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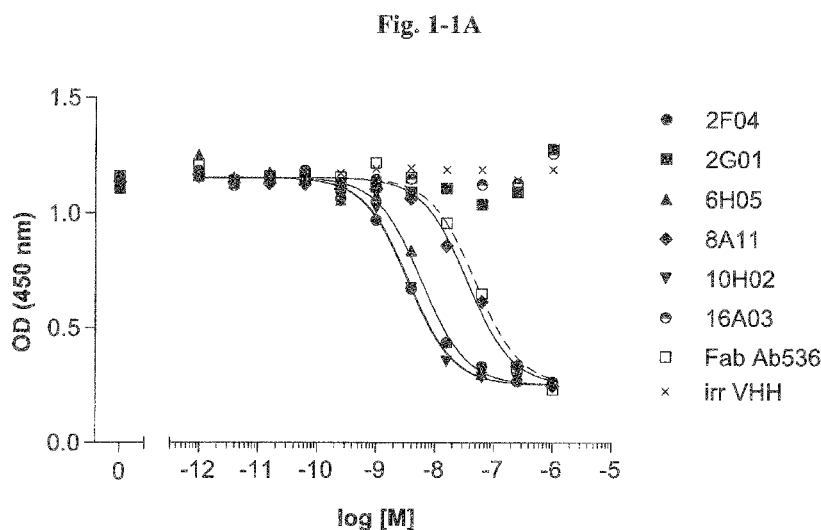
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(54) Title: ANG2-BINDING MOLECULES



(57) Abstract: Ang2-binding molecules, preferably Ang2-binding immunoglobulin single variable domains like VHHs and domain antibodies, pharmaceutical compositions containing same and their use in the treatment of diseases that are associated with Ang2-mediated effects on angiogenesis. Nucleic acids encoding Ang2-binding molecules, host cells and methods for preparing same.

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ANG2-BINDING MOLECULES

FIELD OF THE INVENTION

The invention relates to the field of human therapy, in particular cancer therapy and agents and
5 compositions useful in such therapy.

BACKGROUND OF THE INVENTION

As described in e.g. US 2008/0014196, WO 2008101985 and US 2011/0027286, angiogenesis
is the biological process whereby new blood vessels are formed and being implicated in the
pathogenesis of a number of disorders, including solid tumors and metastasis as well as eye
10 diseases. When tumors reach a critical size of approximately 1 mm³ they become dependent on
angiogenesis for maintaining blood supply with oxygen and nutrients to allow for further growth.
Anti-angiogenesis therapies have become an important treatment option for several types of
tumors.

One of the most important pro-angiogenic factors is Angiopoietin2 (Ang2), a ligand of the Tie2
15 receptor (Tie2), which controls vascular remodeling by enabling the functions of other
angiogenic factors, such as VEGF. Ang2 is also referred to in the art as Tie2 ligand
(US. Pat. No. 5,643,755, Yancopoulos et al. 2000, Nature 407: 242-248).

Ang2 is primarily expressed by endothelial cells, strongly induced by hypoxia and other
angiogenic factors and has been demonstrated to regulate tumor vessel plasticity, allowing
20 vessels to respond to VEGF and FGF2 (Augustin et al., Nat Rev Mol Cell Biol. 2009
Mar;10(3):165-77). Consistent with this role, the deletion or inhibition of Ang2 results in reduced
angiogenesis (Falcón et al., Am J Pathol. 2009 Nov;175(5):2159-70). Elevated Ang2 serum
concentrations have been reported for patients with colorectal cancer, NSCLC and melanoma
(Goede et al., Br J Cancer. 2010 Oct 26;103(9):1407-14),(Park et al., Chest. 2007 Jul;132(1):
25 200-6),(Helfrich et al., Clin Cancer Res. 2009 Feb 15;15(4):1384-92). In CRC cancer Ang2
serum levels correlate with therapeutic response to anti-VEGF therapy.

The Ang-Tie system consists of 2 receptors (Tie1 and Tie2) and 3 ligands (Ang1, Ang2 and Ang4) (Augustin et al., Nat Rev Mol Cell Biol. 2009 Mar;10(3):165-77). Tie2, Ang1 and Ang2 are the best studied members of this family, Tie1 is an orphan receptor and the role of Ang4 for vascular remodelling still needs to be defined. Ang2 and Ang1 mediate opposing functions upon Tie2 binding and activation. Ang2-mediated Tie2 activation results in endothelial cell activation, pericyte dissociation, vessel leakage and induction of vessel sprouting. In contrast to Ang2, Ang1 signaling maintains vessel integrity by recruitment of pericytes, thereby maintaining endothelial cell quiescence.

Angiopoietin 2 (Ang2) is a secreted, 66 kDa ligand for the Tie2 receptor tyrosine kinase (Augustin et al., Nat Rev Mol Cell Biol. 2009 Mar;10(3):165-77). Ang2 consists of an N-terminal coiled-coil domain and a C-terminal fibrinogen-like domain, the latter is required for Tie2 interaction. Ang2 is primarily expressed by endothelial cells and strongly induced by hypoxia and other angiogenic factors, including VEGF. Tie2 is found on endothelial cells, haematopoietic stem cells and tumor cells. Ang2-Tie2 has been demonstrated to regulate tumor vessel plasticity, allowing vessels to respond to VEGF and FGF2.

In vitro Ang2 has been shown to act as a modest mitogen, chemoattractant and inducer of tube formation in human umbilical vein endothelial cells (HUVEC). Ang2 induces tyrosine phosphorylation of ectopically expressed Tie2 in fibroblasts and promotes downstream signaling events, such as phosphorylation of ERK-MAPK, AKT and FAK in HUVEC. An antagonistic role of Ang2 in Ang1-induced endothelial cell responses has been described.

Ang2 -deficiency has been shown to result in a profound lymphatic patterning defect in mice. Although the loss of Ang2 is dispensable for embryonic vascular development, Ang2 -deficient mice have persistent vascular defects in the retina and kidney. Together with the dynamic pattern of Ang2 expression at sites of angiogenesis (for example ovary), these findings indicate that Ang2 controls vascular remodeling by enabling the functions of other angiogenic factors, such as VEGF.

The Ang2-Tie2 system exerts crucial roles during the angiogenic switch and later stages of tumor angiogenesis. Ang2 expression is strongly up-regulated in the tumor-associated endothelium. Reduced growth of tumors has been observed when implanted into Ang2 -deficient

mice, especially during early stages of tumor growth. Therapeutic blocking of Ang2 with Ang2 mAbs has shown broad efficacy in a variety of tumor xenograft models.

As summarized in the above mentioned US 2008/0014196, angiogenesis is implicated in the pathogenesis of a number of disorders, including solid tumors and metastasis.

5 In the case of tumor growth, angiogenesis appears to be crucial for the transition from hyperplasia to neoplasia, and for providing nourishment for the growth and metastasis of the tumor. Folkman *et al.*, Nature 339 -58 (1989), which allows the tumor cells to acquire a growth advantage compared to the normal cells. Therefore, anti-angiogenesis therapies have become an important treatment option for several types of tumors. These therapies have focused on
10 blocking the VEGF pathway (Ferrara *et al.*, Nat Rev Drug Discov. 2004 May;3(5):391-400)).

Antibodies and other peptide inhibitors that bind to Ang2 and Ang1 are mentioned in e.g. U.S. Patent Nos 6,166,185; 7,521,053; 7,205,275; and US Patent Application Nos.: 2006/0018909 and 2006/0246071. Furthermore, US 2011/0027286 discloses specific monoclonal Ang2 antibodies which do not antagonize the related molecule Ang1.

15 However, the state-of-the art monoclonal antibodies (MAbs) and fusion proteins have several shortcomings in view of their therapeutic application: To prevent their degradation, they must be stored at near freezing temperatures. Also, since they are quickly digested in the gut, they are not suited for oral administration. Another major restriction of MAbs for cancer therapy is poor transport, which results in low concentrations and a lack of targeting of all cells in a tumor.

20 It has been an object of the present invention to provide novel improved Ang2-binding molecules, i.e. nanobodies that block binding of Ang2 to Tie2 but not the binding of Ang1 to Tie2.

More in particular, it has been object of the invention to provide novel Ang2- binding molecules, and, specifically, Ang2-binding molecules that bind to mammalian Ang2 but not to mammalian
25 Ang1 and, especially, to human Ang2 but not to human Ang1, wherein such molecules or polypeptides are suitable for the therapeutic and diagnostic purposes as described herein. It has been a further object of the invention to provide immunoglobulin single variable domains that specifically bind to Ang2 but not to Ang1.

Such Ang2-binding molecules, or Ang2 antagonists, are useful as pharmacologically active agents in compositions in the prevention, treatment, alleviation and/or diagnosis of diseases or conditions associated with Ang2-mediated effects on angiogenesis.

Examples for such diseases are cancer or cancerous diseases such as breast cancer, renal cell carcinoma, ovarian cancer and pancreatic cancer, eye diseases such as age-related macular degeneration and diabetic retinopathy, and/or chronic kidney diseases such as diabetic nephropathy, postrenal failure, prerenal azotemia and intrinsic renal failure.

It has been a further object of the invention to provide methods for the prevention, treatment, alleviation and/or diagnosis of such diseases, disorders or conditions, involving the use and/or administration of such Ang2-binding molecules and compositions comprising them. In particular, it is has been an object of the invention to provide such pharmacologically active Ang2-binding molecules, compositions and/or methods that provide advantages compared to the agents, compositions and/or methods currently used and/or known in the art. These advantages include improved therapeutic and/or pharmacological properties and/or other advantageous properties, e.g. for manufacturing purposes, especially as compared to conventional antibodies as those described above, or fragments thereof.

BRIEF SUMMARY OF THE INVENTION

In a first aspect there is provided an Ang2-binding molecule comprising an immunoglobulin single variable domain,

wherein said immunoglobulin single variable domain comprises three complementarity determining regions CDR1, CDR2 and CDR3,

wherein CDR1 has an amino acid sequence shown in SEQ ID NO: 168, CDR2 has an amino acid sequence shown in SEQ ID NO: 171 and CDR3 has an amino acid sequence shown in SEQ ID NO: 175.

In a second aspect there is provided an expression vector comprising a nucleic acid molecule encoding the Ang2-binding molecule according to the first aspect, wherein said nucleic acid molecule is operably linked to a heterologous promoter, enhancer, or terminator sequence.

In a third aspect there is provided a host cell carrying one or more expression vector according to the second aspect.

In a fourth aspect there is provided a method for producing the Ang2-binding molecule according to the first aspect, comprising the steps of:

transfecting a host cell with one or more said expression vector according to the second aspect,

culturing said host cell, and
recovering and purifying said Ang2-binding molecule.

In a fifth aspect there is provided a pharmaceutical composition comprising, as the active ingredient, one or more said Ang2-binding molecule according to the first aspect, and at least a physiologically acceptable carrier. In a sixth aspect there is provided a method of treating cancer or a cancerous disease comprising administering a therapeutically effective amount of the Ang2-binding molecule according to the first aspect, or the pharmaceutical composition according to the fifth aspect to a subject in need thereof.

In a seventh aspect there is provided use of the Ang2-binding molecule according to the first aspect for the manufacture of a medicament for the treatment of cancer or a cancerous disease.

According to an aspect, there is provided an Ang2-binding molecule, comprising an immunoglobulin single variable domain, wherein said immunoglobulin single variable domain comprises three complementarity determining regions CDR1, CDR2 and CDR3, wherein CDR1 has an amino acid sequence selected from amino acid sequences shown in SEQ ID NOs: 168 to 170, CDR2 has an amino acid sequence selected from amino acid sequences shown in SEQ ID Nos: 171 to 173 and CDR3 has an amino acid selected from amino acid sequences shown in SEQ ID NOs: 174 to 177.

The invention further relates to an Ang2-binding molecule consisting of said immunoglobulin single variable domain.

Furthermore, the invention relates to an Ang2-binding molecule having a sequence selected

from a group consisting of SEQ ID Nos: 167, 166, 129 and 138.

According to another aspect, there is provided a nucleic acid encoding said Ang2-binding molecule as well as an expression vector comprising said nucleic acid.

5 The invention further relates to a host cell carrying one or more expression vectors comprising said nucleic acids.

The invention further relates to a method for producing or generating an Ang2-binding molecule according to the invention, comprising the steps of:

- (a) transfecting a host cell with one or more said vectors comprising said nucleic acid molecule,
- 10 (b) culturing said host cell, and
- (c) recovering and purifying said Ang2-binding molecule.

Further aspect of the invention relates to a pharmaceutical composition comprising, as the active ingredient, one or more said Ang2-binding molecules and at least a physiologically acceptable carrier

15 The invention further relates to applications and uses of the Ang2-binding molecules, nucleic acids, host cells, products and compositions described herein, as well as to methods for the prevention and/or treatment for diseases associated with Ang2-mediated effects on angiogenesis, preferably cancer, cancerous diseases and eye diseases.

20 These and other aspects, embodiments, advantages and applications of the invention will become clear from the further description hereinbelow.

DEFINITIONS

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
25 Spring Harbor Laboratory Press (1989); Lewin, "Genes IV", Oxford University Press, New York, (1990), and Roitt *et al.*, "Immunology" (2nd Ed.), Gower Medical Publishing, London, New York (1989), as well as to the general background art cited herein. Furthermore, 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, to the general background art referred to above and to the further references cited therein.

The term "*angiopoietin-2*" or "*Ang2*", unless specified as being from non-human species (e.g. "mouse *Ang2*", etc) refers to human *Ang2* or a biologically active fragment thereof (e.g. a fragment of the *Ang2* protein which is capable of inducing angiogenesis *in vitro* or *in vivo*), i.e. to human *Ang2* (variant 1) with accession no. NM_001147.2, to human *Ang2* (variant 2) having accession no. NM_001118887.1 or to human *Ang2* (variant 3) having accession no. NM_001118888.1, and/or their biologically active fragments thereof. The amino acid sequences of *Ang2* non human species, such as mouse *Ang2* and cyno *Ang2* are available from protein sequence database under Accession No: NM_007426.3 (SEQ ID NO: (SEQ ID 188) and AB172643.1 (SEQ ID NO: 187), respectively.

The term "*angiopoietin-1*" or "*Ang1*", unless specified as being from non-human species (e.g. "mouse *Ang2*", etc) refers to human *Ang1* or a biologically active fragment thereof (e.g. a fragment of the *Ang1* protein which is capable of inducing angiogenesis *in vitro* or *in vivo*), i.e. to human *Ang1* with accession no. NM_001146.3, or a biologically active fragment thereof.

Unless indicated otherwise, the terms "*immunoglobulin*" and "*immunoglobulin sequence*" - whether used herein to refer to a heavy chain antibody or to a conventional 4-chain antibody - are used as general terms 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 VHH domains or VH/VL domains, respectively). In addition, the term "sequence" as used herein (for example in terms like "immunoglobulin sequence", "antibody sequence", "(single) variable domain sequence", "VHH 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.

The term "*domain*" (of a polypeptide or protein) as used herein refers to a folded protein structure which has the ability to retain its tertiary structure independently of the rest of the protein. Generally, domains are responsible for discrete functional properties of proteins and in

many cases may be added, removed or transferred to other proteins without loss of function of the remainder of the protein and/or of the domain.

The term "*immunoglobulin domain*" as used herein refers to a globular region of an antibody chain (such as e.g. a chain of a conventional 4-chain antibody or of a heavy chain antibody), or to a polypeptide that essentially consists of such a globular region. Immunoglobulin domains are characterized in that they retain the immunoglobulin fold characteristic of antibody molecules, which consists of a 2-layer sandwich of about 7 antiparallel beta-strands arranged in two beta-sheets, optionally stabilized by a conserved disulphide bond.

The term "*immunoglobulin variable domain*" as used herein means an immunoglobulin domain essentially consisting of four "framework regions" which are referred to in the art and hereinbelow 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 "complementarity determining regions" or "CDRs", which are referred to in the art and hereinbelow as "complementarity determining region 1" or "CDR1"; as "complementarity determining region 2" or "CDR2"; and as "complementarity determining region 3" or "CDR3", respectively. Thus, the general structure or sequence of an immunoglobulin variable domain can be indicated as follows: FR1 - CDR1 - FR2 - CDR2 - FR3 - CDR3 - FR4. It is the immunoglobulin variable domain(s) that confer specificity to an antibody for the antigen by carrying the antigen-binding site.

The term "*immunoglobulin single variable domain*" as used herein means an immunoglobulin variable domain which is capable of specifically binding to an epitope of the antigen without pairing with an additional variable immunoglobulin domain. One example of immunoglobulin single variable domains in the meaning of the present invention are "domain antibodies", such as the immunoglobulin single variable domains VH and VL (VH domains and VL domains). Another example of immunoglobulin single variable domains are "VHH domains" (or simply "VHHs") from camelids, as defined hereinafter.

In view of the above definition, the antigen-binding domain of a conventional 4-chain antibody (such as an IgG, IgM, IgA, IgD or IgE molecule; known in the art) or of a Fab fragment, a F(ab')₂ fragment, an Fv fragment such as a disulphide linked Fv or a scFv fragment, or a diabody (all known in the art) derived from such conventional 4-chain antibody, would normally not be

regarded as an immunoglobulin single variable domain, as, in these cases, binding to the respective epitope of an antigen would normally not occur by one (single) immunoglobulin domain but by a pair of (associating) immunoglobulin domains such as light and heavy chain variable domains, i.e. by a VH-VL pair of immunoglobulin domains, which jointly bind to an epitope of the respective antigen.

"VHH domains", also known as VHHs, V_HH domains, VHH antibody fragments, and VHH antibodies, have originally been described as the antigen binding immunoglobulin (variable) domain of "heavy chain antibodies" (i.e. of "antibodies devoid of light chains"; Hamers-Casterman C, Atarhouch T, Muyldermans S, Robinson G, Hamers C, Songa EB, Bendahman N, Hamers R.: "Naturally occurring antibodies devoid of light chains"; Nature 363, 446-448 (1993)). The term "VHH domain" has been chosen in order to distinguish these variable domains from the heavy chain variable domains that are present in conventional 4-chain antibodies (which are referred to herein as "V_H domains" or "VH domains") and from the light chain variable domains that are present in conventional 4-chain antibodies (which are referred to herein as "V_L domains" or "VL domains"). VHH domains can specifically bind to an epitope without an additional antigen binding domain (as opposed to VH or VL domains in a conventional 4-chain antibody, in which case the epitope is recognized by a VL domain together with a VH domain). VHH domains are small, robust and efficient antigen recognition units formed by a single immunoglobulin domain.

In the context of the present invention, the terms VHH domain, VHH, V_HH domain, VHH antibody fragment, VHH antibody, as well as "Nanobody®" and "Nanobody® domain" ("Nanobody" being a trademark of the company Ablynx N.V.; Ghent; Belgium) are used interchangeably and are representatives of immunoglobulin single variable domains (having the structure FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4 and specifically binding to an epitope without requiring the presence of a second immunoglobulin variable domain), and which are distinguished from VH domains by the so-called "hallmark residues", as defined in e.g. WO2009/109635, Fig. 1.

The amino acid residues of a immunoglobulin single variable domain, e.g. a VHH, 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 VHH domains from Camelids, as shown e.g. in Figure 2 of Riechmann and Muyldermans, J. Immunol. Methods 231, 25-38 (1999).

According to this numbering,

- FR1 comprises the amino acid residues at positions 1-30,
- CDR1 comprises the amino acid residues at positions 31-35,
- FR2 comprises the amino acids at positions 36-49,
- 5 - CDR2 comprises the amino acid residues at positions 50-65,
- FR3 comprises the amino acid residues at positions 66-94,
- CDR3 comprises the amino acid residues at positions 95-102, and
- FR4 comprises the amino acid residues at positions 103-113.

However, it should be noted that - as is well known in the art for V_H domains and for
10 VHH domains - the total number of amino acid residues in each of the CDRs 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
15 according to Kabat may or may not correspond to the actual numbering of the amino acid residues in the actual sequence.

Alternative methods for numbering the amino acid residues of V_H domains, which methods can also be applied in an analogous manner to VHH domains, are known in the art. However, in the present description, claims and figures, the numbering according to Kabat and applied to
20 VHH domains as described above will be followed, unless indicated otherwise.

The total number of amino acid residues in a VHH domain will usually be in the range of from 110 to 120, often between 112 and 115. It should however be noted that smaller and longer sequences may also be suitable for the purposes described herein.

Immunoglobulin single variable domains, e.g. VHHs and domain antibodies, according to the
25 preferred embodiments of the invention, have a number of unique structural characteristics and functional properties which makes them highly advantageous for use in therapy as functional antigen-binding molecules. In particular, and without being limited thereto, VHH domains (which have been "designed" by nature to functionally bind to an antigen without pairing with a light chain variable domain) can function as single, relatively small, functional antigen-binding
30 structural units.

