYRVRGYYNGEYDYWGQGTQVTVSS
37D5v1      : ....L.....................................G.....................................R.....................................L.....
37D5v3      : ....L.....................................G.....................................R.....................................L.....
37D5v6      : ....L.....................................G.....................................R.....................................L.....
37D5v16     : ....L.....................................G.....................................R.....................................L.....
VH3-23/JH5  : ....L.....................FSSY.MS.......G..S..AI.G..GS.....................D.....R.....------------------.....L.....
```

Figure 51E

```
Kabat#:          1        10        20        30        40        50        60        70        80        90        100                 110
                 |--------|---------|---------|---------|---------|--a------|---------|---------|--abc------|---------|abcdefgh---------|---
124C4       : EVQL ESGGGLVQPGGSLRLSCAASGFTLDDYAIAW RQAPGK  E VSGIDSGDGSAYYADSVKGRFTIS DN KNT YLQMNSLR EDTAVYYCA VRTGWGLNAPDYAMDYWG GTLVTVSS
124C4v1     : ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... .....
124C4v2     : ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... .....
124C4v3     : ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... ..... .....
VH3-23/JH5  : .... .....FSS..MS. ..... . ..A.SGSG..T..... .. ... ..... ..... ----------.. .....
```

Figure 52


23L0064
23L0065
23L0063
OD 450 nm
1.0
0.8
0.6
0.4
0.2
0.0
0.00001
0.0001
0.001
0.01
0.1
1
10
100
Nanobody concentration (nM)

23L0064

Figure 53

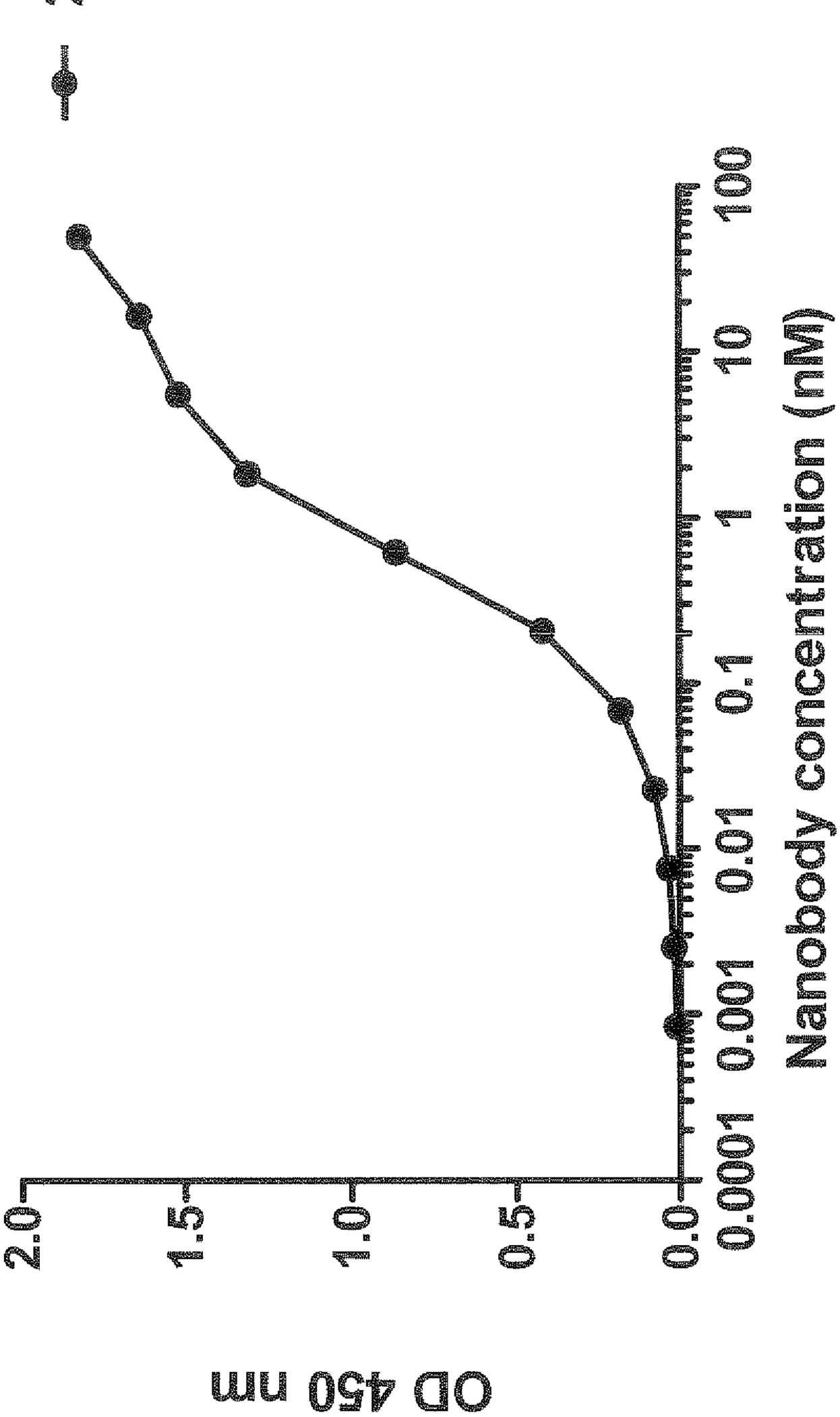
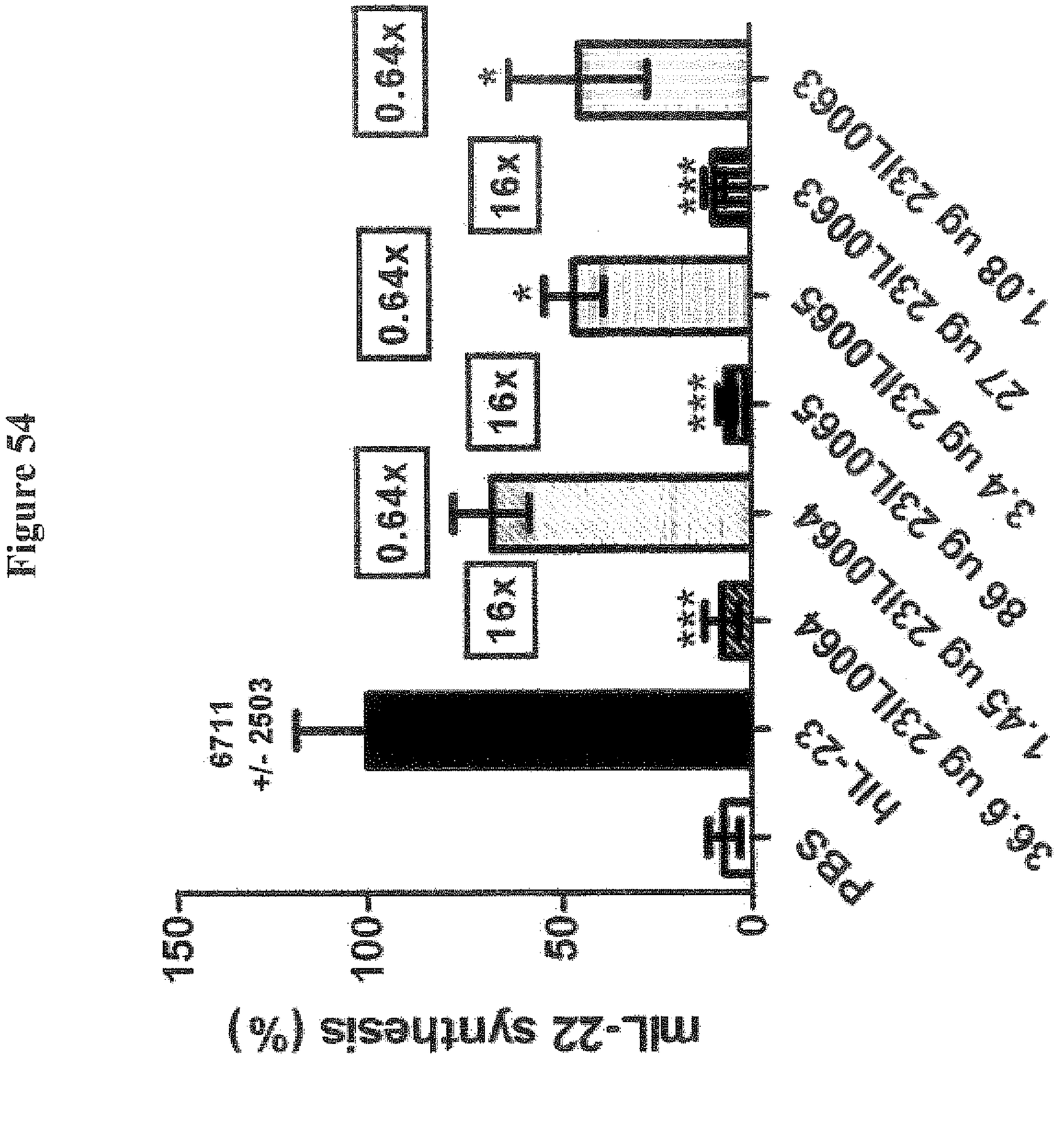


Figure 54


mIL-22 synthesis (%)
150
100
50
0
6711
+/- 2503
0.64x
16x
0.64x
16x
0.64x
16x
***
*
***
*
***
*
pBS
hIL-23
3G6 vg 23IL 006A