Due to their unique properties, immunoglobulin single variable domains, as defined herein, like VHHs or VHs (or VLs) - either alone or as part of a larger polypeptide, e.g. a biparatopic molecule - offer a number of significant advantages:

- 5 • 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 spatial conformation and configuration (i.e. through the use of especially designed linkers, as with scFv's);
- immunoglobulin single variable domains can be expressed from a single nucleic acid molecule and do not require any post-translational modification (like glycosylation);
- 10 • immunoglobulin single variable domains can easily be engineered into multivalent and multispecific formats (as further discussed herein);
- immunoglobulin single variable domains have high specificity and affinity for their target, low inherent toxicity and can be administered via alternative routes than infusion or injection;
- 15 • immunoglobulin single variable domains are highly stable to heat, pH, proteases and other denaturing agents or conditions and, thus, may be prepared, stored or transported without the use of refrigeration equipments;
- immunoglobulin single variable domains are easy and relatively inexpensive to prepare, both on small scale and on a manufacturing scale. For example, immunoglobulin single variable domains can be produced using microbial fermentation (e.g. as further described
- 20 below) and do not require the use of mammalian expression systems, as with for example conventional antibodies;
- immunoglobulin single variable domains are relatively small (approximately 15 kDa, or 10 times smaller than a conventional IgG) compared to conventional 4-chain antibodies
- 25 and antigen-binding fragments thereof, and therefore show high(er) penetration into tissues (including but not limited to solid tumors and other dense tissues) and can be administered in higher doses than such conventional 4-chain antibodies and antigen-binding fragments thereof;

- VHHs have specific so-called "cavity-binding properties" (inter alia due to their extended CDR3 loop, compared to VH domains from 4-chain antibodies) and can therefore also access targets and epitopes not accessible to conventional 4-chain antibodies and antigen-binding fragments thereof;
- 5 • VHHs have the particular advantage that they are highly soluble and very stable and do not have a tendency to aggregate (as with the mouse-derived antigen-binding domains described by Ward *et al.*, Nature 341: 544-546 (1989)).

The immunoglobulin single variable domains of the invention are not limited with respect to a specific biological source from which they have been obtained or to a specific method of
10 preparation. For example, obtaining VHHs may include the following steps:

- (1) isolating the VHH domain of a naturally occurring heavy chain antibody; or screening a library comprising heavy chain antibodies or VHHs and isolating VHHs therefrom;
- (2) expressing a nucleic acid molecule encoding a VHH with the naturally occurring sequence;
- (3) "humanizing" (as described herein) a VHH, optionally after affinity maturation, with a naturally
15 occurring sequence or expressing a nucleic acid encoding such humanized VHH;
- (4) "camelizing" (as described below) a immunoglobulin single variable heavy domain from a naturally occurring antibody from an animal species, in particular a species of mammal, such as from a human being, or expressing a nucleic acid molecule encoding such camelized domain;
- (5) "camelizing" a VH, or expressing a nucleic acid molecule encoding such a camelized VH;
- 20 (6) using techniques for preparing synthetically or semi-synthetically proteins, polypeptides or other amino acid sequences;
- (7) preparing a nucleic acid molecule encoding a VHH domain using techniques for nucleic acid synthesis, followed by expression of the nucleic acid thus obtained;
- (8) subjecting heavy chain antibodies or VHHs to affinity maturation, to mutagenesis (e.g.
25 random mutagenesis or site-directed mutagenesis) and/or any other technique(s) in order to increase the affinity and/or specificity of the VHH; and/or

(9) combinations or selections of the foregoing steps.

Suitable methods and techniques for performing the above-described steps are known in the art and will be clear to the skilled person. By way of example, methods of obtaining VHH domains binding to a specific antigen or epitope have been described in WO2006/040153 and
5 WO2006/122786.

According to specific embodiments, the immunoglobulin single variable domains of the invention or present in the polypeptides of the invention are VHH domains with an amino acid sequence that essentially corresponds to the amino acid sequence of a naturally occurring VHH domain, but that has been "humanized" or "sequence-optimized" (optionally after affinity-maturation), i.e.
10 by replacing one or more amino acid residues in the amino acid sequence of said naturally occurring VHH sequence by one or more of the amino acid residues that occur at the corresponding position(s) in a variable heavy domain of a conventional 4-chain antibody from a human being. This can be performed using methods known in the art, which can be routinely used by the skilled person.

15 A humanized VHH domain may contain one or more fully human framework region sequences, and, in an even more specific embodiment, may contain human framework region sequences derived from the human germline Vh3 sequences DP-29, DP-47, DP-51, or parts thereof, or be highly homologous thereto, optionally combined with JH sequences, such as JH5. Thus, a humanization protocol may comprise the replacement of any of the VHH residues with the
20 corresponding framework 1, 2 and 3 (FR1, FR2 and FR3) residues of germline VH genes such as DP 47, DP 29 and DP 51) either alone or in combination. Suitable framework regions (FR) of the immunoglobulin single variable domains of the invention can be selected from those as set out e.g. in WO 2006/004678 and specifically, include the so-called "KERE" and "GLEW" classes. Examples are immunoglobulin single variable domains having the amino acid sequence
25 G-L-E-W at about positions 44 to 47, and their respective humanized counterparts. A humanized VHH domain may contain one or more fully human framework region sequences.

By way of example, a humanizing substitution for VHHs belonging to the 103 P,R,S-group and/or the GLEW-group (as defined below) is 108Q to 108L. Methods for humanizing immunoglobulin single variable domains are known in the art.

Binding immunoglobulin single variable domains with improved properties in view of therapeutic application, e.g. enhanced affinity or decreased immunogenicity, may be obtained from individual binding molecules by techniques known in the art, such as affinity maturation (for example, starting from synthetic, random or naturally occurring immunoglobulin sequences),
5 CDR grafting, humanizing, 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, also termed "sequence optimization", as described herein. Reference is, for example, made to standard handbooks, as well as to the further description and Examples.

10 If appropriate, a binding molecule with increased affinity may be obtained by affinity-maturation of another binding molecule, the latter representing, with respect to the affinity-matured molecule, the "parent" binding molecule.

Methods of obtaining VHHs that bind to a specific antigen or epitope have been described earlier, e.g. in WO2006/040153 and WO2006/122786. As also described therein in detail,
15 VHH domains derived from camelids can be "humanized" (also termed "sequence-optimized" herein, "sequence-optimizing" may, in addition to humanization, encompass an additional modification of the sequence by one or more mutations that furnish the VHH with improved properties, such as the removal of potential post translational modification sites) by replacing one or more amino acid residues in the amino acid sequence of the original VHH sequence by
20 one or more of the amino acid residues that occur at the corresponding position(s) in a VH domain from a conventional 4-chain antibody from a human being. A humanized VHH domain can contain one or more fully human framework region sequences, and, in an even more specific embodiment, can contain human framework region sequences derived from DP-29, DP-47, DP-51, or parts thereof, optionally combined with JH sequences, such as JH5.

25 "*Domain antibodies*", also known as "Dab"s and "dAbs" (the terms "Domain Antibodies" and "dAbs" being used as trademarks by the GlaxoSmithKline group of companies) have been described in e.g. Ward, E.S., et al.: "Binding activities of a repertoire of single immunoglobulin variable domains secreted from *Escherichia coli*"; *Nature* 341: 544-546 (1989); Holt, L.J. et al.: "Domain antibodies: proteins for therapy"; *TRENDS in Biotechnology* 21(11): 484-490 (2003);
30 and WO2003/002609.

Domain antibodies essentially correspond to the VH or VL domains of antibodies from non-camelid mammals, in particular human 4-chain antibodies. In order to bind an epitope as a single antigen binding domain, i.e. without being paired with a VL or VH domain, respectively, specific selection for such antigen binding properties is required, e.g. by using libraries of human
5 single VH or VL domain sequences.

Domain antibodies have, like VHHs, a molecular weight of approximately 13 to approximately 16 kDa and, if derived from fully human sequences, do not require humanization for e.g. therapeutic use in humans. As in the case of VHH domains, they are well expressed also in prokaryotic expression systems, providing a significant reduction in overall manufacturing cost.

10 Furthermore, it will also be clear to the skilled person that it is possible to "graft" one or more of the CDR's mentioned above onto other "scaffolds", including but not limited to human scaffolds or non-immunoglobulin scaffolds. Suitable scaffolds and techniques for such CDR grafting are known in the art.

The terms "*epitope*" and "*antigenic determinant*", which can be used interchangeably, refer to
15 the part of a macromolecule, such as a polypeptide that is recognized by antigen-binding molecules, such as conventional antibodies or the polypeptides of the invention, and more particularly by the antigen-binding site of said molecules. Epitopes define the minimum binding site for an immunoglobulin, and thus represent the target of specificity of an immunoglobulin.

A polypeptide (such as an immunoglobulin, an antibody, an immunoglobulin single variable
20 domain of the invention, or generally an antigen-binding molecule or a fragment thereof) that can "*bind to*" or "*specifically bind to*", that "*has affinity for*" and/or that "*has specificity for*" a certain epitope, antigen or protein (or for at least one part, fragment or epitope thereof) is said to be "*against*" or "*directed against*" said epitope, antigen or protein or is a "*binding*" molecule with respect to such epitope, antigen or protein. In this context, an Ang2-binding molecule may also
25 be referred to as "*Ang2-neutralizing*".

Generally, the term "*specificity*" refers to the number of different types of antigens or epitopes to which a particular antigen-binding molecule or antigen-binding protein (such as an immunoglobulin single variable domain of the invention) molecule can bind. The specificity of an antigen-binding molecule can be determined based on its affinity and/or avidity. The affinity,

represented by the equilibrium constant for the dissociation of an antigen with an antigen-binding protein (KD), is a measure for the binding strength between an epitope and an antigen-binding site on the antigen-binding protein: the lesser the value of the KD, the stronger the binding strength between an epitope and the antigen-binding molecule (alternatively, the affinity can also be expressed as the affinity constant (KA), which is 1/KD). 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 an immunoglobulin, an antibody, an immunoglobulin single variable domain or a polypeptide containing it and the pertinent antigen. Avidity is related to both the affinity between an epitope and its antigen binding site on the antigen-binding molecule and the number of pertinent binding sites present on the antigen-binding molecule.

The part of an antigen-binding molecule (such as an antibody or an immunoglobulin single variable domain of the invention) that recognizes the epitope is called a "*paratope*".

Unless indicated otherwise, the term "*Ang2-binding molecule*" includes anti- Ang2 antibodies, anti- Ang2 antibody fragments, "*anti- Ang2 antibody-like molecules*" and conjugates with any of these. Antibodies include, but are not limited to, monoclonal and chimerized monoclonal antibodies. The term "*antibody*" encompasses complete immunoglobulins, like monoclonal antibodies produced by recombinant expression in host cells, as well as Ang2-binding antibody fragments or "*antibody-like molecules*", including single-chain antibodies and linear antibodies, so-called "*SMIPs*" ("Small Modular Immunopharmaceuticals"), as e.g. described in WO02/056910. Anti- Ang2 antibody-like molecules include immunoglobulin single variable domains, as defined herein. Other examples for antibody-like molecules are immunoglobulin super family antibodies (IgSF), or CDR-grafted molecules.

"*Ang2-binding molecule*" refers to monovalent Ang2-binding molecules (i.e. molecules that bind to one epitope of Ang2) as well as to Ang2-binding molecules containing more than one Ang2-binding immunoglobulin single variable domain, also termed "*formatted*" Ang2-binding molecules. The formatted Ang-2binding molecules may, in addition to the Ang2-binding immunoglobulin single variable domains, comprise linkers and/or moieties with effector

functions, e.g. half-life-extending moieties like albumin-binding immunoglobulin single variable domains, and/or a fusion partner like serum albumin and/or an attached polymer like PEG.

A formatted Ang2-binding molecule may, albeit less preferred, also comprise two identical Ang2-binding immunoglobulin single variable domains or two different immunoglobulin single variable domains that recognize the same or overlapping epitopes. In this case, the two immunoglobulin single variable domains may bind to the same or an overlapping epitope in each of the two monomers that form the Ang2 dimer. Experimental data including competitive ELISA assay discloses a significant improvement in the potency of the formatted Ang2 dimers when compared to the individual building blocks of mono Ang2-binding molecules (data not shown).

Typically, the Ang2-binding molecules of the invention will bind with a dissociation constant (K_D) of $10E-5$ to $10E-14$ moles/liter (M) or less, and preferably $10E-7$ to $10E-14$ moles/liter (M) or less, more preferably $10E-8$ to $10E-14$ moles/liter, and even more preferably $10E-11$ to $10E-13$ (as measured in a Biacore or in a KinExA assay), and/or with an association constant (K_A) of at least $10E7$ ME-1, preferably at least $10E8$ ME-1, more preferably at least $10E9$ ME-1, such as at least $10E11$ ME-1. Any K_D value greater than $10E-4$ M is generally considered to indicate non-specific binding. Preferably, a polypeptide of the invention will bind to the desired antigen, i.e. Ang2, with a K_D 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 epitope can be determined in any suitable manner known per se, including, for example, the assays described herein, 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.

Amino acid residues will be indicated according to the standard three-letter or one-letter amino acid code, as generally known and agreed upon in the art. When comparing two amino acid sequences, the term "*amino acid difference*" refers to insertions, deletions or substitutions of the indicated number of amino acid residues at a position of the reference sequence, compared to a second sequence. In case of substitution(s), such substitution(s) will preferably be conservative amino acid substitution(s), which means that 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 WO98/49185, wherein conservative amino acid substitutions preferably are substitutions in which one amino acid within the following groups (i) - (v) is substituted by another amino acid residue within the same group:

(i) small aliphatic, nonpolar or slightly polar residues: Ala, Ser, Thr, Pro and Gly; (ii) polar, negatively charged residues and their (uncharged) amides: Asp, Asn, Glu and Gln; (iii) polar, positively charged residues: His, Arg and Lys; (iv) large aliphatic, nonpolar residues: Met, Leu, Ile, Val and Cys; and (v) aromatic residues: Phe, Tyr and Trp. Particularly preferred conservative amino acid 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 or into Phe; Val into Ile or into Leu.

A polypeptide or nucleic acid molecule is considered to be "*in essentially isolated form*" - for example, when 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 protein/polypeptide, another nucleic acid, another biological component or macromolecule or at least one contaminant, impurity or minor component. In particular, a polypeptide or nucleic acid molecule 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 polypeptide or nucleic acid molecule 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.

The term "*N-terminus*" (also known as the amino-terminus, NH₂-terminus, N-terminal end or amine-terminus) refers to the start of a protein/polypeptide (i.e. Ang2-binding molecule) terminated by an amino acid with a free amine group (-NH₂). The convention for writing peptide sequences is to put the N-terminus on the left and write the sequence from N- to C-terminus. When the protein is translated from messenger RNA, it is created from N-terminus to C-terminus.

"Sequence identity" between two Ang2-binding molecule sequences indicates the percentage of amino acids that are identical between the sequences. It may be calculated or determined as described in paragraph f) on pages 49 and 50 of WO08/020079. "Sequence similarity" indicates the percentage of amino acids that either is identical or that represent conservative amino acid substitutions.

Alternative methods for numbering the amino acid residues of V_H domains, which methods can also be applied in an analogous manner to VHH domains, are known in the art. However, in the present description, claims and figures, the numbering according to Kabat and applied to VHH domains as described above will be followed, unless indicated otherwise.

An "affinity-matured" Ang2-binding molecule, in particular a VHH or a domain antibody, has one or more alterations in one or more CDRs which result in an improved affinity for Ang2, as compared to the respective parent Ang2-binding molecule. Affinity-matured Ang2-binding molecules of the invention may be prepared by methods known in the art, for example, as described by Marks *et al.*, 1992, *Biotechnology* 10:779-783, or Barbas, *et al.*, 1994, *Proc. Nat. Acad. Sci, USA* 91: 3809-3813.; Shier *et al.*, 1995, *Gene* 169:147-155; Yelton *et al.*, 1995, *Immunol.* 155: 1994-2004; Jackson *et al.*, 1995, *J. Immunol.* 154(7):3310-9; and Hawkins *et al.*, 1992, *J. Mol. Biol.* 226(3): 889 896; KS Johnson and RE Hawkins, "Affinity maturation of antibodies using phage display", Oxford University Press 1996.

For the present invention, an "amino acid sequences of SEQ ID NO: x": includes, if not otherwise stated, an amino acid sequence that is 100% identical with the sequence shown in the respective SEQ ID NO: x;

- a) amino acid sequences that have at least 80% amino acid identity with the sequence shown in the respective SEQ ID NO: x;
- b) amino acid sequences that have 3, 2, or 1 amino acid differences with the sequence shown in the respective SEQ ID NO: x.

The terms "cancer" and "cancerous" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth/proliferation. Examples of cancer to be treated with an Ang2-binding molecule of the invention include but are not limited to carcinoma, lymphoma, blastoma, sarcoma, and leukemia. More particular examples of such cancers,

include squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, colorectal
5 cancer, renal cell carcinoma, endometrial or uterine carcinoma, salivary gland carcinoma, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, gastric cancer, melanoma, and various types of head and neck cancer. Dysregulation of angiogenesis can lead to many disorders that can be treated by compositions and methods of the invention. These disorders include both non-neoplastic and neoplastic conditions. Neoplasies include but
10 are not limited those described above.

Non-neoplastic disorders include, but are not limited to undesired or aberrant hypertrophy, arthritis, rheumatoid arthritis (RA), psoriasis, psoriatic plaques, sarcoidosis, atherosclerosis, atherosclerotic plaques, diabetic and other proliferative retinopathies including retinopathy of
15 prematurity, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, diabetic macular edema, corneal neovascularization, corneal graft neovascularization, corneal graft rejection, retinal/choroidal neovascularization, neovascularization of the angle (rubeosis), ocular neovascular disease, vascular restenosis, arteriovenous malformations (AVM), meningioma, hemangioma, angiofibroma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, chronic inflammation, lung inflammation, acute lung
20 injury/ ARDS, sepsis, primary pulmonary hypertension, malignant pulmonary effusions, cerebral edema (e.g., associated with acute stroke/ closed head injury/ trauma), synovial inflammation, pannus formation in RA, myositis ossificans, hypertrophic bone formation, osteoarthritis (OA), refractory ascites, polycystic ovarian disease, endometriosis, 3rd spacing of fluid diseases (pancreatitis, compartment syndrome, burns, bowel disease), uterine fibroids, premature labor,
25 chronic inflammation such as IBD (Crohn's disease and ulcerative colitis), renal allograft rejection, inflammatory bowel disease, nephrotic syndrome, undesired or aberrant tissue mass growth (non-cancer), hemophilic joints, hypertrophic scars, inhibition of hair growth, Osier-Weber syndrome, pyogenic granuloma retrolental fibroplasias, scleroderma, trachoma, vascular adhesions, synovitis, dermatitis, preeclampsia, ascites, pericardial effusion (such as that
30 associated with pericarditis), and pleural effusion.

The term "eye diseases" refers to proliferative retinopathies including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, diabetic macular edema, corneal neovascularization, corneal graft neovascularization, corneal graft rejection, retinal/choroidal neovascularization.

5 The term "chronic kidney diseases" refers to diabetic nephropathy, postrenal failure, prerenal azotemia and intrinsic renal failure.

DETAILED DESCRIPTION OF THE INVENTION

10 In a first aspect, the present invention relates to an Ang2-binding molecule comprising an immunoglobulin single variable domain, wherein said immunoglobulin single variable domain comprises three complementarity determining regions CDR1, CDR2 and CDR3, wherein CDR1 has an amino acid sequence selected from amino acid sequences shown in SEQ ID NOs: 168 to 170, CDR2 has an amino acid sequence selected from amino acid sequences shown in SEQ ID NOs: 171 to 173 and CDR3 has an amino acid selected from amino acid sequences
 15 SEQ ID NOs: 174 to 177.

CDR1 has a sequence selected from

- SEQ ID NO: 168 DYAIG
- SEQ ID NO: 169 DYALG
- 20 SEQ ID NO: 170 YYAIG

CDR2 has a sequence selected from

- SEQ ID NO: 171 AIRSSGGSTYYADSVKG
- SEQ ID NO: 172 CIRCSGGSTYYADSVKG
- SEQ ID NO: 173 CISSSGGITYYADSVKG

25

CDR3 has a sequence selected from

- SEQ ID NO: 174 VPAGRLRFGEQWYPLYEYDA
- SEQ ID NO: 175 VPAGRLRYGEQWYPIYEYDA
- SEQ ID NO: 176 SIVPRSKLEPYEYDA
- 30 SEQ ID NO: 177 DSGGYIDYDCSGLGYDY

According to preferred embodiments, the Ang2-binding molecule comprises an immunoglobulin single variable domain, wherein

- 5 (a) CDR1 has an amino acid sequence shown in SEQ ID NO: 168, CDR2 has an amino acid sequence shown in SEQ ID NO: 171 and CDR3 has an amino acid sequence shown in SEQ ID NO: 174, or wherein
- (b) CDR1 has an amino acid sequence shown in SEQ ID NO: 168, CDR2 has an amino acid sequence shown in SEQ ID NO: 171 and CDR3 has an amino acid sequence shown in SEQ ID NO: 175, or wherein
- 10 (c) CDR1 has an amino acid sequence shown in SEQ ID NO: 169, CDR2 has an amino acid sequence shown in SEQ ID NO: 172 and CDR3 has an amino acid sequence shown in SEQ ID NO: 176, or wherein
- (d) CDR1 has an amino acid sequence shown in SEQ ID NO: 170, CDR2 has an amino acid sequence shown in SEQ ID NO: 173 and CDR3 has an amino acid sequence shown in SEQ ID NO: 177.

15 According to another preferred embodiments, the Ang2-binding molecule comprises an immunoglobulin single variable domain, wherein said immunoglobulin single variable domain is a VHH or a domain antibody.

According to still more preferred embodiments, the Ang2-binding molecule comprises an immunoglobulin single variable domain, wherein said immunoglobulin single variable domain is
20 a VHH.

According to specific embodiments, said VHH consists of an immunoglobulin single variable domain having a sequence selected from a group consisting of SEQ ID NOs: 167, 166, 129 and 138.

In another aspect, the present invention relates to an Ang2-binding molecule consisting of said
25 immunoglobulin single variable domain.

The sequence of the Ang2 binders according to the invention can be modified at their N-terminus (i.e. deletion or exchange of the first amino acid) without significant reduction of their binding activity. This modification enhances the co-/post-translational cleavage of N-terminal

methionine during intracellular/cytoplasmic expression in bacterial hosts (e.g. but not limited to *Escherichia coli*).

5 In one aspect said VHH consisting of an immunoglobulin single variable domain has a modification or exchange on N terminus, wherein said modification is a deletion of a first amino acid and said exchange is a replacement of the first amino acid by another amino acid.

In one of preferred embodiments the first amino acid on N terminus is Valine (V) or Aspartic acid (D) replaced by e.g. by Alanine (A).

10 Ang2-binding components with improved properties in view of therapeutic application, e.g. enhanced affinity or decreased immunogenicity, may be obtained from individual Ang2-binding components of the invention by techniques such as affinity maturation (for example, starting from synthetic, random or naturally occurring immunoglobulin sequences), CDR grafting, humanizing, combining fragments derived from different immunoglobulin sequences, PCR
15 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 standard handbooks, as well as to the further description and Examples.

20 Preferably, an Ang2-binding component of the invention with increased affinity is obtained by affinity-maturation of another Ang2-binding component, the latter representing, with respect to the affinity-matured molecule, the "parent" Ang2-binding component.

Thus, in yet another preferred embodiment, an Ang2-binding molecule of the invention is an immunoglobulin single variable domain that has been obtained by affinity maturation of a parent immunoglobulin single variable domain defined above.

25 In yet another preferred embodiment, the invention relates to an immunoglobulin single variable domain obtained by affinity-maturation of a VHH.

In a preferred embodiment, the invention relates to an immunoglobulin single variable domain that has been used for humanization of a VHH with an amino acid sequence shown in SEQ ID NOs: 1, 17 and 80.

In another preferred embodiment, the invention relates to an immunoglobulin single variable domain that has been obtained by humanization of a VHH with an amino acid sequence shown in SEQ ID NOs: 127, 132 and 146.

5 The invention also relates to Ang2-binding molecules that have been obtained by affinity maturation and/or sequence optimization of an above-defined VHH, e.g. to a VHH that has been obtained by sequence optimization of a VHH having an amino acid sequence shown as SEQ ID NOs: 167, 166, 129 and 138.

10 In another more preferred embodiment, the invention relates to an immunoglobulin single variable domain that has been obtained by affinity maturation of a VHH with an amino acid sequence shown in SEQ ID NO: 167.

In even more preferred embodiment, the invention relates to an immunoglobulin single variable domain that has been obtained by affinity maturation of a VHH with an amino acid sequence shown in SEQ ID NO: 166.

15 In yet another preferred embodiment, the invention relates to an immunoglobulin single variable domain that has been obtained by affinity maturation of a VHH with an amino acid sequence shown in SEQ ID NO: 129.

20 In still further preferred embodiment, the invention relates to an immunoglobulin single variable domain that has been obtained by affinity maturation of a VHH with an amino acid sequence shown in SEQ ID NO: 138.

25 In yet another embodiment, the representatives of the class of Ang2-binding immunoglobulin single variable domains of the invention or present in the polypeptides of the invention have amino acid sequences that correspond to the amino acid sequence of a naturally occurring VH domain that has been "camelized", i.e. by replacing one or more amino acid residues in the amino acid sequence of a naturally occurring variable heavy chain from a conventional 4-chain antibody by one or more amino acid residues that occur at the corresponding position(s) in a VHH domain of a heavy chain antibody. This can be performed in a manner known per se, which will be clear to the skilled person, and reference is additionally be made to WO 1994/04678.

Such camelization may preferentially occur at amino acid positions which are present at the VH-VL interface and at the so-called Camelidae Hallmark residues (see for example also WO 1994/04678). A detailed description of such "humanization" and "camelization" techniques and preferred framework region sequences consistent therewith can additionally be taken from
5 e.g. pp. 46 and pp. 98 of WO 2006/040153 and pp. 107 of WO 2006/122786.

The Ang2-binding components of the invention, e.g. immunoglobulin single variable domains and or polypeptides containing them, have specificity for Ang2 in that they comprise one or more immunoglobulin single variable domains specifically binding to one or more epitopes within the Ang2 molecule.

10 Specific binding of an Ang2-binding component to its antigen Ang2 can be determined in any suitable manner known per se, including, for example, the assays described herein, Scatchard analysis and/or competitive binding assays, such as radioimmunoassays (RIA), enzyme immunoassays (EIA and ELISA) and sandwich competition assays, and the different variants thereof known per se in the art.

15 With regard to the antigen Ang2, an Ang2-binding component of the invention, e.g. an immunoglobulin single variable domain, is not limited with regard to the species. Thus, the immunoglobulin single variable domains of the invention or polypeptides containing them preferably bind to human Ang2, if intended for therapeutic purposes in humans. However, immunoglobulin single variable domains that bind to Ang2 from another mammalian species, or
20 polypeptides containing them, are also within the scope of the invention. An immunoglobulin single variable domain of the invention binding to one species form of Ang2 may cross-react with Ang2 from one or more other species. For example, immunoglobulin single variable domains of the invention binding to human Ang2 may exhibit cross reactivity with Ang2 from one or more other species of primates and/or with Ang2 from one or more species of animals that are used in
25 animal models for diseases, for example monkey (in particular Cynomolgus or Rhesus), mouse, rat, rabbit, pig, dog or) and in particular in animal models for diseases and disorders associated with Ang2-mediated effects on angiogenesis (such as the species and animal models mentioned herein). Immunoglobulin single variable domains of the invention that show such cross-reactivity are advantageous in a research and/or drug development, since it allows the immunoglobulin

single variable domains of the invention to be tested in acknowledged disease models such as monkeys, in particular *Cynomolgus* or Rhesus, or mice and rats.

Also, the Ang2-binding components of the invention are not limited to or defined by a specific domain or an antigenic determinant of Ang2 against which they are directed. Preferably, in view of cross-reactivity with one or more Ang2 molecules from species other than human that is/are intended for use as an animal model during development of a therapeutic Ang2 antagonist, a Ang2-binding component recognizes an epitope in a region of the Ang2 of interest that has a high degree of identity with human Ang2. By way of example, in view of using a mouse model, an immunoglobulin single variable domain of the invention recognizes an epitope which is, totally or in part, located within the FLD-domain published in Kim H-Z, Jung K, Kim HM, Cheng Y, and Koh GY (2009). A designed angiopoietin-2 variant, pentameric COMP-Ang2, strongly activates Tie2 receptor and stimulated angiogenesis. *Biochim Biophys Acta* 1793, 772-780.

Therefore, according to a preferred embodiment, the invention relates to a Ang2-binding component, in particular an immunoglobulin single variable domain or a polypeptide containing same, wherein said immunoglobulin single variable domain is selected from the group that binds to an epitope that is totally or partially contained within the FLD domain (SEQ ID NOs: 188 to 190).

Preferably, an immunoglobulin single variable domain of the invention binds to Ang2 with an affinity less than 500 nM, preferably less than 200 nM, more preferably less than 10 nM, such as less than 500 pM (as determined by Surface Plasmon Resonance analysis).

Preferably, the immunoglobulin single variable domains of the invention have IC_{50} values, as measured in a competition ELISA assay in the range of 10^{-6} to 10^{-10} moles/litre or less, more preferably in the range of 10^{-8} to 10^{-10} moles/litre or less and even more preferably in the range of 10^{-9} to 10^{-10} moles/litre or less.

According to a non-limiting but preferred embodiment of the invention, Ang2-binding immunoglobulin single variable domains of the invention or polypeptides containing them bind to Ang2 with an dissociation constant (K_D) of 10^{-5} to 10^{-12} moles/liter (M) or less, and preferably 10^{-7} to 10^{-12} moles/liter (M) or less and more preferably 10^{-8} to 10^{-12} moles/liter (M), and/or with an association constant (K_A) of at least $10^7 M^{-1}$, preferably at least $10^8 M^{-1}$, more preferably at least

10^9 M^{-1} , such as at least 10^{12} M^{-1} ; and in particular with a K_D less than 500 nM, preferably less than 200 nM, more preferably less than 10 nM, such as less than 500 pM. The K_D and K_A values of the immunoglobulin single variable domain of the invention against Ang2 can be determined.

5 According to another embodiment, the immunoglobulin single variable domains are domain antibodies, as defined herein.

10 Immunoglobulin single variable domains present in the monospecific binding molecules of the invention have sequences that correspond to the amino acid sequence of a naturally occurring VH domain that has been "camelized", i.e. by replacing one or more amino acid residues in the amino acid sequence of a naturally occurring variable heavy chain from a conventional 4-chain antibody by one or more amino acid residues that occur at the corresponding position(s) in a VHH domain of a heavy chain antibody. This can be performed in a manner known per se, which will be clear to the skilled person, and reference is additionally made to WO 94/04678. Such camelization may preferentially occur at amino acid positions which are present at the VH-VL interface and at the so-called Camelidae Hallmark residues (see for example also
15 WO 94/04678). A detailed description of such "humanization" and "camelization" techniques and preferred framework region sequences consistent therewith can additionally be taken from e.g. pp. 46 and pp. 98 of WO 2006/040153 and pp. 107 of WO 2006/122786.

20 The binding components have specificity for Ang2, in that they comprise in a preferred embodiment one immunoglobulin single variable domains specifically binding to one or more epitopes within the Ang2 molecule.

25 Specific binding of a binding component to its antigen Ang2 can be determined in any suitable manner known *per se*, including, for example, the assays described herein, Scatchard analysis and/or competitive binding assays, such as radioimmunoassays (RIA), enzyme immunoassays (EIA and ELISA) and sandwich competition assays, and the different variants thereof known *per se* in the art.

With regard to the antigen Ang2, an immunoglobulin single variable domain is not limited with regard to the species. Thus, the immunoglobulin single variable domains preferably bind to human Ang2, if intended for therapeutic purposes in humans. However, immunoglobulin single variable domains that bind to Ang2, from another mammalian species, or polypeptides

containing them, are also within the scope of the invention. An immunoglobulin single variable domain binding to one species form of Ang2 may cross-react with the respective antigen from one or more other species. For example, immunoglobulin single variable domains binding to the human antigen may exhibit cross reactivity with the respective antigen from one or more other species of primates and/or with the antigen from one or more species of animals that are used in animal models for diseases, for example monkey (in particular Cynomolgus or Rhesus), mouse, rat, rabbit, pig, dog or) and in particular in animal models for diseases and disorders that can be modulated by inhibition of Ang2 (such as the species and animal models mentioned herein). Immunoglobulin single variable domains of the invention that show such cross-reactivity are advantageous in a research and/or drug development, since it allows the immunoglobulin single variable domains of the invention to be tested in acknowledged disease models such as monkeys, in particular Cynomolgus or Rhesus, or mice and rats.

Also, the binding components are not limited to or defined by a specific domain or an antigenic determinant of the antigen against which they are directed. Preferably, in view of cross-reactivity with one or more antigen molecules from species other than human that is/are intended for use as an animal model during development of a therapeutic Ang2 antagonist, a binding component recognizes an epitope in a region of the the respective antigen that has a high degree of identity with the human antigen. By way of example, in view of using a mouse model, an anti-Ang2 immunoglobulin single variable domain contained in the monospecific binding molecules of the invention recognizes an epitope which is, totally or in part, located within the EGF-2 domain of Ang2, which shows a high identity between human and mouse.

Therefore, according to a preferred embodiment, the monospecific binding molecule of the invention comprises an Ang2-binding molecule which is an immunoglobulin single variable domain that is selected from the group consisting of SEQ ID NOs: 167, 166, 129 and 138 that binds to an epitope that is totally or partially contained within the FLD domain.

The present invention also relates to a nucleic acid encoding the Ang2-binding molecule according to the invention.

In a preferred embodiment an Ang2-binding molecule according to the invention when expressed in *Escherichia coli* is encoded by a nucleotide sequence selected from:

SEQ ID NO: 178

GAGGTACAGCTGGTCGAGTCAGGTGGCGGATTAGTGCAGCCTGGGGGTTCTCTGCGCTTA
5 TCTTGTGCCGCATCAGGCTTCACACTGGATGACTACGCCATCGGCTGGTTCCGGCAAGCG
CCTGGAAAAGAACGCGAAGGTGTTTCAGCAATCCGTTCAAGCGGTGGTTCAACATATTACG
CCGACTCTGTTAAAGGACGCTTCACCATTAGCTCCGACAATAGTAAAATACAGTCTACTTA
CAAATGAACAGTTTACGCCCAGAAGATACTGCGGTATACTATTGCGCTGCCGTGCCTGCTG
10 GTCGCTTACGCTTTGGCGAGCAATGGTATCCTCTGTACGAGTACGACGCCTGGGGACAGG
GTACGCTGGTAACGGTTTCAAGC

SEQ ID NO: 179

GAAGTGCAACTGGTTGAGTCAGGTGGCGGACTGGTGCAACCGGGTGGTTCACTGCGCCTG
AGTTGCGCAGTTAGCGGTATTACCCTGGATGATTATGCAATTGGTTGGTTTCGCCAAGCCC
CAGGCAAAGAGCGTGAAGGCGTTAGCGCAATTCGTAGCAGCGGTGGTAGCACCTATTATG
15 CCGATTCAAGTTAAAGGCCGTTTTACGATCAGCAGCGATAACAGTAAAACACGGTTTTATCTG
CAAATGAACTCATTACGTCCAGAGGACACTGCAGTTTACTATTGCGCAGCAGTTCCGGCAG
GTCGTCTGCGTTATGGTGAACAGTGGTATCCGATTTATGAATATGATGCATGGGGTCAAGG
TACACTGGTTACAGTGAGTAGC

SEQ ID NO: 180

GAAGTGCACTTAGTTCGAAAGTGGCGGAGGCCTGGTACAACCTGGTGGCAGTCTGCGCTTA
20 TCTTGTGCCGCTTCAGGTTTTACATTGACGACTACGCCCTGGGGTGGTTCCGGCAAGCGC
CTGGAAAAGAACGTGAGGGCGTTTTATGCATTCGTTGTTTCAAGGTGGTTCAACCTATTATGC
CGATAGTGTAAGGTCGGTTCACCATTAGTAGCGACAATAGCAAGAATACAGTCTATCTGC
AAATGAACTCTTTACGTCCCTGAAGATACTGCGGTGTAATACTGCGCTGCATCAATCGTTCCT
25 CGTTCAAACCTTGAACCTTACGAGTACGACGCCTGGGGTCAGGGTACGTTAGTAACGGTGT
CAAGC

And

SEQ ID NO: 181

GAAGTGCAACTGGTTGAGTCAGGTGGCGGTTTTAGTGCACCGGGTGGTTCACTGCGCCTG
30 AGTTGCGCAGCCAGCGGTTTTGCACTGGATTATTATGCAATTGGTTGGTTTCGCCAAGCCC
CAGGCAAAGAGCGTGAAGGCGTTAGCTGTATTAGCAGCAGCGGTGGTATTACCTATTATGC

CGATTCAGTTAAAGGCCGTTTTACGATCTCTCGTGATAATAGTAAAAACACGGTTTACCTGC
AGATGAACTCATTAAGACCAGAGGACACTGCAGTTTACTATTGTGCAACCGATAGCGGTGG
CTATATTGATTATGATTGTAGCGGTCTGGGCTACGATTATTGGGGACAAGGTACGCTGGTG
ACAGTTAGCAGC

5

The invention relates to nucleic acid molecules that encode monospecific binding molecules of the invention. Such nucleic acid molecules will also be referred to herein as "nucleic acids of the invention" and may also be in the form of a genetic construct, as defined herein. A nucleic acid of the invention may be genomic DNA, cDNA or synthetic DNA (such as DNA with a codon
10 usage that has been specifically adapted for expression in the intended host cell or host organism). According to one embodiment of the invention, the nucleic acid of the invention is in essentially isolated form, as defined hereabove.

Further aspect of the invention relates to an expression vector comprising the nucleic acid molecule encoding said Ang2- binding molecule according to invention.

15 In preferred embodiments, the nucleic acid of the invention may also be in the form of, may be present in and/or may be part of a vector, such as for example a plasmid, cosmid or YAC.

The vector may especially be an expression vector, i.e. a vector that can provide for expression of the monospecific binding molecule *in vitro* and/or *in vivo* (i.e. in a suitable host cell, host organism and/or expression system). Such expression vector generally comprises at least one
20 nucleic acid of the invention that is operably linked to one or more suitable regulatory elements, such as promoter(s), enhancer(s), terminator(s), and the like. Such elements and their selection in view of expression of a specific sequence in a specific host are common knowledge of the skilled person. Specific examples of regulatory elements and other elements useful or necessary for expressing bispecific binding molecules of the invention, such as promoters, enhancers,
25 terminators, integration factors, selection markers, leader sequences, reporter genes, and the like, are disclosed e.g. on pp. 131 to 133 of WO 2006/040153.

Such vectors express or are capable of expressing one or more monospecific binding molecules of the invention; and/or contain a nucleic acid of the invention.

The nucleic acids of the invention may be prepared or obtained in a manner known *per se* (e.g. by automated DNA synthesis and/or recombinant DNA technology), based on the information on the amino acid sequences for the polypeptides of the invention given herein, and/or can be isolated from a suitable natural source.

- 5 In another aspect, the invention relates to a host cell carrying one or more expression vectors comprising a nucleic acid molecule encoding the Ang2-binding molecule according to the invention.

According to a particularly preferred embodiment, said host cells are bacterial cells; other useful cells are yeast cells, fungal cells or mammalian cells.

- 10 Suitable bacterial cells include cells from gram-negative bacterial strains such as strains of *Escherichia coli*, *Proteus*, and *Pseudomonas*, and gram-positive bacterial strains such as strains of *Bacillus*, *Streptomyces*, *Staphylococcus*, and *Lactococcus*. Suitable fungal cell include cells from species of *Trichoderma*, *Neurospora*, and *Aspergillus*. Suitable yeast cells include cells from species of *Saccharomyces* (for example *Saccharomyces cerevisiae*),
15 *Schizosaccharomyces* (for example *Schizosaccharomyces pombe*), *Pichia* (for example *Pichia pastoris* and *Pichia methanolica*), and *Hansenula*.

Suitable mammalian cells include for example CHO cells, BHK cells, HeLa cells, COS cells, and the like. However, amphibian cells, insect cells, plant cells, and any other cells used in the art for the expression of heterologous proteins can be used as well.

- 20 The invention further provides methods of manufacturing a monospecific binding molecule of the invention, such methods generally comprising the steps of:
- culturing host cells comprising a nucleic acid capable of encoding a monospecific binding molecule under conditions that allow expression of the monospecific binding molecule of the invention; and
 - 25 - recovering or isolating the polypeptide expressed by the host cells from the culture; and
 - optionally further purifying and/or modifying and/or formulating the monospecific binding molecule of the invention.

The preferred embodiment represents a method for producing an Ang2 binding molecule having sequence SEQ ID NOs: 167, 166, 129 and 138 comprising the steps of:

- (a) transfecting a host cell with one or more said vectors
- (b) culturing said host cell, and
- 5 (c) recovering and purifying said Ang2 binding molecule.

For production on an industrial scale, preferred host organisms include strains of *E. coli*, *Pichia pastoris*, and *S. cerevisiae* that are suitable for large scale expression, production and fermentation, and in particular for large scale pharmaceutical expression, production and fermentation.

10 The choice of the specific expression system depends in part on the requirement for certain post-translational modifications, more specifically glycosylation. The production of a monospecific binding molecule of the invention for which glycosylation is desired or required would necessitate the use of mammalian expression hosts that have the ability to glycosylate the expressed protein. In this respect, it will be clear to the skilled person that the glycosylation
15 pattern obtained (i.e. the kind, number and position of residues attached) will depend on the cell or cell line that is used for the expression.

Monospecific binding molecules of the invention may be produced either in a cell as set out above intracellularly (e.g. in the cytosol, in the periplasma or in inclusion bodies) and then isolated from the host cells and optionally further purified; or they can be produced
20 extracellularly (e.g. in the medium in which the host cells are cultured) and then isolated from the culture medium and optionally further purified.

Methods and reagents used for the recombinant production of polypeptides, such as specific suitable expression vectors, transformation or transfection methods, selection markers, methods of induction of protein expression, culture conditions, and the like, are known in the art. Similarly,
25 protein isolation and purification techniques useful in a method of manufacture of a polypeptide of the invention are well known to the skilled person.

These peptides correspond to CDR3s derived from the VHHs of the invention. They, in particular the nucleic acid molecules encoding them, are useful for CDR grafting in order to replace a CDR3 in an immunoglobulin chain, or for insertion into a non-immunoglobulin scaffold, e.g. a

5 protease inhibitor, DNA-binding protein, cytochrome b562, a helix-bundle protein, a disulfide-bridged peptide, a lipocalin or an anticalin, thus conferring target-binding properties to such scaffold. The method of CDR-grafting is well known in the art and has been widely used, e.g. for humanizing antibodies (which usually comprises grafting the CDRs from a rodent antibody onto the Fv frameworks of a human antibody).

10 In order to obtain an immunoglobulin or a non-immunoglobulin scaffold containing a CDR3 of the invention, the DNA encoding such molecule may be obtained according to standard methods of molecular biology, e.g. by gene synthesis, by oligonucleotide annealing or by means of overlapping PCR fragments, as e.g. described by Daugherty *et al.*, 1991, Nucleic Acids Research, Vol. 19, 9, 2471-2476. A method for inserting a VHH CDR3 into a non-immunoglobulin scaffold has been described by Nicaise *et al.*, 2004, Protein Science, 13, 1882-1891.