1.45 vg 23IL 006A
98 vg 23IL 006A
3.4 vg 23IL 006A
27 vg 23IL 006A
1.08 vg 23IL 006A

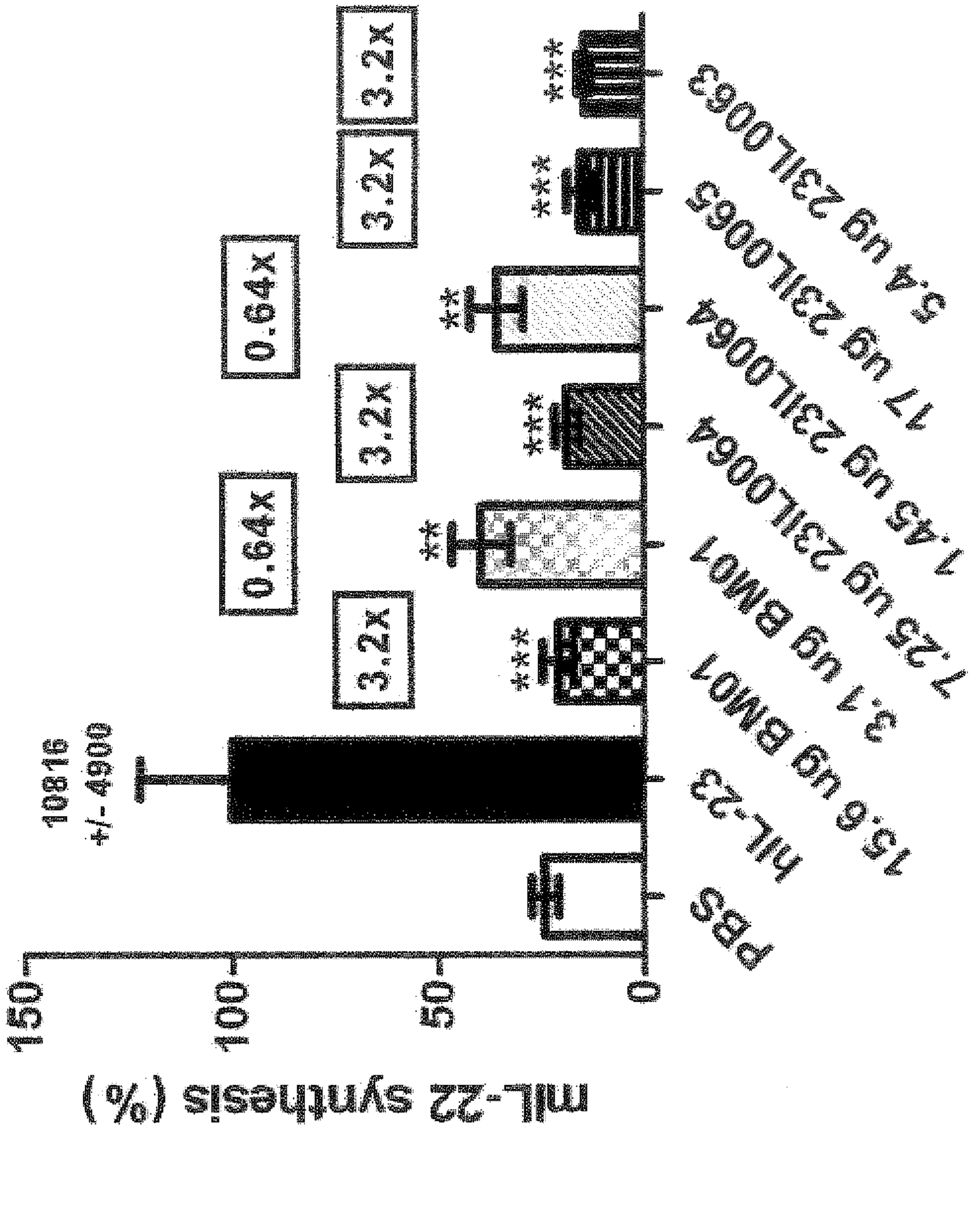
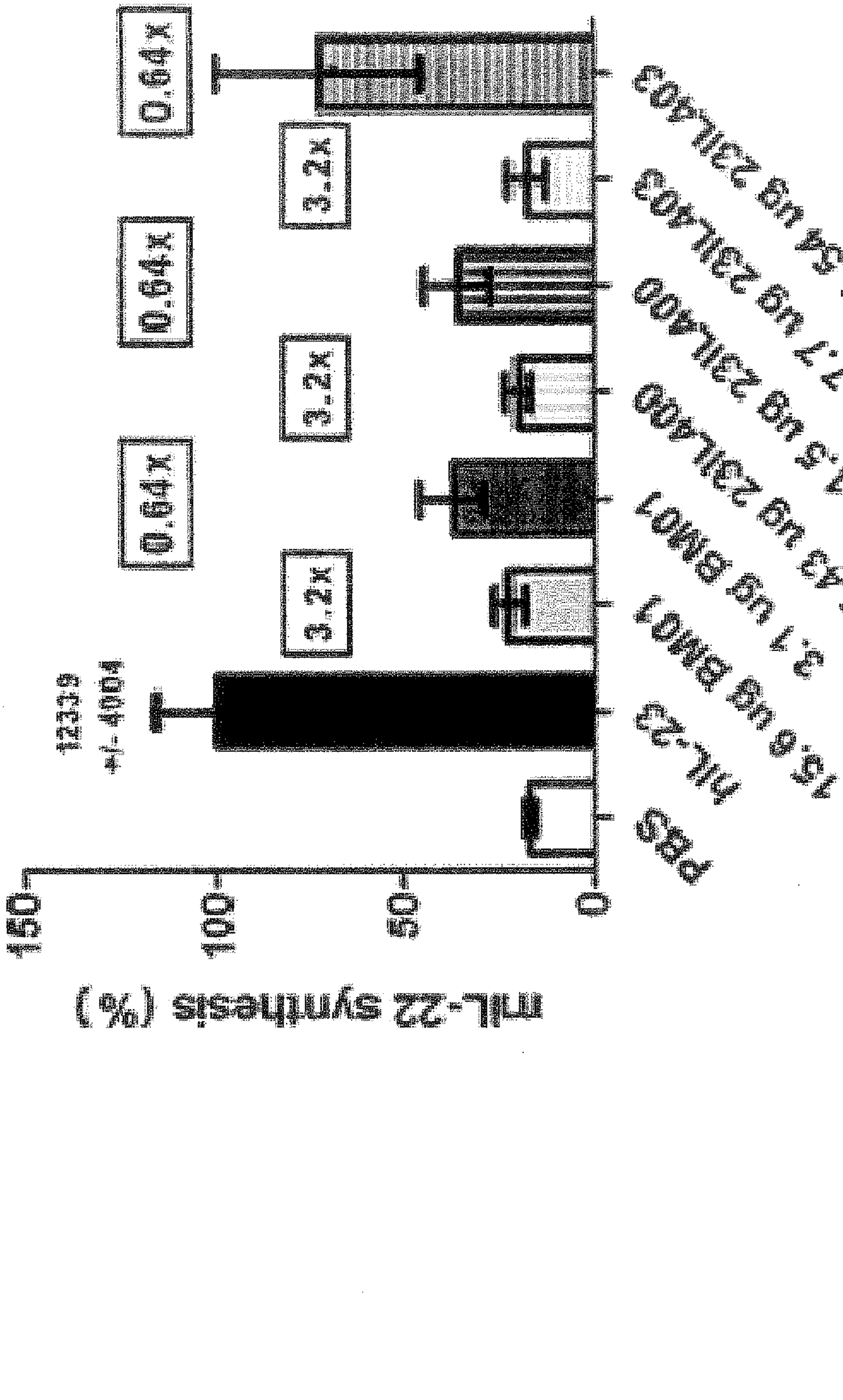

IL-22 synthesis (%)
150
100
50
0
PBS
hIL-23
15.6 ug BMO1
3.1 ug BMO1
1.23 ug BMO1
4900Ll6 ug BMO1
4900Ll17 ug BMO1
4900Ll5.4 ug BMO1
10816
+/- 4900
3.2x
0.64x
3.2x
3.2x
3.2x
0.64x
0.64x
***
**
***
***
**
***

Figure 55

Figure 56


mIL-22 synthesis (%)
150
100
50
0
Control
Control Ab 1
Control Ab 2
Control Ab 3
Control Ab 4
Control Ab 5
Control Ab 6
Control Ab 7
Control Ab 8
Control Ab 9
Control Ab 10
Control Ab 11
Control Ab 12
Control Ab 13
Control Ab