15 The invention further relates to a product or composition containing or comprising at least one monospecific binding molecule 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.

In further aspect, the invention relates to use of a monospecific binding molecule of the invention as a medicament.

In still another aspect, the invention relates to use of a monospecific binding molecule of the invention for method of treating of cancer, cancerous or eye diseases.

20 For pharmaceutical use, a monospecific binding molecule of the invention or a polypeptide containing same may be formulated as a pharmaceutical preparation or composition comprising at least one monospecific binding molecule of the invention and at least one physiologically acceptable carrier, diluent or excipient and/or adjuvant, and optionally one or more further pharmaceutically active polypeptides and/or compounds. By means of non-limiting examples, 25 such a formulation may be in a form suitable for oral administration, for parenteral administration (such as by intravenous, intramuscular or subcutaneous injection or intravenous infusion), for topical administration, for administration by inhalation, by a skin patch, by an implant, by a suppository, etc. Such suitable administration forms - which may be solid, semi-solid or liquid,

depending on the manner of administration - as well as methods and carriers for use in the preparation thereof, will be clear to the skilled person, and are further described herein.

Thus, in a further aspect, the invention relates to a pharmaceutical composition that contains at least one monospecific binding molecule, in particular one immunoglobulin single variable domain of the invention or a polypeptide containing same and at least one suitable carrier, diluent or excipient (i.e. suitable for pharmaceutical use), and optionally one or more further active substances.

The monospecific binding molecules of the invention may be formulated and administered in any suitable manner known per se: Reference, in particular for the immunoglobulin single variable domains, is for example made to WO 2004/041862, WO 2004/041863, WO 2004/041865, WO 2004/041867 and WO 2008/020079, as well as to the standard handbooks, such as Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Company, USA (1990), Remington, the Science and Practice of Pharmacy, 21th Edition, Lippincott Williams and Wilkins (2005); or the Handbook of Therapeutic Antibodies (S. Dubel, Ed.), Wiley, Weinheim, 2007 (see for example pages 252-255).

For example, an immunoglobulin single variable domain of the invention may be formulated and administered in any manner known per se for conventional antibodies and antibody fragments (including ScFv's and diabodies) and other pharmaceutically active proteins. Such formulations and methods for preparing the same will be clear to the skilled person, and for example include preparations suitable for parenteral administration (for example intravenous, intraperitoneal, subcutaneous, intramuscular, intraluminal, intra-arterial or intrathecal administration) or for topical (i.e. transdermal or intradermal) administration.

Preparations for parenteral administration may for example be sterile solutions, suspensions, dispersions or emulsions that are suitable for infusion or injection. Suitable carriers or diluents for such preparations for example include, without limitation, sterile water and pharmaceutically acceptable aqueous buffers and solutions such as physiological phosphate-buffered saline, Ringer's solutions, dextrose solution, and Hank's solution; water oils; glycerol; ethanol; glycols such as propylene glycol or as well as mineral oils, animal oils and vegetable oils, for example peanut oil, soybean oil, as well as suitable mixtures thereof. Usually, aqueous solutions or suspensions will be preferred.

Thus, the monospecific binding molecule of the invention may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. For oral therapeutic administration, the bispecific binding molecule of the invention may be combined with one or more excipients and used in the form of ingestible
5 tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of the Ang2-binding molecule of the invention. Their percentage in the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of the bispecific binding molecule of the invention in such therapeutically useful
10 compositions is such that an effective dosage level will be obtained.

The tablets, pills, capsules, and the like may also contain binders, excipients, disintegrating agents, lubricants and sweetening or flavouring agents, for example those mentioned on pages 143-144 of WO 08/020079. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol.
15 Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the bispecific binding molecules of the invention, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used
20 in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the bispecific binding molecules of the invention may be incorporated into sustained-release preparations and devices.

Preparations and formulations for oral administration may also be provided with an enteric coating that will allow the constructs of the invention to resist the gastric environment and pass
25 into the intestines. More generally, preparations and formulations for oral administration may be suitably formulated for delivery into any desired part of the gastrointestinal tract. In addition, suitable suppositories may be used for delivery into the gastrointestinal tract.

The monospecific binding molecules of the invention may also be administered intravenously or intraperitoneally by infusion or injection, as further described on pages 144 and 145 of
30 WO 2008/020079.

For topical administration of the monospecific binding molecules of the invention, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid, as further described on page 145 of WO 2008/020079.

- 5 Generally, the concentration of the monospecific binding molecules of the invention in a liquid composition, such as a lotion, will be from about 0.1-25 wt-%, preferably from about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt-%, preferably about 0.5-2.5 wt-%.

The amount of the monospecific binding molecules of the invention required for use in treatment
10 will vary not only with the particular monospecific binding molecule selected, but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician. Also, the dosage of the monospecific binding molecules of the invention varies depending on the target cell, tumor, tissue, graft, or organ. The desired dose may conveniently be presented in a single
15 dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, *e.g.*, into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

An administration regimen may include long-term, daily treatment. By "long-term" is meant at
20 least two weeks and preferably, several weeks, months, or years of duration. Necessary modifications in this dosage range may be determined by one of ordinary skill in the art using only routine experimentation given the teachings herein. See Remington's Pharmaceutical Sciences (Martin, E.W., ed. 4), Mack Publishing Co., Easton, PA. The dosage can also be adjusted by the individual physician in the event of any complication.

25 According to a further embodiment, the invention relates to the use of monospecific binding molecules of the invention, *e.g.* immunoglobulin single variable domains or polypeptides containing them, for therapeutic purposes, such as

- for the prevention, treatment and/or alleviation of a disorder, disease or condition, especially in a human being, that is associated with Ang2-mediated and/or Ang2-related effects on

angiogenesis or that can be prevented, treated or alleviated by modulating the Notch signaling pathway and/or the Tie2 signalling pathway with a monospecific binding molecule according to the invention;

- 5 - in a method of treatment of a patient in need of such therapy, such method comprising administering, to a subject in need thereof, a pharmaceutically active amount of at least one monospecific binding molecule of the invention, e.g. an immunoglobulin single variable domain, or a pharmaceutical composition containing same;
- for the preparation of a medicament for the prevention, treatment or alleviation of disorders, diseases or conditions associated with Ang2-mediated and/or Ang2-mediated effects on
10 angiogenesis;
- as an active ingredient in a pharmaceutical composition or medicament used for the above purposes.

According to a specific aspect, said disorder disorder, disease or condition is a cancer or cancerous disease, as defined herein.

- 15 In preferred embodiments, the invention relates to said pharmaceutical composition for treatment of cancer and cancerous diseases, such as breast, renal cell carcinoma, ovarian cancer and pancreatic cancer.

According to another aspect, the disease is an eye disease associated with Ang2-mediated and/or Ang2-mediated effects on angiogenesis or which can be treated or alleviated by
20 modulating the Notch signaling pathway and/or the Tie2 signalling pathway with a monospecific binding molecule.

In another preferred embodiments, the invention relates to said pharmaceutical composition for treatment of eye diseases, such as age-related macular degeneration and diabetic retinopathy.

- 25 In still another preferred embodiments, the invention relates to said pharmaceutical composition for treatment of chronic kidney diseases.

Depending on cancer/ cancerous diseases, eye diseases and/or chronic kidney diseases to be treated, a monospecific binding molecule of the invention may be used on its own or in combination with one or more additional therapeutic agents.

5 In preferred embodiments, the invention relates to the pharmaceutical composition comprising, as the active ingredient one or more said Ang-2 binding molecules, further comprising one or more additional therapeutic agents, such as chemotherapeutic agents like DNA damaging agents and/or anti-mitotic drugs in cancer cells (e.g. taxol) or therapeutically active compounds that inhibit angiogenesis (an anti- angiogenic drug such as anti VEGF/VEGF receptor inhibitor, e.g. avastin, nitedanib and sunitinib), or signal transduction pathway inhibitors such as mTOR
10 inhibitors (e.g. temsirolimus) or hormonal therapy agents (e.g. tamoxifen).

The additional therapeutic agent may be administered simultaneously with, optionally as a component of the same pharmaceutical preparation, or before or after administration of the monospecific binding molecule.

15 In certain embodiments, the additional therapeutic agent may be, without limitation (and in the case of the receptors, including the respective ligands), one or more inhibitors selected from the group of inhibitors of EGFR, VEGF, VEGFR, HER2-neu, Her3, AuroraA, AuroraB, PLK and PI3 kinase, FGFR, PDGFR, Raf, KSP, PDK1, PTK2, IGF-R or IR.

Further examples of additional therapeutic agents are inhibitors of CDK, Akt, src/bcr abl, cKit, cMet/HGF, c-Myc, Flt3, HSP90, hedgehog antagonists, inhibitors of JAK/STAT, Mek, mTor,
20 NFkappaB, the proteasome, Rho, an inhibitor of wnt signaling or an inhibitor of the ubiquitination pathway or another inhibitor of the Notch signaling pathway.

Examples for Aurora inhibitors are, without limitation, PHA-739358, AZD-1152, AT 9283, CYC-116, R-763, VX-680, VX-667, MLN-8045, PF-3814735.

An example for a PLK inhibitor is GSK-461364.

25 Examples for VEGF inhibitor are avastin (Roche), aflibercept (Regeneron.)

Examples for raf inhibitors are BAY-73-4506 (also a VEGFR inhibitor), PLX 4032, RAF-265 (also in addition a VEGFR inhibitor), sorafenib (also in addition a VEGFR inhibitor), and XL 281.

Examples for KSP inhibitors are ispinesib, ARRY-520, AZD-4877, CK-1122697, GSK 246053A, GSK-923295, MK-0731, and SB-743921.

Examples for a src and/or bcr-abl inhibitors are dasatinib, AZD-0530, bosutinib, XL 228 (also an IGF-1R inhibitor), nilotinib (also a PDGFR and cKit inhibitor), imatinib (also a cKit inhibitor), and
5 NS-187.

An example for a PDK1 inhibitor is BX-517.

An example for a Rho inhibitor is BA-210.

Examples for PI3 kinase inhibitors are PX-866, BEZ-235 (also an mTor inhibitor), XL 418 (also an Akt inhibitor), XL-147, and XL 765 (also an mTor inhibitor).

10 Examples for inhibitors of cMet or HGF are XL-184 (also an inhibitor of VEGFR, cKit, Flt3), PF-2341066, MK-2461, XL-880 (also an inhibitor of VEGFR), MGCD-265 (also an inhibitor of VEGFR, Ron, Tie2), SU-11274, PHA-665752, AMG-102, and AV-299.

An example for a c-Myc inhibitor is CX-3543.

Examples for Flt3 inhibitors are AC-220 (also an inhibitor of cKit and PDGFR), KW 2449,
15 lestaurtinib (also an inhibitor of VEGFR, PDGFR, PKC), TG-101348 (also an inhibitor of JAK2), XL-999 (also an inhibitor of cKit, FGFR, PDGFR and VEGFR), sunitinib (also an inhibitor of PDGFR, VEGFR and cKit), and tandutinib (also an inhibitor of PDGFR, and cKit).

Examples for HSP90 inhibitors are tanespimycin, alvespimycin, IPI-504 and CNF 2024.

Examples for JAK/STAT inhibitors are CYT-997 (also interacting with tubulin), TG 101348 (also
20 an inhibitor of Flt3), and XL-019.

Examples for Mek inhibitors are ARRY-142886, PD-325901, AZD-8330, and XL 518.

Examples for mTor inhibitors are temsirolimus, AP-23573 (which also acts as a VEGF inhibitor), everolimus (a VEGF inhibitor in addition). XL-765 (also a PI3 kinase inhibitor), and BEZ-235 (also a PI3 kinase inhibitor).

25 Examples for Akt inhibitors are perifosine, GSK-690693, RX-0201, and triciribine.

Examples for cKit inhibitors are AB-1010, OSI-930 (also acts as a VEGFR inhibitor), AC-220 (also an inhibitor of Flt3 and PDGFR), tandutinib (also an inhibitor of Flt3 and PDGFR), axitinib (also an inhibitor of VEGFR and PDGFR), XL-999 (also an inhibitor of Flt3, PDGFR, VEGFR, FGFR), sunitinib (also an inhibitor of Flt3, PDGFR, VEGFR), and XL-820 (also acts as a
5 VEGFR- and PDGFR inhibitor), imatinib (also a bcr-abl inhibitor), nilotinib (also an inhibitor of bcr-abl and PDGFR).

Examples for hedgehog antagonists are IPI-609 and CUR-61414.

Examples for CDK inhibitors are seliciclib, AT-7519, P-276, ZK-CDK (also inhibiting VEGFR2 and PDGFR), PD-332991, R-547, SNS-032, PHA-690509, and AG 024322.

10 Examples for proteasome inhibitors are bortezomib, carfilzomib, and NPI-0052 (also an inhibitor of NFkappaB).

An example for an NFkappaB pathway inhibitor is NPI-0052.

An example for an ubiquitination pathway inhibitor is HBX-41108.

In preferred embodiments, the additional therapeutic agent is an anti-angiogenic agent.

15 Examples for anti-angiogenic agents are inhibitors of the FGFR, PDGFR and VEGFR or the respective ligands (e.g VEGF inhibitors like pegaptanib or the anti-VEGF antibody bevacizumab), and thalidomides, such agents being selected from, without limitation, bevacizumab, motesanib, CDP-791, SU-14813, telatinib, KRN-951, ZK-CDK (also an inhibitor of CDK), ABT-869, BMS-690514, RAF-265, IMC-KDR, IMC-18F1, IMiDs (immunomodulatory
20 drugs), thalidomide derivative CC-4047, lenalidomide, ENMD 0995, IMC-D11, Ki 23057, brivanib, cediranib, XL-999 (also an inhibitor of cKit and Flt3), 1B3, CP 868596, IMC 3G3, R-1530 (also an inhibitor of Flt3), sunitinib (also an inhibitor of cKit and Flt3), axitinib (also an inhibitor of cKit), vemurafenib (also known as PLX4032, RG7204 or RO5185426, marketed as
25 zelboraf) a B-Raf enzyme inhibitor, crizotinib known as an ALK (anaplastic lymphoma kinase) and ROS1(c-ros oncogene1, receptor tyrosine kinase) inhibitor, lestaurtinib (also an inhibitor of Flt3 and PKC), vatalanib, tandutinib (also an inhibitor of Flt3 and cKit), pazopanib, GW 786034, PF-337210, IMC-1121B, AVE-0005, AG-13736, E-7080, CHIR 258, sorafenib tosylate (also an inhibitor of Raf), RAF-265 (also an inhibitor of Raf), vandetanib, CP-547632, OSI-930, AEE-788

(also an inhibitor of EGFR and Her2), BAY-57-9352 (also an inhibitor of Raf), BAY-73-4506 (also an inhibitor of Raf), XL 880 (also an inhibitor of cMet), XL-647 (also an inhibitor of EGFR and EphB4), XL 820 (also an inhibitor of cKit), and nilotinib (also an inhibitor of cKit and bcr-abl) and nitedanib.

- 5 The additional therapeutic agent may also be selected from EGFR inhibitors; it may be a small molecule EGFR inhibitor or an anti-EGFR antibody. Examples for anti-EGFR antibodies, without limitation, are cetuximab, panitumumab, matuzumab; an example for a small molecule EGFR inhibitor is gefitinib. Another example for an EGFR modulator is the EGF fusion toxin.

Among the EGFR and Her2 inhibitors useful for combination with the bispecific binding molecule
10 of the invention are lapatinib, gefitinib, erlotinib, cetuximab, trastuzumab, nimotuzumab, zalutumumab, vandetanib (also an inhibitor of VEGFR), pertuzumab, XL-647, HKI-272, BMS-599626 ARRY-334543, AV 412, mAB-806, BMS-690514, JNJ-26483327, AEE-788 (also an inhibitor of VEGFR), ARRY-333786, IMC-11F8, Zemab.

Other agents that may be advantageously combined in a therapy with the monospecific binding
15 molecule of the invention are tositumumab and ibritumomab tiuxetan (two radiolabelled anti-CD20 antibodies), alemtuzumab (an anti-CD52 antibody), denosumab, (an osteoclast differentiation factor ligand inhibitor), galiximab (a CD80 antagonist), ofatumumab (a CD20 inhibitor), zanolimumab (a CD4 antagonist), SGN40 (a CD40 ligand receptor modulator), rituximab (a CD20 inhibitor) or mapatumumab (a TRAIL-1 receptor agonist) or OMP-21M18
20 (DII4 inhibitors).

Other chemotherapeutic drugs that may be used in combination with the bispecific binding
molecules of the present invention are selected from, but not limited to hormones, hormonal
analogues and antihormonals (e.g. tamoxifen, toremifene, raloxifene, fulvestrant, megestrol
acetate, flutamide, nilutamide, bicalutamide, cyproterone acetate, finasteride, buserelin acetate,
25 fludrocortisone, fluoxymesterone, medroxyprogesterone, octreotide, arzoxifene, pasireotide, vapreotide), aromatase inhibitors (e.g. anastrozole, letrozole, liarozole, exemestane, atamestane, formestane), LHRH agonists and antagonists (e.g. goserelin acetate, leuprolide, abarelix, cetorelix, deslorelin, histrelin, triptorelin), antimetabolites (e.g. antifolates like methotrexate, pemetrexed, pyrimidine analogues like 5 fluorouracil, capecitabine, decitabine,
30 nelarabine, and gemcitabine, purine and adenosine analogues such as mercaptopurine

thioguanine, cladribine and pentostatin, cytarabine, fludarabine); antitumor antibiotics (e.g. anthracyclines like doxorubicin, daunorubicin, epirubicin and idarubicin, mitomycin-C, bleomycin dactinomycin, plicamycin, mitoxantrone, pixantrone, streptozocin); platinum derivatives (e.g. cisplatin, oxaliplatin, carboplatin, lobaplatin, satraplatin); alkylating agents (e.g. estramustine, 5 meclorethamine, melphalan, chlorambucil, busulphan, dacarbazine, cyclophosphamide, ifosfamide, hydroxyurea, temozolomide, nitrosoureas such as carmustine and lomustine, thiotepa); antimetabolic agents (e.g. vinca alkaloids like vinblastine, vindesine, vinorelbine, vinflunine and vincristine; and taxanes like paclitaxel, docetaxel and their formulations, larotaxel; simotaxel, and epothilones like ixabepilone, patupilone, ZK-EPO); topoisomerase inhibitors (e.g. 10 epipodophyllotoxins like etoposide and etopophos, teniposide, amsacrine, topotecan, irinotecan) and miscellaneous chemotherapeutics such as amifostine, anagrelide, interferone alpha, procarbazine, mitotane, and porfimer, bexarotene, celecoxib.

Particularly preferred combination partners of the bispecific binding molecules of the present invention are VEGF antagonists, like bevacizumab (Avastin[®]), nitedanib, Sorafenib and 15 Sunitinib.

According to another embodiment of the invention, there is provided a method of diagnosing a disease by

- a) contacting a sample with a binding molecule of the invention as defined above, and
- 20 b) detecting binding of said binding molecule to said sample, and
- c) comparing the binding detected in step (b) with a standard, wherein a difference in binding relative to said sample is diagnostic of a disease or disorder associated with VEGF- and/or Ang2-mediated effects on angiogenesis.

For this and other uses, it may be useful to further modify a monospecific binding molecule of 25 the invention, such as by introduction of a functional group that is one part of a specific binding pair, such as the biotin-(strept)avidin binding pair. Such a functional group may be used to link the binding molecule of the invention to another protein, polypeptide or chemical compound that is bound to the other half of the binding pair, i.e. through formation of the binding pair. For example, a monospecific binding molecule of the invention may be conjugated to biotin, and

linked to another protein, polypeptide, compound or carrier conjugated to avidin or streptavidin. For example, such a conjugated monospecific binding molecule of the invention may be used as a reporter, for example in a diagnostic system where a detectable signal-producing agent is conjugated to avidin or streptavidin.

- 5 The efficacy of monospecific binding molecule of the invention or polypeptides, 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 of interest. Suitable assays and animal models will be clear to the skilled person, and for example include the assays described herein and used in the
- 10 Examples below, e.g. a proliferation assay.

Monospecific binding molecules of the invention have undergone an extensive sequence optimization process involving affinity maturation, humanization and removal of potential posttranslational modification sites to ensure low immunogenicity potential in man and improved biophysical stability. Unexpectedly, the data show that monospecific binding molecules of the

15 invention have properties that are superior to those of binding molecules of the prior art. Among such properties are high selectivity for Ang2 neutralization as compared to Ang1 neutralization, as can e.g. be taken from the data of Figures 9 to 10, 13 to 14, 16 to 19; complete inhibition of the Ang2-Tie2 interaction with high potency, as can e.g. be taken from the ELISA data of

20 Figures 6, 9, 13, 16, 18 and 20 and Tables 12 to 13, 16 to 17, 20 to 22, as well as the IC50 (nM) values for VHHs in the AlphaScreen assay as shown e.g. in Table 7 (Example 7); and the affinity KD (nM) of purified VHHs on recombinant human Ang2, cyno Ang2, mouse Ang2 in Tables 8, 14, 18 and 23.

This indicates that monospecific binding molecules of the invention are promising candidates to have therapeutic efficacy in diseases and disorders associated with Ang2-mediated effects on

25 angiogenesis, such as cancer, cancerous diseases, eye diseases and/or chronic kidney diseases.

Brief description of the Figures:

The axes annotation in Figures 1 to 4, 6 to 7, 9 to 10, 12 to 14 and 16 to 20: X axes stand for OD 450 (nm) and Y axes stand for log competitor (M).

5

Figure 1 (Figure 1-1A to 1-2C): Purified VHHs blocking hAng2-hTie2 interaction (ELISA).

Figure 2 (Figure 2-1A to 2-2C): Purified VHHs blocking mAng2-mTie2 interaction (ELISA).

Figure 3 (Figure 3A to 3B): Purified VHHs blocking cAng2-cTie2 interaction (ELISA).

Figure 4 (Figure 4A to 4I): Purified VHHs blocking hAng1-hTie2 interaction (ELISA).

10 **Figure 5:** Sequence alignment of affinity matured variants of VHH 28D10. The amino acid sequence is aligned to the human germline VH3/JH consensus sequence. Residues are numbered according to Kabat, CDRs are shown in bold according to AbM definition. Residues that have been substituted are underlined.

15 **Figure 6 (Figure 6A to 6C):** Purified affinity matured variants of VHH 28D10 blocking hAng2-hTie2 interaction (ELISA).

Figure 7 (Figure 7A to 7C): Purified affinity matured variants of VHH 28D10 blocking hAng1-hTie2 interaction (ELISA).

20 **Figure 8 (Figure 8A to 8B):** Sequence alignment of VHH 1D01 with hVH3-JH consensus (A) and of sequence optimized variants of VHH 1D01 (B). The amino acid sequence is aligned to the human germline VH3/JH consensus sequence. Residues are numbered according to Kabat, CDRs are shown in bold according to AbM definition. Residues to be mutated to their human counterpart are underlined. Potential post-translational modification sites to be tackled are boxed.

25 **Figure 9 (Figure 9-1A to 9-3B):** Purified sequence optimized variants of VHH 1D01 blocking hAng2-hTie2 (10-1), mAng2-mTie2 (10-2) and cAng2-cTie2 (11-3) interaction (ELISA).

Figure 10: Purified sequence optimized variants of VHH 1D01 blocking hAng1-hTie2 interaction (ELISA).

30 **Figure 11 (Figure 11A to 11C):** Sequence alignment of VHH 37F02 with hVH3-JH consensus (A), of cycle 1 (B) and of cycle 2 (C) sequence optimized variants of VHH 37F02. The amino acid sequence is aligned to the human germline VH3/JH consensus

sequence. Residues are numbered according to Kabat, CDRs are shown in bold according to AbM definition. Residues to be mutated to their human counterpart are underlined. Potential post-translational modification sites to be tackled are boxed.

Figure 12 (Figure 12-1 to 12-3): Purified cycle 1 sequence optimized variants of VHH 37F02 blocking hAng2-hTie2 (14-1), mAng2-mTie2 (14-2) and cAng2-cTie2 (14-3) interaction (ELISA).

Figure 13 (Figure 13-1A to 13-3): Purified cycle 2 sequence optimized variants of VHH 37F02 blocking hAng2-hTie2 (15-1), mAng2-mTie2 (15-2) and cAng2-cTie2 (15-3) interaction (ELISA).

Figure 14: Purified cycle 2 sequence optimized variants of VHH 37F02 blocking hAng1-hTie2 interaction (ELISA).

Figure 15 (Figure 15A to 15D): Sequence alignment of VHH 28D10 with hVH3-JH consensus (A), of cycle 1 sequence optimized variants (B), of cycle 2 variants (C) and of cycle 3 (D) sequence optimized variants of VHH 28D10. The amino acid sequence is aligned to the human germline VH3/JH consensus sequence. Residues are numbered according to Kabat, CDRs are shown in bold according to AbM definition. Residues to be mutated to their human counterpart are underlined. Potential post-translational modification sites to be tackled are boxed.

Figure 16 (Figure 16-1A to 16-3C): Purified cycle 1 sequence optimized variants of VHH 28D10 blocking hAng2-hTie2 (18-1), mAng2-mTie2 (18-2) and cAng2-cTie2 (18-3) interaction (ELISA).

Figure 17 (Figure 17A to 17B): Purified cycle 1 sequence optimized variants of VHH 28D10 blocking hAng1-hTie2 interaction (ELISA).

Figure 18 (Figure 18 -1A to 18 -3): Purified sequence optimized C₅₀X-S₅₃X variants of VHH 28D10 blocking hAng2-hTie2 (20-1), mAng2-mTie2 (20-2) and cAng2-cTie2 (20-3) interaction (ELISA).

Figure 19: Purified sequence optimized C₅₀X-S₅₃X variant of VHH 28D10 blocking hAng1-hTie2 interaction (ELISA).

Figure 20 (Figure 20-1A to 20-3C): Purified cycle 2 sequence optimized variants of VHH 28D10 blocking hAng2-hTie2 (22-1), mAng2-mTie2 (22-2) and cAng2-cTie2 (22-3) interaction (ELISA).

Examples

Materials and methods

a) Generation of HEK293H stable cell lines overexpressing human or mouse Tie2 receptor

5

The cDNAs encoding human Tie2 (NM_000459.3; SEQ ID NO:182;), mouse Tie2 (NM_013690.2; SEQ ID NO:183) and cyno Tie2 (SEQ ID NO:184); are cloned in pcDNA3.1-neo expression vector (Invitrogen, Carlsbad, CA, USA). To establish Human Embryonic Kidney (HEK) cells overexpressing human Tie2 or mouse Tie2, parental HEK293H cells undergo lipid mediated transfection with Fugene (Roche) with pcDNA3.1-neo-hTie2 or pcDNA3.1-neo-mTie2, respectively. For all conditions, transfectants are selected 2 days post-transfection by adding 10 1 mg/mL geneticin (Invitrogen, Carlsbad, CA, USA). For human, mouse and cyno Tie2, final high expressing clones are selected by single cell sorting clones binding to PE labeled anti-human Tie2 (R&D Systems, Minneapolis, MN, US), PE labeled anti-mouse Tie2 (eBioscience, San 15 Diego, CA, USA) and a 2-step goat-anti-human Tie2 (R&D Systems, Minneapolis, MN, US) followed by PE labeled donkey-anti-goat (Jackson ImmunoResearch, West Grove, PA, USA), respectively, using the FACSAria Cell Sorter (BD Biosciences, San Jose, CA, USA).

b) Generation of HEK293T cell lines overexpressing mouse or cynomolgus Ang2 and 20 production of recombinant mouse and cynomolgus Ang2 conditioned medium

The cDNAs encoding N-terminally FLAG-tagged mouse Ang2 (NM_007426.3; SEQ ID NO: 185) and cynomolgus Ang2 (AB172643.1; SEQ ID NO: 186) are cloned in a pSecTag2B expression vector (Invitrogen, Carlsbad, CA, USA). Human Embryonic Kidney (HEK) cells 25 transiently overexpressing mouse Ang2 or cynomolgus Ang2 are generated by lipid-mediated transfection (Fugene; Roche) of pSecTag2B-mAng2 or pSecTag2B-cAng2, respectively, in the HEK293T parental cell line. Productions are performed in 1.5 liter CF10 Bag, and 1.5L conditioned medium (CM) is collected 5 days post-transfection.

30

c) Production of recombinant cynomolgus Tie2/Fc chimera in HEK293-F Cells

The cDNA encoding for the extracellular domain of Tie-2 is subcloned into the expression plasmid pSecTag2b using appropriate restriction sites to generate an Fc-fusion protein.

Transfection into HEK293-F cells (Invitrogen) is performed as described by the manufacturer using Megaprep (Qiagen) preparations of plasmids, Optimem-Medium (Invitrogen), 293-fectin (Invitrogen) at an initial cell density of 1×10^6 viable cells/mL with $1 \mu\text{g}$ plasmid DNA/ 10^6 cells. Transfected cells are cultivated in shaker flasks for 7 days at 37°C . Conditioned Medium (CM) is harvested by centrifugation at $4000g$ for 10 min and filtered through a sterile filter ($0.45 \mu\text{m}$ membrane).

Fc-fusion proteins are purified using affinity chromatography by loading the CM at 5 ml/min onto a 5 ml MabSelect SuRe Protein A column equilibrated with DPBS. After a washing step with DPBS, bound Fc-protein is eluted with 10 mM sodium citrate buffer pH 3.0 and subsequently neutralized to pH 7.0 by adding 1M Tris/HCl pH 8.0. The purified protein is concentrated and buffer exchanged to DPBS with a Millipore Amicon Ultra (10 kDa molecular weight cutoff) centrifugal concentrator. Presence of the protein is confirmed with standard analytical methods (electrophoresis with Experion Pro 260 kit- BioRad; mass spectrometry). The protein is further analysed by size-exclusion chromatography and the endotoxin-content is determined (Endosafe PTS kit – Charles River).

d) Production of recombinant human, cynomolgus, mouse and rat Ang2-FLD in HEK293-F Cells

Molecular cloning and cell culture is performed as described for Tie2-Fc-fusion protein. For purification of His-tagged proteins the CM is loaded at 5 ml/min on a 2 ml Ni^{2+} chelating sepharose fast flow column (His-Trap - GE Healthcare Life Sciences) equilibrated with DPBS.

After loading in the presence of 4% elution buffer (DPBS + 0.5% imidazol) to prevent unspecific binding, the column is washed with DPBS. Ang2-FLD-proteins are eluted from the column with DPBS containing 0.5% imidazol. Subsequently an ultrafiltration step was done for concentration and buffer exchange (10 kDa molecular weight cut off). An aliquot of the protein is retained for analytical characterization as described for Tie2-Fc.

30

Example 1

Immunization with recombinant human Ang2 induces a humoral immune response in llama

5 1.1. Immunizations

After approval of the Ethical Committee of the faculty of Veterinary Medicine (University Ghent, Belgium), 4 llamas (designated No. 406, 408, 454, 455) are immunized with 4 intramuscular injections (day 0: 50 µg, day 14: 20 µg, day 28: 17.5 µg and day 42: 17.5 µg dose) of recombinant human Ang2 (R&D Systems, Minneapolis, MN, US). The antigen is formulated in Complete Freund's Adjuvant for the prime injection at day 0 (Difco, Detroit, MI, USA) and in Incomplete Freund's Adjuvant for the booster injections (Difco, Detroit, MI, USA).

1.2. Evaluation of induced immune responses in llama

To evaluate the induction of an immune response in the animals against human Ang2 by ELISA, sera are collected at day 0 (pre-immune), day 35 and day 46 (time of peripheral blood lymphocyte [PBL] collection). In short, 1 µg/mL of recombinant human Ang2 (R&D Systems, Minneapolis, MN, USA) is immobilized overnight at 4°C in a 96-well MaxiSorp plate (Nunc, Wiesbaden, Germany). Wells are blocked with a casein solution (PBS + 1% casein). After addition of serial serum dilutions, specifically bound immunoglobulins are detected using a horseradish peroxidase (HRP)-conjugated goat anti-llama immunoglobulin (Bethyl Laboratories Inc., Montgomery, TX, USA) and a subsequent enzymatic reaction in the presence of the substrate TMB (3,3',5,5'-tetramethylbenzidine) (Pierce, Rockford, IL, USA), showing that a significant antibody dependent immune response against human Ang2 is induced. The antibody response is mounted both by conventional and heavy-chain only antibody expressing B-cell repertoires, since bound immunoglobulins can be detected with antibodies specifically recognizing the conventional llama IgG1 antibodies or the heavy chain only llama IgG2 or IgG3 antibodies. In all llamas injected with human Ang2, an antibody response is mounted by conventional and heavy chain only antibody expressing B-cells specifically against human Ang2. The Ang2 serum titer responses for each llama are depicted in Table 1.

Table 1: Antibody mediated specific serum response against recombinant human Ang2.

Llama	Immunogen	IgG reponse		
		IgG1	IgG2	IgG3
406	rec. human Ang2	+++	++	++
408	rec. human Ang2	+++	++	++
454	rec. human Ang2	+++	++	++
455	rec. human Ang2	+++	++	+++

Legend: (*)

- 5 Low (or +/-): $1,000 \geq \text{HSD}_{\text{S/N} \geq 2} < 1,500$
- Moderate (or +): $1,500 \geq \text{HSD}_{\text{S/N} \geq 2} < 13,500$
- Good (or ++): $13,500 \geq \text{HSD}_{\text{S/N} \geq 2} < 365,000$
- Excellent (or +++): $\text{HSD}_{\text{S/N} \geq 2} \geq 365,000$

10 (*) HSD, Highest Serum Dilution; S/N ≥ 2 , signal-to-noise ratio ≥ 2

Example 2

Cloning of the heavy-chain only antibody fragment repertoires and preparation of phage

Following the final immunogen injection, immune tissues as the source of B-cells that produce the heavy-chain only antibodies are collected from the immunized llamas. Typically, two 150 mL blood samples collected 4 and 10 days after the last antigen injection, and one lymph node biopsy, collected 4 days after the last antigen injection are collected per animal. From the blood samples, peripheral blood mononuclear cells (PBMCs) are prepared using Ficoll-Hypaque according to the manufacturer’s instructions (Amersham Biosciences, Piscataway, NJ, USA).

20 From the PBMCs and the lymph node biopsy (not prelevated from animal No. 406), total RNA is extracted, which is used as starting material for RT-PCR to amplify the VHH encoding DNA segments, as described in Example 3 (page 46) of WO 05/044858. For each immunized llama, a library is constructed by pooling the total RNA isolated from all collected immune tissues of that animal. In short, the PCR-amplified VHH repertoire is cloned via specific restriction sites into a

25 vector designed to facilitate phage display of the VHH library. The vector is derived from pUC119 and contains the LacZ promoter, a M13 phage gIII protein coding sequence, a

resistance gene for ampicillin or carbenicillin, a multiple cloning site and a hybrid gIII-peIB leader sequence. In frame with the VHH coding sequence, the vector encodes a C-terminal c-myc tag and a His6 tag. Phage are prepared according to standard protocols and stored after filter sterilization at 4°C for further use.

5

Example 3

Selection of Ang2 specific VHHs via phage display

VHH repertoires obtained from all llamas and cloned as phage library are used in different selection strategies, applying a multiplicity of selection conditions. Variables include i) the Ang2 protein format: biotinylated C-terminally His-tagged full length recombinant human Ang2 (R&D Systems, Minneapolis, MN, USA) and C-terminally His-tagged full length mouse Ang2 (produced at GeneArt, now Invitrogen, Carlsbad, CA, USA), ii) the Ang2 presentation method: plates directly coated with mouse Ang2 or incubation in solution with biotinylated human Ang2 followed by capturing on neutravidin-coated plates, and iii) the antigen concentration. All selections are done in 96 well MaxiSorp plates (Nunc, Wiesbaden, Germany).

Multi-round selections are performed as follows: Ang2 preparations for solid and solution phase selection formats are presented as described above at multiple concentrations (biotinylated human Ang2: 50, 5, 0.5, 0.05 and 0.005 nM; mouse Ang2: 10, 1, 0.1 and 0.01 µg/mL). After 2h incubation with the phage libraries, followed by extensive washing, bound phages are eluted with trypsin (1 mg/mL) for 15-30 minutes at room temperature. Trypsin activity is then immediately neutralized by applying 0.8 mM protease inhibitor ABSF. As background control, selections w/o antigen are performed in parallel. Phage outputs that show enrichment over background are used to infect *E. coli*. Infected *E. coli* cells are either used to prepare phage for the next selection round (phage rescue) or plated on LB agar plates (ampicillin + glucose^{2%}) for analysis of individual VHH clones. In order to screen a selection output for specific binders or blockers, single colonies are picked from the agar plates and grown in 1 mL 96-deep-well plates. LacZ-controlled VHH expression is induced by adding IPTG (0.1-1mM final) in the absence of glucose. Periplasmic extracts (in a volume of ~80 µL) are prepared according to standard protocols (as disclosed in for example WO 2006/040153 cited herein). Briefly, cultures were centrifuged for 15 minutes at 4,500 rpm. The pellet was frozen overnight or for 1 hour at -20°C. Next, the pellet was thawed at room temperature for 40 minutes, re-suspended in 15 ml peri

buffer (50 mM NaHPO₄, 300mM NaCl) and shaken for 1 hour. Periplasmic fraction was isolated by centrifugation for 20 minutes at 14000 rpm.

Example 4

5 **Screening of periplasmic extracts in Ang2-Tie2 and Ang1-Tie2 ELISA and AlphaScreen competition assays**

Periplasmic extracts containing expressed VHHs are screened in a human Ang2-human Tie2 AlphaScreen competition assay to assess their blocking capacity. In brief, human Tie2/Fc chimera (R&D Systems, Minneapolis, MN, USA) is biotinylated using *N*-

10 hydroxysulfosuccinimide ester of biotin (Thermo Fisher Scientific, Rockford, IL, USA). FLAG tagged human Ang2 (Alexis Biochemicals, San Diego, CA, USA) is captured using Acceptor beads (Perkin Elmer, Waltham, MA, US) coated with anti-FLAG M2 antibody (Sigma, St Louis, MO, USA). To evaluate the capacity of the VHHs to inhibit binding of human Ang2 to its receptor human Tie2, 1:25 dilutions of the periplasmic extracts containing expressed VHHs are incubated

15 with 0.1 nM FLAG tagged human Ang2. To this mixture, the Acceptor beads and 0.3 nM biotinylated human Tie2/Fc chimeras are added and further incubated for 2 hours at room temperature. Finally, streptavidin conjugated Donor beads (Perkin Elmer, Waltham, MA, US) are added and the mixture is incubated for an additional 2 hours at room temperature. Assay buffer is PBS + 0.03% Tween-20 + 0.1% BSA. Fluorescence is measured using the Envision Multilabel

20 Plate reader (Perkin Elmer, Waltham, MA, USA) using an excitation wavelength of 680 nm and an emission wavelength of 520 nm. Decrease in fluorescence signal indicates that the binding of human Ang2 to human Tie2 is blocked by the VHH expressed in the periplasmic extract. VHHs able to block the human Ang2-human Tie2 interaction for at least 50% are screened in a confirmatory ELISA based competition assay. Additionally, cross-reactivity for binding to mouse

25 Ang2 and selectivity over human Ang1 is also assessed in a competition ELISA. In brief, human or mouse Tie2/Fc chimera (R&D Systems, Minneapolis, MN, USA) are immobilized at 2 µg/mL overnight at 4°C in a 96-well MaxiSorp plate (Nunc, Wiesbaden, Germany). Wells are blocked with a 1% casein solution. A 1:5 dilution of periplasmic extract containing expressed VHHs is incubated with the following Ang species according to the type of assay: 0.02 nM FLAG tagged

30 human Ang2, a 1:3,000 dilution of HEK293 conditioned medium containing FLAG tagged mouse Ang2 or 0.02 nM FLAG-tagged human Ang1 (Alexis Biochemicals, San Diego, CA, USA). This mixture is added to the Tie2/Fc coated well and incubated for 2 hours at room temperature.

Residual binding of Ang is detected using HRP-conjugated anti-FLAG M2 antibody (Sigma, St Louis, MO, USA).

In a second screening cycle, periplasmic extracts containing expressed VHHs of selection outputs that yielded a high diversity of mouse Ang2 cross-reactive blocking VHHs are screened at a 1:300 dilution. VHHs inhibiting the binding of human Ang2 to human Tie2, mouse Ang2 to mouse Tie2 and showing no inhibition of human Ang1 binding to human Tie2 are selected.

Sequence analysis revealed 86 unique VHHs belonging to 38 different B-cell lineages. The total number of unique sequence variants found for each B-cell lineage, a representative VHH and the selection condition used, is depicted in Table 2. An overview of AlphaScreen and ELISA based screening data is given in Table 3. The amino acid sequences of all unique VHHs are shown in the Sequence Listing (SEQ ID NOs: 1 to 86) and in Table 4.

Table 2: Selection parameters used for the identification of Ang2 specific VHH B-cell lineages.

B-cell Lineage no.	Representative VHH ID	# Unique variants	Library	Selection format	Selection rounds
1	2F04	3	408	biot-hAng2 biot-hAng2 > biot-hAng2 rmAng2 > rmAng2	1 or 2
2	1D01	2	406	biot-hAng2 biot-hAng2 > rmAng2	1 or 2
3	10H02	7	408	biot-hAng2 > biot-hAng2 rmAng2 > rmAng2	1 or 2
4	3A07	3	454	biot-hAng2 biot-hAng2 > rmAng2	1 or 2
5	7G08	3	454	biot-hAng2 > biot-hAng2	1 or 2
6	2G01	1	408	biot-hAng2	1
7	8A11	1	455	biot-hAng2 > biot-hAng2	2
8	16A03	4	455	biot-hAng2 biot-hAng2 > rmAng2	1 or 2
9	14A09	2	408	biot-hAng2 biot-hAng2 > rmAng2	1 or 2
10	11B07	18	454	biot-hAng2 biot-hAng2 > biot-hAng2 biot-hAng2 > rmAng2 rmAng2 > rmAng2	1 or 2
11	1E01	1	406	biot-hAng2	1
12	13A03	2	406	biot-hAng2 > rmAng2	2

B-cell Lineage no.	Representative VHH ID	# Unique variants	Library	Selection format	Selection rounds
13	15A06	1	454	biot-hAng2 > rmAng2	2
14	11A03	2	454	rmAng2 > rmAng2	2
15	14H02	3	408	biot-hAng2 > rmAng2 rmAng2 > rmAng2	2
16	14A08	1	408	biot-hAng2 > rmAng2	2
17	15H04	1	454	biot-hAng2 > rmAng2	2
18	16G09	3	455	biot-hAng2 > rmAng2	2
19	13A02	1	406	biot-hAng2 > rmAng2	2
20	10C06	4	408	rmAng2 > rmAng2	2
21	12A08	1	455	rmAng2 > rmAng2	2
22	12B03	2	455	biot-hAng2 > rmAng2 rmAng2 > rmAng2	2
23	10A03	1	408	rmAng2 > rmAng2	2
24	16A02	2	455	biot-hAng2 > rmAng2 rmAng2 > rmAng2	2
25	10A09	3	408	biot-hAng2 > rmAng2 rmAng2 > rmAng2	2
26	22C07	1	408	rmAng2 > rmAng2	2
27	21G10	2	408	biot-hAng2 > rmAng2 rmAng2 > rmAng2	2
28	19A03	1	406	biot-hAng2 > rmAng2	2
29	23C10	1	454	biot-hAng2 > rmAng2	2
30	25B01	1	455	biot-hAng2 > rmAng2	2
31	25F01	1	455	biot-hAng2 > rmAng2	2
32	25D08	1	455	biot-hAng2 > rmAng2	2
33	24B05	1	454	rmAng2 > rmAng2	2
34	22G11	1	408	rmAng2 > rmAng2	2
35	25G04	1	455	biot-hAng2 > rmAng2	2
36	28D10	1	408	biot-hAng2 > rmAng2	2
37	32H10	1	408	rmAng2 > rmAng2	2
38	29B08	1	408	biot-hAng2 > rmAng2	2

Table 3: Screening of periplasmic extracts containing expressed anti-Ang2 VHH^(a)

B-cell Lineage No.	Representative VHH ID	# Unique variants	AlphaScreen	ELISA		
			hAng2 (% inh)	hAng2 (% inh)	mAng2 (% inh)	hAng1 (% inh)
1	2F04	3	79-84	50-86	13-27	0-4
2	1D01	2	77-83	97-101	85-102	0
3	10H02	7	54-94	65-101	42-98	0-3
4	3A07	3	53-80	0-75	1-27	0-4
5	7G08	3	96-96	101	101	0
6	2G01	1	55	39	2	0
7	8A11	1	57	67	13	0
8	16A03	4	54-96	0	0-4	0-2
9	14A09	2	0-69	6-13	0-2	0
10	11B07	18	46-92	26-107	9-93	0-2
11	1E01	1	0	2	3	4
12	13A03	2	50-53	28-40	0	0-2
13	15A06	1	72	0	0	0
14	11A03	2	57-74	0-3	0	0
15	14H02	3	54-63	54-56	36-48	0-7
16	14A08	1	52	5-5	4	0
17	15H04	1	57	82	38	0
18	16G09	3	55-95	57-99	21-96	1-7
19	13A02	1	91	96	97	1
20	10C06	4	64-85	84-90	43-50	0-2
21	12A08	1	98	0	2	3
22	12B03	2	83-92	92-94	11-99	0-7
23	10A03	1	67	0	0	0
24	16A02	2	67-90	0	0-1	0-1
25	10A09	3	52-65	0-11	0-1	0-4
26	22C07	1	73	78	82	0
27	21G10	2	55-85	45-72	13-30	0
28	19A03	1	74	74	22	0
29	23C10	1	57	37	24	0
30	25B01	1	61	5	24	4
31	25F01	1	67	85	42	14
32	25D08	1	78	94	6	10
33	24B05	1	97	102	98	3

B-cell Lineage No.	Representative VHH ID	# Unique variants	AlphaScreen	ELISA		
			hAng2 (% inh)	hAng2 (% inh)	mAng2 (% inh)	hAng1 (% inh)
34	22G11	1	96	100	98	0
35	25G04	1	90	87	9	0
36	28D10	1	89	118	93	4
37	32H10	1	55	112	58	17
38	29B08	1	60	112	63	0

^(a) if multiple unique VHH variants within a B-cell lineage are identified, the range (min-max) of % inhibition is given.

5 **Table 4:** Amino acid sequence of unique anti-Ang2 VHHs identified during screening

VHH ID/ SEQ ID NOs:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
001D01/ 1	EVQLVES GGGLVQA GGSLRLS CAASGFT FD	DYAL G	WFRQA AGKERE GVS	CIRCSD GSTYYA DSVKG	RFTISSDNAKN TVYLQMNSLK PEDTAVYYCA A	SIVPRSKLEP YEYDA	WGQ GTQV TVSS
001E01/ 2	EVQLVES GGGLVQP GGSLRLS CVHSGTIS S	THAM G	WYRQA PGKQRE HVA	TFTNRG STYYAG SVKG	RFTISRDNAKN TMYLQMNSLK PEDTAVYYCN T	GPY	WGQ GTQV TVSS
002A01/ 3	EVQLVES GGGLVQA GGSLRLS CAASGRT FS	SSVM G	WFRQA PGKERE FVA	AISGSG SSTDSA QG	RFTISRDNAKN TVYLQMNSLK PEDTAVYYCA A	GRAFLARDT FYYDI	WGQ GTQV TVSS

VHH ID/ SEQ ID NOs:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
002F04/ 4	EVQLVES GGGLVQA GGSLRLS CAASGFA FD	DHLI G	WFRQA PGKERE AVS	CISRSA GSTYYA DSVKG	RFTISSDNAKN TVYLMNSLK ADDTAVYYCA A	GPAWGRPA SPLPYEYDY	WGQ GTQV TVSS
002G01/ 5	EVQLVES GGGLVQA GGSLRLS CAASGRTI S	SYAM A	WFRQA PGKERE FVA	AISLSGD STYYAD SVKG	RFTISRDNAKN TVYLMNSLK PEDTAEYYCA A	TDWDFEDIP EYYCSGYG CDESLFDS	WGQ GTQV TVSS
003A07/ 6	EVQLVES GGGLVQP GGSLRLS CAASGFTL D	YDAI G	WFRQA PGKERE GVS	CITSSD GITYYA DSVKG	RFTISRDNAKN TVYLMNSLK PEDTAVYYCA T	GNRRIYYSD YALACFPYE YDY	WGQ GTQV TVSS
003D01/ 7	EVQLVES GGGLVQV GDLSRLS CAASGRT FS	TYLM VG	WFRQA PGKERE FAA	VIWSSG DTAYAD SVKG	RFTISRDSA KN TVYLMNSLK AEDTAVYYCA G	SYDGNYYIP GFYKD	WGQ GTQV TVSS
003E10/ 8	EVQLVES GGGLVQP GGSLRLS CTTSGFTL D	YYAV G	WFRQA PGKERE GVS	CISSSD GSTYYA DSVKG	RFTISRDNAKN TVYLMNSLK PEDTAVYYCA T	GNLRIYYSD YALACFPYE YDY	WGQ GTQV TVSS
003F02/ 9	EVQLVES GGGLVQV GDLSRLA CAASGRT FS	TYLM VG	WFRQA PGKERE FAA	GIWSSG DTAYAD SVKG	RFTISRDNAKN TVYLMNSLK TEDTAVYYCA G	SYDGNYYIP GFYKD	WGQ GTQV TVSS

VHH ID/ SEQ ID NOs:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
003F07/ 10	EVQLVES GGGLVQV GDSLRLS CAASGRT FS	TYLM VG	WFRQA PGKERE FAA	AMWSS GVPAYA DSVKG	RFTISRDNKN TVYLMNSLK AEDTAVYYCA G	SYGGNYYIP GFYED	WGQ GTQV TVSS
004B06/ 11	EVQLVES GGGLVQA GGSLRLS CAASGHT FS	RYAM G	WFRRVP GKEREF VT	HITWNR GSTYYA DSVKG	RFTISRDKASN TLYLMNSLK PEDTAVYYCA A	QIKYGAVTH PEEYSY	WGQ GTQV TVSS
006F05/ 12	KVQLVES GGGLVQA GGSLRLS CAASGFA FD	DHLI G	WFRQA PGKERE AVS	CISRSA GSTYYA DSVKG	RFTISSDNKN TVYLMNSLK ADDTAVYYCA A	GPAWGRPA SPLPYEYDY	WGQ GTQV TVSS
006H05/ 13	EVQLVES GGGLVQA GGSLRLS CAASGFT FD	DYAI G	WFRQA PGKERE GVS	CISSSD GSTAYA DSVKG	RFTISSDNKN TVYLMNSLK PEDTAVYYCT A	VPATRRTPQ MVAANVCW LAEYEYDY	WGQ GTQV TVSS
007B09/ 14	EVQLVES GGGLVQV GDSLRLS CAASGRT FS	TYLM VG	WFRQA PGKERE FAA	GIWSSG GTAYAD SVKG	RFTVSRDNAK NTVYLMNSL KAEDTAVYYC AG	SYDGNYYIP GFYKD	WGQ GTQV TVSS
007C01/ 15	EVQLVEF GGGLVQV GDSLRLS CAASGRT FS	TYLM VG	WFRQA PGKERE FAA	GIWSSG GTAYAD SVKE	RFTVSRDNDK NTVYLMNSL QAEDTAVYYC AG	SYDGNYYIP GFYKD	WGQ GTQV TVSS

VHH ID/ SEQ ID NOs:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
007C07/ 16	EVQLVES GGGLVQV GDSLRLS CAASGHT FS	TYLM VG	WFRQTP GKEREF AA	VIWSSG DTAYAD SVKG	RFTISRDNACKN TVYLMNSLK AEDTAVYYCA G	SYGGNYYP GFYED	WGQ GTQV TVSS
007G08/ 17	EVQLVES GGGLVQP GGSLRLS CAASGFALD	YYAIG	WFRQV PGKERE GVS	CISSSD GITYYV DSVKG	RFTISRDNACKN TVYLMNSLK PEDTAVYYCA T	DSGGYIDYD CMGLGYDY	WGQ GTQV TVSS
008A11/ 18	EVQLVES GGGLVQA GGSLRLS CAASGRT FS	SYAMG	WFRQA PGKELE FVT	AVSWS GGSTYY ADSVKG	RFTISRDSA KN TVYLMNSLK PEDTAVYYCA A	QSTIVEVTTL EAYDY	WGQ GTQV TVSS
010A03/ 19	EVQLVES GGGSVQA GGSLRLS CAASERT FS	PYAMG	WFRQA PGKERE FVA	HITWSA GSTYYA DSVKG	RFTISRDNACKN TVYLMNSLK PEDTAVYYCA A	KRRYGIVDR DYND	WGQ GTQV TVSS
010A09/ 20	EVQLVES GGGLVQA GGSLRLA CIASGRDIF	SVSATG	WYRQA PGKQRE FVA	GISNIGA TKFADS VKG	RFTISRDNACKN TVYLMNSLK PEDTAVYYCN V	LLWSGNL	WGQ GTQV TVSS
010A10/ 21	EVQLVES GGGLVQA GGSLRLS CIASGRDIF	SITAI G	WYRQA PGKQRE FVA	GISNIGA TKYTDS VKG	RFTISGDNAEN TVYLMNSLK PEDTAVYYCN V	LLWSANY	WGQ GTQV TVSS

VHH ID/ SEQ ID NOs:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
010B02/ 22	EVQLVES GGGLVQA GGSLRLS CAASGFA FD	DHLI G	WFRQA PGKERE AVS	CISRSA GSTYYA DSVKG	RFTISGDNAKN TVYLMNSLK ADDTAVYYCA A	GPAWGRPA SPLPYEYDY	WGQ GTQV TVSS
010B08/ 23	EVQLVES GGGLVQA GGSLRLS CAASGFT FD	DYAI G	WFRQA PGKERE GVS	CISSSD GSTAYA DSVKG	RFTISSDNAKN TVYLMNSLK PEDTAVYYCT A	VPATRRTPQ MVVANVCW LAEYEYDY	WGQ GTQV TVSS
010C06/ 24	EVQLVES GGGLVQA GGSLRLS CVASGFT FD	DYAI G	WFRQA PGKERE GVS	CISSSD GSTYYA DSVKG	RFTISGDNAKN TVYLMNSLK PEDTAVYYCA A	GITPCSDYT QTYEYDV	WGQ GTQV TVSS
010C07/ 25	EVQLVES GGGLVQA GGSLRLS CAASGFT FD	DYAI G	WFRQA PGKERE GVS	CISRSD GSTSYA DSVKG	RFTISSDNAKN TVYLMNSLK PEDTAVYYCT A	VPATRRTPQ MVVANMCW LAEYEYDY	WGQ GTQV TVSS
010D04/ 26	EVQLVES GGGLVQA GGSLRLS CAASGFT FD	DYAI G	WFRQA PGKERE GVS	CISSSD GSTYYA DSVKG	RFTISSDNAKN TVYLMNSLK PEDTAVYYCA A	GITPCSDYT QTYEYDV	WGQ GTQV TVSS
010E02/ 27	EVQLVES GGGLVQA GGSLRLS CAVSGFT FD	DYAI G	WFRQA PGKERE GVS	CISSSD GSTAYA DSVKG	RFTISSDNAKN TVYLMNSLK PEDTAVYYCT A	VPATRRTPQ MVVANVCW LAEYEYDY	WGQ GTQV TVSS

VHH ID/ SEQ ID NOs:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
010F10/ 28	EVQLVES GGGLVQA GGSLRLS CAASGFT FD	DYAI G	WFRQA PGKERE GVS	YISSSD GSTYYA DSVKG	RFTSSSDNAK NTVYLQMNSL KPEDTAVYYC AA	RPTLRVRLD NDRHHLLYE YEYDY	WGQ GTQV TVSS
010G02/ 29	EVQLVES GGGLVQA GGSLRLS CAASGFT FD	DYTI G	WFRQA PGKERE GVS	CISSSD GSTSYA DSVKG	RFTISSDNAKN TVYLQMNSLK PEDTAVYYCT A	VPATRRTPQ MVVLNMCW LAEYEYDY	WGQ GTQV TVSS
010G11/ 30	EVQLVES GGGLVQA GGSLRLS CVASGFT FD	DYAI G	WFRQA PGKERE GVS	CISSSD GSTYYA DSVKG	RFTISSDNAKN TVYLQMNSLK PEDTAVYYCA A	GITPCSDYT QTYEYDV	WGQ GTQV TVSS
010H02/ 31	EVQLVES GGGSVQA GGSLRLS CAASGFT FD	DYAI G	WFRQA PGKERE GVS	CISSSD GSTNYA DSVKG	RFTISSDTAKN TVYLQMNSLK PEDTAVYYCT A	VPATRRTPQ MVDANMCW LAEYEYDY	WGQ GTQV TVSS
011A02/ 32	EVQLVES GGGLAQA GGSLRLS CAASGRR FG	GHA MG	WFRQA PGEERE FVA	TIYWTS GMTRYA GSVKG	RFTISRDNAEN TVFLQMNSLK PEDTAVYYCA V	IKDFQLRVD VTSASAYDY	WGQ GTQV TVSS
011A03/ 33	GVQLVES GGGLAQA GGSLRLS CAASGRR FG	GHA MG	WFRQA PGKDRE FVA	TIYWTT GMTRYA DSVKG	RFTISRDNAEN TVFLQMNSLK PEDTAVYYCA L	IRDFNIRLDV TSASAYGY	WGQ GTQV TVSS

VHH ID/ SEQ ID NOs:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
011B07/ 34	EVQLVES GGGLVQV GDSLRLS CAASGRT FS	TYLM VG	WFRQA PGKERE FAA	GIWSSG DTAYAD SVRG	RFTISRDNACKN TVYLMNSLK TEDTAVYYCA G	SYDGNYYIP GFYKD	WGQ GTQV TVSS
011C01/ 35	EVQLVES GGGLVQV GDSLRLS CAASGRT FS	TYLV VG	WFRQA PGKERE FAA	AIWSSG DTAYAD SVKG	RFTISRDNACKN TVYLMNSLK AEDTAVYYCA G	SYGGNYYIP GFYED	WGQ GTQV TVSS
012A02/ 36	EVQLVES GGGLVQA GGSLRLS CAASGRT FS	RNAM A	WFRQV PGKVRE FVA	GIRWNV GRLDYA DSVKG	RFTISRDNAEN TVYLMNDLK TEDTAVYYCA A	YAGLVFSGI PDY	WGQ GTQV TVSS
012A08/ 37	EVQLVES GRGLVQA GGSLRLS CAASGSIF S	INAM L	WYRQA PGKQRE LVA	AITSGG STNYAD SVKG	RFTISRDNACKN TVYLMNSLK PEDTAVYYCA A	DSDYSSDY Y	WGQ GTQV TVSS
012B03/ 38	EVQLVES GGGLVQS GGSLRLS CAASGFA LD	YYTI G	WFRQA PGKERE GVS	CISGGD TSTYYA DSVKG	RFTISRDNACKN TVYLMNSLK PEDTAVYYCA T	DSAGVPAGP AAVYGSTCS RLEYDY	WGQ GAQV TVSS
013A02/ 39	EVQLVES GGGLVQA GGSLRLS CAASGGT FS	SYSM G	WFRQA PGKERE FIA	AINWNG DSTYYE DSVKG	RFTVSRDNAK NTVYLMNSL KPEDTAVYYC AA	TGWGRAYE QAYEYDV	WGQ GTQV TVSS

VHH ID/ SEQ ID NOs:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
013A03/ 40	EVQLVES GGGLVQP GGSLRLS CAASGFT VD	DYAM S	WVRQA PGKGLE WVS	TISWND EYTYA ESMKG	RFTISRDNKN TLYLQMNSLK SEDTAVYYCA K	GGSRLYDYH Y	WGQ GTQV TVSS
014A08/ 41	EVQLVES GGGLVQA GGSLRLS CASSGFT FD	DYAI G	WFRQA PGKERE GVS	CISSSD GSTYYA DSVKG	RFTISSDNKN TVYLQMNSLK PEDTAVYYCA A	RPPFHSCSE YENDY	WGQ GTQV TVSS
014A09/ 42	EVQLVES GGGLVQA GGSLRLS CAASGRTI S	SSVL G	WFRQA PGKERE FVA	AISGSG SSTDSA KD	RFTISRDNKN TVYLQMNSLK PEDTAVYYCA A	GRAFLTRDP FYYDI	WGQ GTQV TVSS
014A11/ 43	EVQLVES GGGLVQA GGSLRLT CIASGRDI F	SVTA MG	WYRQA PGKQRE FVA	GLSNIG ATKYAD SVKG	RFTVSGDAAK NTVYLQMNSL KPEDTAVYYC NV	LLWSGNY	WGQ GTQV TVSS
014D03/ 44	EVQLVES GGGLVQA GGSLRLS CAASGFT FD	DYAI G	WFRQA PGKERE GVS	YISKSD GTTYA DSVKG	RFTSSSDNAK NTVYLQINSLK PEDTAVYYCA A	RPTLRVRLD NDRHHLLYE YEYDY	WGQ GTQV TVSS
014H02/ 45	EVQLVES GGGLVQA GGSLRLS CAASGFT FD	EYAI G	WFRQA PGKERE GVS	YISSSD GSTYYA DSVKG	RVTSSSDNAK NTVYLQMNSL KPEDTAVYYC AA	RPTLRVRLD NDRHHLLYE YEYDY	WGQ GTQV TVSS

VHH ID/ SEQ ID NOs:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
015A06/ 46	EVQLVES GGGLVQA GGSLRLS CAASGRT FS	SYAM G	WFRQA PGKERE FVA	RISWNG GSTYHA DSVKG	RFTISRDNPKN TVYLQMDSLK PEDAAIYYCAA	SIALVGGVT PHSYDY	WGQ GTQV TVSS
015C05/ 47	EVQLVES GGGLVQV GDLSRLS CAASGRT FS	TYLM VG	WFRQA PGKERE FAA	VIWSSG DTDYAD SVKG	RFTISRDNNAKN TVYLQMNSLK AEDTAVYYCA G	SYGGNYYP GFYKD	WGQ GTQV TVSS
015D05/ 48	EVQLVES GGGLVQV GDLSRLS CAASGRT FS	TYLM VG	WFRQA PGKERE FAA	GIWSSG GTAYAD SVKG	RFTISRDNNAKN TVYLQMNSLK AEDTAVYYCA G	SYDGNYYYP GFYKD	WGQ GTQV TVSS
015H04/ 49	EVQLVES GGGLVQA GGSLGLS CAASERTL P	SYVM G	WFRQA PGKELE FVA	GISWSS GRTYYT DSVKG	RFTISRDAEN TWYLQMNSLK PEDTAVYYCA S	NSVSEPTLH TWQYEASY DY	WGQ GTQV TVSS
016A01/ 50	EVQLVES GGGLVQA GGSLRLS CAASGHT FS	RYAM G	WFRRVP GEEREF VT	HITWNR GSTYYA DSVKG	RFTISRDKASN TLYLQMNSLK PEDTAVYYCA A	QIKYGEITHP EEYSY	WGQ GTQV TVSS
016A02/ 51	EVQLVES GGGLVQA GGSLRLS CAASGRT FS	RNAM G	WFRQV PGKARE FVA	AIRWNV GRLDYA DSVKG	RFAISRDAEN TVYLQMNDLK TEDTAVYYCA A	YAGLVYSGI PDY	WGQ GTQV TVSS

VHH ID/ SEQ ID NOs:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
016A03/ 52	EVQLVES GGGLVQA GGSLRLS CAASGHT FS	RYAM G	WFRRVP GKREF VT	HITWNR GSTYYA DSVKG	RFTISRDKASN TLYLQMNSLK PEDTAVYYCA A	QIKYGEIHP EEESY	WGQ GTQV TVSS
016A05/ 53	EVQLVES GGGLVQA GDSLRLS CAASGHT FS	RYAM G	WFRRVP GKREF VT	HITWNR GSTYYA DSVKG	RFTISRDKASN TLYLQMNSLK SEDTAVYYCA A	QTKYGEITR PEESY	WGQ GTQV TVSS
016G09/ 54	EVQLVES GGGLVQA GGSLRLV CSASGIDF S	INAM A	WYRQA PGKQRE WVA	FMINDS STDYTD SVKG	RFTISRDKASN ILYLQMNNLNV EDTAVYYCNT	AYEQHTY	WGQ GTQV TVSS
019A03/ 55	EVQLVES GGGLVQA GGSLRLS CAASGFT FD	DYAI A	WFRQA PGKERE GIS	CITPSD DRTYYA DSVKG	RFISSDNAKN TVYLQMNSLK PEDTADYYCA A	VPRLRGLGY WPYPEY DY	WGQ GTQV TVSS
019G07/ 56	KVQLVES GGGLVQA GGSLRLS CAASGFT FD	DYAL G	WFRQA AGKERE GVS	CIRCSD GSTYYA DSVKG	RFTISSDNAKN TVYLQMNSLK PEDTAVYYCA A	SIVPRSKLEP YEYDA	WGQ GTQV TVSS
019G08/ 57	EVQLVES GGGLVQP GGSLRLS CAVSGFT VD	DYAM S	WVRQA PGKGLE WVS	TISWND EYTYA ESMKG	RFTISRDKASN TLYLQMNSLK SEDTAVYYCA K	GGSRLYDYH Y	WGQ GTQV TVSS

VHH ID/ SEQ ID NOs:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
021G10/ 58	EVQLVES GGGLVQA GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	CISSSD GSTTYA DSVKG	RFTVSSDNAK NTVYLQMNSL KPEDTAVYYC AA	GLRGRYYR GTYSLVCAP YEYDF	WGQ GTQV TVSS
022B09/ 59	EVQLVES GGGLVQA GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	CISSSD GSTYYA DSVKG	RFTISADNAKN TVYLQMNSLK PEDTAVYYCA A	GLRGRYYR GSNYLVCAP YEYDY	WGQ GTQV TVSS
022C07/ 60	EVQLVES GGGLVQA GGSLRLS CAASGFT FD	DYAI G	WFRQA PGKERE GVS	CISSSD GSTYYA DSVKG	RFTISSDNAKN TVYLQMNSLK PEDTAVYYCA A	DFIISSKRLC LDLFGS	RGQG TQVT VSS
022G03/ 61	EVQLVES GGGSVQA GGSLRLS CAASGFT FD	DYAI G	WFRQA PGKERE GVS	CISSSD GSTYYA DSVKG	RFTISSDNAKN TVYLQMNSLK PGDTAVYYCA A	GITPCSDYT QTYEYDV	WGQ GTQV TVSS
022G05/ 62	EVQLVES GGGLVQA GGSLRLS CAASGFT FD	DYAI G	WFRRAP GKERE VS	CITSSD GSTSYA DSVKG	RFTISSDSAKN TVYLQMNSLK PEDTAVYYCS V	VPATRRNPQ MVVAKKCW LAEYDY	WGQ GTQV TVSS
022G11/ 63	EVQLVES GGGLVQA GGSLRLS CAVSGFT FD	DYAI G	WFRQA PGKERE GVS	CISRSD GSPYYA DSVKG	RFTISSDNAKG TVYLQMSSLK PEDTAVYYCA A	SWSGAYYS GTYCDRLY EYDA	WGQ GTQV TVSS

VHH ID/ SEQ ID NOs:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
023A04/ 64	EVQLVES GGGLVQV GDSLRLS CAASERT FS	TYLM VG	WFRQA PGKERE FAA	TMWSS GDTAYA DSVKG	RFTISRDNACKN TVYLQMNSLK AEDTAVYYCA G	SYGGNYYIP GFYED	WGQ GTQV TVSS
023C10/ 65	EVQLVES GGGLVQP GGSLRLS CAASGFALD	YYAIG	WFRQA PGKERE GVS	CISSSD GSTYYA DSVKG	RFTISRDNACKN TVYLQMNSLK PEDTAVYYCA T	DSLGYGSSC RMAPYEYDY	WGQ GTQV TVSS
023D01/ 66	EVQLVES GGGLVQV GDSLRLS CAASGRT FS	TYLM VG	WFRQA PGKERE FAA	VIWSSG GTAYAD SVKG	RFTISRDNACKN TVYLQMNSLK AEDTAVYYCA G	SYDGNYYIP GFYKD	WGQ GTQV TVSS
023E02/ 67	EVQLVES GGGLVQP GGSLRLS CAASGFTSD	DYAI G	WFRQA PGKERE GVS	CISSSD GITYYA DSVKG	RFTISRDNACKN TVYLQMNSLK PEDTAVYYCA T	GNNRIYSD YALACFPYE YDY	WGQ GTQV TVSS
023E08/ 68	EVQLVES GRRLVQV GDSLRLA CAASGRT FS	TYLM VG	WFRQA PGKERE FAA	GIWSSG DTAYAD SVKG	RFTISRDNACKN TVYLQMNSLK TEDTAVYYCA G	SYDGNYYIP GFYKD	WGQ GTQV TVSS
023F10/ 69	EVQLVES GGGLVQV GDSLRLS CAASERT FS	TYLM VG	WFRQA PGKERE FAA	TMWVS GDTAYA DSVKG	RFTISRDNPKN TVYLQMNSLK AEDTAVYYCA G	SYGGNYYIP GFYKD	WGQ GTQV TVSS

VHH ID/ SEQ ID NOs:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
023F11/ 70	EVQLVES GGGLVQI GDSLRLS CAASGRT FS	TYLM VG	WFRQA PGKERE FAA	AIWSSG DTAVAD SVKG	RFTISRDNACKN TVYLQMNSLK AEDTAVYYCA G	SYGGNYYIP GFYED	WGQ GTQV TVSS
024B05/ 71	EVQLVES GGGLVQP GGSLRLS CAASGFTL D	YYAI G	WFRQA PGKEW EGVS	CISSSD GSTYYA DSVKG	RFTISRDNACKN TVYLQMNSLK PEDTAVYYCA T	DSIVCGSY GMDY	WGKG TQVT VSS
024G05/ 72	EVQLVES GGASVQP GGSLRLS CAASGRT FS	TYLM VG	WFRQA PGKERE FAA	GIWSSG GTAYAD SVKE	RFTVSRDNDK NTVYLQMNSL QAEDTAVYYC AG	SYDGNYYIP GFYKD	WGQ GTQV TVSS
025B01/ 73	EVQLVES GGGLVQA GGSLRLS CAASGFT FD	DYAI G	WFRQA PGKERE GVS	CISSSD GSTYYA DSVKG	RFTISSDNACKN TVYLQMNSLK PEDTAVYYCA A	AWGASRLPI GTMPPYEYD Y	WGQ GTQV TVSS
025C06/ 74	EVQLVES GGGLVQA GGSLRLV CSASGIDF S	INVM G	WYRQA PGKQRE WVA	FIGSGG STDYIDY TDSVKG	RFTISRDNACKN ILYLRMNNLNV EDTAVYYCNT	AYEQHTY	WGQ GTQV TVSS
025D08/ 75	EVQLVES GGGLVQA GGSLRLS CAASGFT FD	DYAI G	WFRQA PGKDL E GVS	CISSSD GSTYYA DSVKG	RFTISSDNACKN TVYLQMNSLK PEDTAVYYCA A	VNGLGPFV S PVPVYDF	WGQ GTQV TVSS

VHH ID/ SEQ ID NOs:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
025F01/ 76	EVQLVES GGGLVQA GGSLRLS CAVSLP FD	DYVI G	WFRQA PGKERE GVS	CISSSD GSTYYA DSVKG	RFTISSDNAKN TVYLQMNSLK PEDTAAYYCA A	GGPRINIAT MTCSHDEYE YDY	WGQ GTQV TVSS
025F07/ 77	EVQLVES GGGLVQP GGSLRLS CAASGFA LD	YYAI G	WFRQA PGKERE GVS	CISSD GSTYYA DSVKG	RFTISRDNAKN TVYLQMNSLK PEDTAVYYCA T	DSAGVPAGP AAVYGSSCS RLEYDY	WGQ GTQV TVSS
025G04/ 78	EVQLVES GGGLVQP GGSLRLS CAASGFT FG	SYDM S	WVRQA PGKGPE WVS	AINSRG GSTYYA DSVKG	RFTISRDNAKN TLYLQMNSLK PEDTAVYYCA T	DPYLSYYG YPLYDY	WGQ GTQV TVSS
025G10/ 79	EVQLVES GGGLVQA GGSLRLV CSASGIDF S	INVM G	WYRQA PGKQRE WVA	FIGSGS STGYTD SVKG	RFSISRSTKN ILYLQMNNLN EDTAVYYCNT	AYEQHTY	WGQ GTQV TVSS
028D10/ 80	EVQLVES GGGLVQA GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	CIRDSD GSTYYA DSVKG	RFTISSDNDKN TVYLQMNSLK PEDTAVYYCA A	VPAGRRLRFG EQWYPLYEY DA	WGQ GTQV TVSS
029B08/ 81	EVQLVES GGGVVQA GDSVRLS CAASGPT FR	SYTM A	WFRQTP GKERDI VA	AISSSLG RTYYAD SVKG	RFQILRDNAKE TVWLQMNSLK PEDTAVYICAA	SRSLNLAYT TKPYDY	WGQ GTQV TVSS

VHH ID/ SEQ ID NOs:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
032H10/ 82	EVQLVES GGGLVQA GGSLRLS CAASGFD FE	DYDM G	WFRQA PGKERE GVS	YISSSD GSTYYT DSVKG	RFTISSDNAKN TVYLMNSLIP EDTAVYYCAA	RPWTRRVY GSSWLARSL DEYEYDY	WGQ GTQV TVSS
036H10/ 83	EVQLVES GGGLVQV GDLSRLS CAASGHT FS	TYLM VG	WFRQTP GKEREF AA	VIWSSG DTAYAD SAKG	RFTISRDNAKN TVYLMNSLK AEDTAVYYCA G	SYGGNYIIP GFYED	WGQ GTQV TVSS
037A09/ 84	EVQLMES GGGLVQP GGSLRLS CAASGFA LD	YYAI G	WFRQV PGKERE GVS	CISSSD GITYYV DSVKG	RFTISRDNAKN TVYLMNSLK PGDTAVYYCA T	DSGGYIDYD CMGLGYDY	WGQ GTQV TVSS
037F02/ 85	EVQLVES GGGLVQP GGSLRLS CAASGFA LD	YYAI G	WFRQA PGKERE GVS	CISSSD GITYYV DSVKG	RFTISRDNAKN TVYLMNSLK PEDTAVYYCA T	DSGGYIDYD CMGLGYDY	WGQ GTQV TVSS
043E10/ 86	EVQLVES GGGLVQV GDLSRLS CAASGRT FS	TYLM VG	WFRQA PGKERE FAA	VIWSSG DTAYAD SVKG	RFTISRDNAKN TVYLMNSLK AEDTAVYYCA G	SYDGNYYIP GFYKD	WGQ GTQV TVSS

Example 5

Characterization of purified anti-Ang2 VHHs

A subset of inhibitory anti-Ang2 VHHs selected from the screening described in Example 4 are further purified and characterized. Selected VHHs are expressed in *E. coli* TG1 as c-myc, His6-tagged proteins. Expression is induced by addition of 1 mM IPTG and allowed to continue for 4 hours at 37°C. After spinning the cell cultures, periplasmic extracts are prepared by freeze-thawing the pellets. These extracts are used as starting material and VHHs are purified via IMAC and size exclusion chromatography (SEC) resulting in $\geq 95\%$ purity as assessed via SDS-PAGE.

5.1. Evaluation of hAng2 blocking VHHs in ELISA

The blocking capacity of the VHHs is evaluated in a human Ang2-human Tie2 blocking ELISA. In brief, 2 $\mu\text{g/mL}$ of Tie2/Fc chimera (R&D Systems, Minneapolis, MN, USA) is coated in a 96-well MaxiSorp plate (Nunc, Wiesbaden, Germany). A fixed concentration of 0.02 nM FLAG-tagged human Ang2 (Alexis Biochemicals, San Diego, CA, USA) is added to a dilution series of the purified VHH (diluted in PBS+0.1% casein+0.05% Tween-20), and incubated on the coated human Tie2 receptor for 2 hours. Residual binding of human Ang2 is detected using horseradish peroxidase (HRP) conjugated anti-FLAG M2 (Sigma, St. Louis, MO, USA) (Figure 1). Reference molecule is the Fab fragment of Ab536 (US2009/0191212) (Figure 1-1) or the peptide moiety of peptibody AMG386 (SEQ ID NO:25 in WO2004/092215) (Figure 1-2). As negative control an irrelevant VHH is used. The IC_{50} values for VHHs blocking the human Ang2-human Tie2 interaction are depicted in Table 5-1 and Table 5-2, respectively.

Table 5-1: IC_{50} (nM) values of purified VHHs blocking the hAng2/hTie2 interaction (competition ELISA; VHH: n=2-3; Fab Ab536: n=6)

VHH ID	IC_{50} (nM)
1D01	3.4
2F04	2.8
3A07	21.0
3F02	9.1
6H05	5.3

VHH ID	IC ₅₀ (nM)
7G08	0.07
8A11	30.2
10C06	7.7
10H02	3.0
11B07	5.4
12B03	4.6
13A02	4.1
14H02	64.4
15H04	18.6
16G09	11.3
21G10	6.2
22C07	11.0
24B05	1.0
25F01	6.5
Fab Ab536	39.3

Table 5-2: IC₅₀ (nM) values of purified VHHs blocking the hAng2-hTie2 interaction (competition ELISA; VHH: n=1-3; AMG386 peptide: n=3)

5

VHH ID	IC ₅₀ (nM)
1D01	6.2
7G08	0.04
10H02	8.7
11B07	14.0
13A02	23.0
24B05	1.1
28D10	1.3
32H10	4.0
37A09	0.1

37F02	0.08
AMG386 peptide	3.4

5.2. Evaluation of cross-reactivity towards mouse and cynomolgus Ang2 in blocking ELISA

In order to determine if the VHH inhibits binding of mouse Ang2 to mouse Tie2 and cyno Ang2 to cyno Tie2, a competition ELISA is performed. In brief, 2 µg/mL of recombinant mouse Tie2-Fc or cyno Tie2-Fc is coated overnight at 4°C in a 96-well MaxiSorp plate (Nunc, Wiesbaden, Germany). Coated wells are blocked with a 1% casein solution. FLAG-tagged mouse Ang2 (1:3,000 dilution of conditioned medium from transient HEK transfection) or FLAG-tagged cyno Ang2 (1:800 dilution of conditioned medium from transient HEK transfection) and a dilution series of purified VHH (diluted in PBS+0.1% casein+0.05% Tween-20) are incubated on the coated Tie2-Fc receptor for 2 hours at room temperature to reach binding equilibrium. Residual binding of FLAG-mAng2 or FLAG-cAng2 is detected using HRP conjugated anti-FLAG M2 mAb (Sigma, St. Louis, MO, USA). Reference molecule is the Fab fragment of Ab536 (mouse: Figure 2-1) or the peptide moiety of peptibody AMG386 (mouse: Figure 2-2; cyno: Figure 3). As negative control an irrelevant VHH is used. The IC₅₀ values for VHHs blocking the mouse Ang2-mouse Tie2 interaction are depicted in Table 6-1. The IC₅₀ values for VHHs blocking the mouse and cyno Ang2 binding to mouse and cyno Tie2, respectively, is shown in Table 6-2.

Table 6-1: IC₅₀ (nM) values of purified VHHs blocking the interaction of mAng2 to mTie2 (competition ELISA; VHH: n=2-3; Fab Ab536: n=5)

	mAng2
VHH ID	IC ₅₀ (nM)
1D01	6.3
2F04	57.4
3A07	99.3
3F02	32.7
6H05	7.7
7G08	0.09
8A11	442.1

	mAng2
10C06	45.2
10H02	5.2
11B07	21.0
12B03	6.7
13A02	6.1
14H02	143.2
15H04	124.6
16G09	19.4
21G10	16.8
22C07	13.6
24B05	1.5
25F01	13.3
Fab Ab536	15.3

Table 6-2: IC₅₀ (nM) values of purified VHHs blocking the interaction of mAng2 and cAng2 to mTie2 and cTie2, respectively (competition ELISA; VHH: n=1-3; AMG386 peptide: n=3; n.d., not determined)

5

	mAng2	cAng2
VHH ID	IC₅₀ (nM)	IC₅₀ (nM)
1D01	10.0	16.4
7G08	0.07	0.14
10H02	21.4	23.7
11B07	39.7	24.8
13A02	26.6	33.1
24B05	1.1	2.1
28D10	6.1	2.0
32H10	13.0	n.d.
37A09	0.1	0.2

	mAng2	cAng2
VHH ID	IC₅₀ (nM)	IC₅₀ (nM)
37F02	0.09	0.1
AMG386 peptide	5.2	6.6

5.3. Evaluation of selectivity of human Ang2 blocking VHHs towards human Ang1 in ELISA

In order to determine whether the anti-Ang2 blocking VHHs are selective over human Ang1 binding to human Tie2, a competition ELISA is performed. In brief, 2 µg/mL of recombinant human Tie2-Fc (R&D Systems, Minneapolis, MN, USA) is coated overnight at 4°C in a 96-well MaxiSorp plate (Nunc, Wiesbaden, Germany). Coated wells are blocked with a 1% casein solution. A fixed concentration (0.02 nM) of FLAG-tagged recombinant human Ang1 (Alexis Biochemicals, San Diego, CA, USA) and a dilution series of VHH (diluted in PBS+0.1%casein+0.05%Tween-20) are incubated on the coated receptor Tie2-Fc for 2 hours at room temperature to reach binding equilibrium. Residual binding of FLAG-hAng1 is detected using HRP conjugated anti-FLAG M2 mAb. Reference molecule is the peptide moiety of AMG386 peptibody (Figure 4). As negative control an irrelevant VHH is used. The indicative IC₅₀ values for VHHs blocking the human Ang1 – human Tie2 interaction are depicted in Table 7.

Table 7: IC₅₀ (nM) values of purified VHHs blocking the interaction of human Ang1 to human Tie2 (competition ELISA; VHH: n=2-3; AMG386 peptide: n=3)

VHH ID	IC₅₀ (nM)	hAng1/hAng2 ratio
1D01	>67,000	>10,800
7G08	>84,000	>2,333,333
10H02	2,000	230
11B07	120,000	8,570
13A02	17,000	739
24B05	120,000	109,090

VHH ID	IC ₅₀ (nM)	hAng1/hAng2 ratio
28D10	>4,000	> 3,076
37A09	>10,000	> 100,000
37F02	>10,000	> 100,000
AMG386 peptide	4,000	1,176

5.4. Determining the affinity of the human, mouse, cyno Ang2 – VHH interaction

Affinities of the VHH for binding to human, mouse and cyno Ang2 are determined using surface plasmon resonance (SPR) analysis (Biacore T100). In brief, VHH and benchmark compounds are immobilized on a CM5 chip via amine coupling. A multi-cycle kinetic approach is used: different concentrations of human, mouse and cyno Ang2-FLD (0.4-1-2.6-6.4-16-40-100 nM) are injected. Ang2-FLD species are allowed to associate for 2 min and to dissociate for 20 min at a flow rate of 45 μ L/min. In between injections, the surfaces are regenerated with a 10 sec pulse of 25 mM NaOH and 60 sec stabilization period. Association/dissociation data are evaluated by fitting a 1:1 interaction model (Langmuir binding). The affinity constant K_D is calculated from resulting association and dissociation rate constants k_a and k_d and are depicted in Table 8.

Table 8: Affinity K_D (nM) of purified VHHs for human, mouse and cyno Ang2

VHH ID	human Ang2-FLD			mouse Ang2-FLD			cyno Ang2-FLD		
	k_a (1/Ms)	k_d (1/s)	K_D (M)	k_a (1/Ms)	k_d (1/s)	K_D (M)	k_a (1/Ms)	k_d (1/s)	K_D (M)
1D01	7.7E+06	1.5E-02	2.0E-09	3.3E+06	1.5E-02	4.6E-09	9.9E+06	1.4E-02	1.4E-09
7G08	1.0E+06	1.0E-04	9.7E-11	8.1E+05	1.4E-04	1.8E-10	1.5E+06	1.1E-04	7.2E-11
10H02	5.7E+06	2.1E-02	3.6E-09	2.5E+06	2.6E-02	1.1E-08	6.9E+06	2.3E-02	3.4E-09

VHH ID	human Ang2-FLD			mouse Ang2-FLD			cyno Ang2-FLD		
	k_a (1/Ms)	k_d (1/s)	K_D (M)	k_a (1/Ms)	k_d (1/s)	K_D (M)	k_a (1/Ms)	k_d (1/s)	K_D (M)
11B07	9.2E+06	6.2E-02	6.7E-09	4.8E+06	1.4E-01	2.9E-08	1.2E+07	7.3E-02	6.1E-09
13A02	9.2E+06	9.1E-02	9.9E-09	1.9E+06	3.4E-02	1.8E-08	1.1E+07	9.4E-02	8.7E-09
24B05	2.6E+06	2.5E-03	9.6E-10	1.7E+06	2.9E-03	1.7E-09	4.1E+06	2.4E-03	5.9E-10
28D10	4.9E+06	6.2E-03	1.3E-09	1.9E+06	1.1E-02	5.6E-09	1.8E+07	2.5E-02	1.4E-09
mAb 3.19.3	5.0E+07	5.5E-02	1.1E-09	1.1E+07	6.1E-02	5.5E-09	n.d.	n.d.	n.d.
Fab Ab536	3.1E+06	3.7E-02	1.2E-08	1.6E+06	1.7E-02	1.1E-08	4.1E+06	4.5E-02	1.1E-08

Example 6

Affinity maturation of selected VHH

5 A variant of VHH 28D10 (00027 carrying C₅₀S/S₅₃N and Q₁₀₈L substitution – Example 7.3) is subjected to affinity maturation.

In a first cycle, amino acid substitutions are introduced randomly in both framework (FW) and complementary determining regions (CDR) using the error-prone PCR method. Mutagenesis is performed in a two-round PCR-based approach using the Genemorph II Random Mutagenesis
10 kit (Stratagene, La Jolla, CA, USA) using 1 ng of VHH 00027 cDNA template, followed by a second error-prone PCR using 0.1 ng of product of round 1. After a polish step, PCR products are inserted via unique restriction sites into a vector designed to facilitate phage display of the VHH library. Consecutive rounds of in-solution selections are performed using decreasing concentrations of biotinylated recombinant human Ang2 (R&D Systems, Minneapolis, MN, USA)
15 and trypsin elutions. Periplasmic extracts (in a volume of ~ 80 uL) are prepared according to standard methods and screened for binding to recombinant human Ang2-FLD in a ProteOn

(BioRad, Hercules, CA, USA) off-rate assay. In brief, a GLC ProteOn Sensor chip is coated with recombinant human Ang2-FLD on the “ligand channels” L3, L4, L5 and L6 (with L1/L2 as reference channel). Periplasmic extract of affinity matured clones is diluted 1:10 and injected across the “analyte channels” A1-A6. An average off-rate is calculated of the reference VHH 00027 which is prepared and tested in the same way as the affinity matured VHHs and serves as a reference to calculate off-rate improvements. The top 25 affinity matured variants are shown in Table 9. VHH are sequenced (Table 10-A) to identify amino acid mutations beneficial for improving the off-rate (Table 10-B).

10 **Table 9:** Off-rate and fold improvement of affinity matured variants of VHH 00027.

VHH ID	k_d (1/s)	fold improvement
64G03	7.4E-05	15.7
64F03	1.1E-04	10.8
64D11	1.1E-04	10.3
64G11	1.2E-04	9.6
55D06	1.2E-04	9.4
64F07	1.2E-04	9.4
64G02	1.2E-04	9.4
55A06	1.3E-04	9.2
64C03	1.3E-04	9.2
64G12	1.3E-04	8.9
65F03	1.4E-04	8.9
55F02	1.4E-04	8.7
64E12	1.3E-04	8.7
60C09	1.6E-04	8.5
64B02	1.4E-04	8.5
64A03	1.4E-04	8.3
64C07	1.4E-04	8.3
60A06	1.6E-04	8.3

VHH ID	k_d (1/s)	fold improvement
64B01	1.4E-04	8.2
64G01	1.4E-04	8.2
56A07	1.5E-04	8.1
58D10	1.3E-04	8.1
65F01	1.6E-04	8.1
53A06	1.6E-04	8.0
55G03	1.5E-04	8.0

Initially 12 VHH variants containing combinations of mutations on Kabat position 27, 29, 100b and 100i (Table 11; Figure 5) are constructed. The different combinations of these 4 mutations are grafted on the sequence optimized VHH 00042 backbone (Figure 17-B) containing an additional D₅₄G substitution (Example 6.3). The amino acid sequence is aligned to the human germline VH3/JH consensus sequence. Residues are numbered according to Kabat, CDRs are shown in grey according to AbM definition (Oxford Molecular's AbM antibody modeling software). Constructs are cloned into the expression vector pAX100 in frame with a C-terminal c-myc tag and a (His)₆ tag. VHH variants are produced in *E. coli* and purified by IMAC and SEC.

Sequences are represented in Table 11. All these VHH are analysed in the hAng2/hTie2 (Example 5.1; results shown in Figure 6 and Table 12), and hAng1/hTie2 competition ELISA (Example 5.3; results shown in Figure 7 and Table 12). Additionally, the melting temperature (T_m) of each variant at pH7 is determined in a thermal shift assay, which is based on the temperature dependent change in fluorescence signal upon incorporation of Sypro Orange (Invitrogen, Carlsbad, CA, USA) (Ericsson et al, Anal. Biochem. 357 (2006), pp289-298) (Table 12).

Table 10-A: Amino acid sequence of affinity matured anti-Ang2 VHHs

VHH ID/ SEQ ID NOs:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
64G03/ 87	EVQLVES GGGLVQA GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	SIRDND GSTYYA DSVKG	RSTISSDNDKN TVYLQMDSLK PEDTAVYYCA A	VPAGRLRYG EQWYPIY EYDA	WGQ GTLV TVSS
64F03/ 88	EVQLVES GGGLVQA GGSLRLS CAVSGITL D	DYAV G	WFRQA PGKERE GVS	TIRDND GSTYYA DSVKG	RFTISSDNDKN TVYLQMNSLK PKDTAVYYCA A	VPAGRLRFG EQWYPIY EYDA	WGQ GTLV TVSS
64D11/ 89	EVQLVES GGGQAQA GGSLRLS CAVSGFTL D	DYAI G	WFRQA PGKERE GVS	SIRDND GSTYYT DSVKG	RFTISSDNDKN TVYLQMNSLK PEDTAVYYCA A	VPAGRLRFG EQWYPIY EYDA	WGQ GTLV TVSS
64G11/ 90	EVQLVES GGGLVQA GGSLRLS CAASGITL D	DYAI G	WFRQA PGKERV GVS	SIRDND GSTYYA DSVKG	RFTISSDNDKN TVYLQMNSLK PEDTAVYYCA A	VPAGRLRFG EQWYPIY EYDA	WGQ GTLV TVSS
55D06/ 91	EVQLVES GGGLVQA GGSLRLS CAASGLTL D	DYAI G	WFRQA PGKERE GVS	SIRDND GSTYYA DSVKG	RFTISSDNDKN TVYLQMNSLK PEDTAVYYCA A	VPAGRLRFG EQWYPIY EYDA	WGQ GTLV TVSS

VHH ID/ SEQ ID NOs:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
64F07/ 92	QVQLVES GGGLVQA GGSLRLS CAVSGFTL D	DYAI G	WFRQA PGKERE GVS	SIRDND GSTYYA DSVKG	RFTISSDNDQ NTVYLQMNSL KSEDTAVYYC AA	VPAGRLRFG EQWYPIY EY DA	WGQ GTLV TVSS
64G02/ 93	EVQLVES GGGLVQA GGSLRLS CAISGFTL V	DYAI G	WFRQA PGKERE GVS	SIRDND GSTYYA DSVKG	RFISSDNDKN TVYLQMNSLK PEDTAVYYCA A	VPAGRLRFG EQWYPIY EY DA	WGQ GTLV TVSS
55A06/ 94	EVQLMES GGGLVQA GGSLRLS CAASGITL D	DYAI G	WFRQA PGKERE GVS	SIRDND GSTYYA DSVKG	RFTISSDNDKN TVNLQMNSLK PEDTAVYYCA A	VPAGRLRFG EQWYPIY EY DA	WGQ GTLV TVSS
64C03/ 95	EVQLVES GGGLVQA GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	SIRDND GSTYYA DSVKG	RFTISSDNDKN TVYLQMNSLK PEDTAVYYCA A	VPAGRLRYG EQWYPIY EY DA	WGQ GTLV TVSS
64G12/ 96	EVQLVES GGGLVQA GGSLRLS CAVSGFTL D	DYAI G	WFRQA PGKERE GVS	SIREND GSTYYA DSVQG	RFTISSDNDKN TVYLRMNSLK PEDTAVYYCA A	VPAGRLRFG EQWYPIY EY DA	WGQ GTLV TVSS
65F03/ 97	EVQMVES GGGLVQA GGSLRLS CAASGLTL D	DYAI G	WFRQA PGKERE GVS	SIRDND GSTYYA DSVKG	RFTISSDNDKN TVYLQMNGLK PEDTAVYYCA A	VPAGRLRFG EQWYPIY EY DA	WGQ GTLV TVSS

VHH ID/ SEQ ID NOs:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
55F02/ 98	EVQLVES GGGLVQS GGSLRLS CAASGLTL D	DYAI G	WFRQA PGKERE GVS	SIRDND GSTYYA DSVKG	RFTISSDNDKN TVYLMNSLK PEDTAVYYCA A	VPAGRLRFG EQWYPIY EYDA	WGQ GTLV TVSS
64E12/ 99	EVQLVES GGGLVQA GGSLRLS CAVSGFTL D	DYAI G	WFRQA PGKERE GVS	SIRDND GSTYYA DSVKG	RSTISSDNDKN TVYLMNSLK PEDTAVYYCA A	VPAGRLRFG EQWYPIY EYDA	WGQ GTLV TVSS
60C09/ 100	EVQLVES GGGLVQA GGSLRLS CAVSGITL D	DYAI G	WFRQA PGKERE GVS	SIRDND GSTYYA DSVKW	RFTISSDNDKN TVYLMNSMK PEDTAVYYCA A	VPAGRLRFG EQWYPIY EYDA	WGQ GILVT VSS
64B02/ 101	EVQLVES GGGLVQA GGFLRLT CAVSGFTL D	DYAI G	WFRQA PGKERE GVS	SIRDND GSTYYA DSVKG	RFTISSDNDKN TVYLMNSLK PEDTAVYYCA A	VPAGRLRFG EQWYPIY EYDA	WGQ GTLV TVSS
64A03/ 102	EVQLLES GGGLVQA GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	SIRDND GSTYYA DSVKG	RFTISSDNDKN TVYLMNSLK PEDTAVYYCA A	VPAGRLRIG EQWYPIY EYDA	WGQ GTLV TVSS
64C07/ 103	EVHLVES GGGLVQA GGSLRLS CAASGLTL D	DYAI G	WFRQA PGVERE GVS	SIRDND GSTYYA DSVKG	RFTISSDNDKN TVYLMNSLK PEDTAVYYCA A	VPAGRLRFG EQWYPIY EYDA	WGQ GTLV TVSS

VHH ID/ SEQ ID NOs:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
60A06/ 104	EVQLVES GGGLVQA GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKDRE GVS	SIRDND GSTYYA DSVKG	RFTISSDNDKN TVYLQMNSLK PEDTAVYYCA A	VPAGRLRYG EQWYPIY EYDA	WGQ GTVV TVSS
64B01/ 105	EVQLVES GGGLVQA GGTLRLS CAVSGFTL D	DYAI G	WFRQA PGKERE GVS	SIRDND GSTYYA DSVKG	RFTISSDNDKN TVYLQMNSLK PEDTAVYYCA A	VPAGRLRFG EQWYPIY EYDA	WGQ GILVT VSS
64G01/ 106	EVQLVES GGGLVQA GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	SIRDND GSTYYA DSVKG	RFIISSDNDKN TVYLQMNNLK PEDTAVYYCA A	VPAGRLRYG EQWYPIY EYDA	WGQ GTLV TVSS
56A07/ 107	EVQLVES GGGLVQA GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	SIRDND GSTYYA DSVKG	RSTISSDNARN TVFLQMNSLK PEDTAVYYCA A	VPAGRLRFG EQWYPIY EYDA	WGQ GTLV TVSS
58D10/ 108	EELLVESG GGSVQAG GSLKLSCA ASGLTLD	DYAI G	WFRQA PGKERE GVS	SIRDND GSTYYA DSVKG	RFTISSDNDKN TVYLQMNSLK PEDTAVYYCA A	VPAGRLRFG EQWYPIY EYDA	WGQ GTLV TVSS
65F01/ 109	EVQLVES GGGLVQA GGSLRLS CAASGLTL D	DYAI G	WFRQA PGKERE GVS	SIRDND GSRYYA DSVKG	RFTISSDNDKN TVYLQMNSLK PEDTAVYYCA A	VPAGRLRFG EQWYPIY EYDA	WGQ GTLV TVSS

VHH ID/ SEQ ID NOs:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
53A06/ 110	EVQLVES GGSLVQA GGSLRLS CAASGLTL D	DYAI G	WFRQA PGKERE GVS	SIRDND GSTYYA DSVKG	RFTISSDNDKN TVYLQMNSLK PEDTAVYYCA A	VPAGRLRFG EQWYPIY EYDA	WGQ GTLV TVSS
55G03/ 111	EVQLVES GGSLVQA GGSLRLS CAASGLTL D	DYAI G	WFRQA PGKERE GVS	SIRDND GSTYYA DSVKG	RFTISSDNDKN TVYLQMNSLK PEDTAVYYCA A	VPAGRLRFG EQWYPIY EYDA	WGQ GTLV TVSS

Table 10-B: Single mutations or combination thereof yielding improvements in off-rate

5

Mutation(s)	Fold improvement off-rate
A24V	2
F27I	1.9 - 2.2
F27L ; L100il	9.4
L29I ; L100il	5.6 - 6.0
F100bY ; L100il	5.1 – 9.2
L100il	3.1 - 7.0

Table 11: Amino acid sequence of affinity matured anti-Ang2 VHHs

VHH ID/ SEQ ID NO:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
00903/ 112	EVQLVES GGGLVQP GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	SIRDNG GSTYYA DSVKG	RFTISSDNSKN TVYLMNSLR PEDTAVYYCA A	VPAGRLRFG EQWYPIY EYDA	WGQ GTLV TVSS
00904/ 113	EVQLVES GGGLVQP GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	SIRDNG GSTYYA DSVKG	RFTISSDNSKN TVYLMNSLR PEDTAVYYCA A	VPAGRLRYG EQWYPIY EYDA	WGQ GTLV TVSS
00905/ 114	EVQLVES GGGLVQP GGSLRLS CAASGFTI D	DYAI G	WFRQA PGKERE GVS	SIRDNG GSTYYA DSVKG	RFTISSDNSKN TVYLMNSLR PEDTAVYYCA A	VPAGRLRFG EQWYPIY EYDA	WGQ GTLV TVSS
00906/ 115	EVQLVES GGGLVQP GGSLRLS CAASGFTI D	DYAI G	WFRQA PGKERE GVS	SIRDNG GSTYYA DSVKG	RFTISSDNSKN TVYLMNSLR PEDTAVYYCA A	VPAGRLRYG EQWYPIY EYDA	WGQ GTLV TVSS
00907/ 116	EVQLVES GGGLVQP GGSLRLS CAASGITL D	DYAI G	WFRQA PGKERE GVS	SIRDNG GSTYYA DSVKG	RFTISSDNSKN TVYLMNSLR PEDTAVYYCA A	VPAGRLRFG EQWYPIY EYDA	WGQ GTLV TVSS

VHH ID/ SEQ ID NO:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
00908/ 117	EVQLVES GGGLVQP GGSLRLS CAASGITL D	DYAI G	WFRQA PGKERE GVS	SIRDNG GSTYYA DSVKG	RFTISSDNSKN TVYLMNSLR PEDTAVYYCA A	VPAGRLRYG EQWYPIY EYDA	WGQ GTLV TVSS
00909/ 118	EVQLVES GGGLVQP GGSLRLS CAASGITI D	DYAI G	WFRQA PGKERE GVS	SIRDNG GSTYYA DSVKG	RFTISSDNSKN TVYLMNSLR PEDTAVYYCA A	VPAGRLRFG EQWYPIY EYDA	WGQ GTLV TVSS
00910/ 119	EVQLVES GGGLVQP GGSLRLS CAASGITI D	DYAI G	WFRQA PGKERE GVS	SIRDNG GSTYYA DSVKG	RFTISSDNSKN TVYLMNSLR PEDTAVYYCA A	VPAGRLRYG EQWYPIY EYDA	WGQ GTLV TVSS
00911/ 120	EVQLVES GGGLVQP GGSLRLS CAASGLTL D	DYAI G	WFRQA PGKERE GVS	SIRDNG GSTYYA DSVKG	RFTISSDNSKN TVYLMNSLR PEDTAVYYCA A	VPAGRLRFG EQWYPIY EYDA	WGQ GTLV TVSS
00912/ 121	EVQLVES GGGLVQP GGSLRLS CAASGLTL D	DYAI G	WFRQA PGKERE GVS	SIRDNG GSTYYA DSVKG	RFTISSDNSKN TVYLMNSLR PEDTAVYYCA A	VPAGRLRYG EQWYPIY EYDA	WGQ GTLV TVSS
00913/ 122	EVQLVES GGGLVQP GGSLRLS CAASGLTI D	DYAI G	WFRQA PGKERE GVS	SIRDNG GSTYYA DSVKG	RFTISSDNSKN TVYLMNSLR PEDTAVYYCA A	VPAGRLRFG EQWYPIY EYDA	WGQ GTLV TVSS

VHH ID/ SEQ ID NO:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
00914/ 123	EVQLVES GGGLVQP GGSLRLS CAASGLTI D	DYAI G	WFRQA PGKERE GVS	SIRDNG GSTYYA DSVKG	RFTISSDNSKN TVYLMNSLR PEDTAVYYCA A	VPAGRLRYG EQWYPIYEEY DA	WGQ GTLV TVSS

Table 12: Overview of T_m , IC_{50} (pM) in human, mouse and cyno Ang2 competition ELISA and hAng1/hAng2 IC_{50} ratios of affinity matured variants of VHH 00027

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VHH ID	TSA	IC ₅₀ in Ang2/Tie2 ELISA			hAng1/hAng2 IC ₅₀ ratio
	T _m @ pH 7.0 (°C)	hAng2 (pM)	mAng2 (pM)	cAng2 (pM)	
00027	61.1	672	1975	728	> 14,878
00042	61.9	646	1910	753	> 15,476
00903	64.0	89	n.d.	n.d.	> 112,202
00904	64.4	62	n.d.	n.d.	> 162,181
00905	64.0	79	n.d.	n.d.	> 125,893
00906	64.4	45	n.d.	n.d.	> 223,872
00907	67.3	62	n.d.	n.d.	> 162,181
00908	67.3	45	85	79	> 192,014
00909	66.1	53	n.d.	n.d.	> 190,546
00910	66.1	42	n.d.	n.d.	> 239,883
00911	66.1	59	n.d.	n.d.	> 169,824
00912	66.1	62	n.d.	n.d.	> 162,181
00913	64.0	42	n.d.	n.d.	> 239,883
00914	64.4	37	n.d.	n.d.	> 269,153

From potency, T_m and sequence perspective VHH 00908 is taken forward into a second cycle of combined affinity maturation and sequence optimization (Example 7.3).

Example 7

5 Sequence optimization of selected VHH 1D01, 28D10 and 37F02

7.1 VHH 1D01

The amino acid sequence of anti-Ang2 VHH 1D01 (see Figure 8-A) is aligned to the human germline VH3/JH consensus sequence. Residues are numbered according to Kabat, CDRs are shown in grey according to AbM definition (Oxford Molecular's AbM antibody modeling software). Residues to be mutated to their human counterpart are underlined. Potential post-translational modification sites to be tackled are boxed. The alignment shows that 1D01 contains 6 framework mutations relative to the reference germline sequence. Non-human residues at positions 14, 41, 71, 74, 83 and 108 are selected for substitution with their human germline counterpart. A set of seven 1D01 variants carrying different combinations of human residues on these positions (Figure 8-B) is constructed and produced (Example 5). In parallel, in 3 of these 7 variants a potential Asp isomerization site at position $D_{54}G_{55}$ is removed by introducing a $D_{54}G$ substitution, and in 1 of these 7 variants a potential pyroGlu formation site at position E_1 is removed by an E_1D substitution (AA sequences are listed in Table 15).

20 These variants are characterized as purified protein in the human (Figure 9-1), mouse (Figure 9-2) and cyno (Figure 9-3) Ang2/Tie2 competition ELISA (Example 5.1; Example 5.2), the hAng1/hTie2 competition ELISA (Example 5.3; Figure 10). Additionally, melting temperature (T_m) of each variant is determined in thermal shift assay (Example 6). An overview of the data can be found in Table 13. Additionally, % FR identity to the human germline is calculated according to AbM definition (Oxford Molecular's AbM antibody modeling software). Affinity of VHH 00921 for human, cyno, mouse and rat Ang2 is shown in Table 14 (Example 5.4).

Table 13: Overview of T_m , IC_{50} (nM) in human, mouse and cyno Ang2 competition ELISA and hAng1/hAng2 IC_{50} ratios of sequence optimized variants of VHH 1D01

VHH ID	TSA	IC ₅₀ in Ang2-Tie2 ELISA			hAng1/hAng2 IC ₅₀ ratio	% FR identity
	T _m (°C) @ pH7	hAng2 (nM)	mAng2 (nM)	cAng2 (nM)		AbM
1D01	65.0	6.6	12.4	9.1	> 1,511	85.4
00039	61.5	11.9	28.1	6.4	n.d	91.0
00040	64.0	6.4	29.0	5.8	n.d	92.1
00049	66.1	6.9	20.3	4.5	n.d	89.9
00050	67.7	6.0	18.6	4.8	n.d	91.0
00051	64.8	16.1	37.9	15	n.d	89.9
00921	67.3	30.4	27.0	37	> 329	91.0
00925	66.5	22.1	28.4	33	> 453	89.9

n.d., not determined

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Table 14: Affinity K_D of purified VHH 00921 for recombinant human, cyno, mouse and rat Ang2

	human Ang2-FLD			cyno Ang2-FLD		
	k _a (1/Ms)	k _d (1/s)	K _D (M)	k _a (1/Ms)	k _d (1/s)	K _D (M)
00921	4.0E+06	2.7E-02	6.6E-09	1.1E+06	2.5E-02	2.3E-09

	mouse Ang2-FLD			rat Ang2-FLD		
	k _a (1/Ms)	k _d (1/s)	K _D (M)	k _a (1/Ms)	k _d (1/s)	K _D (M)
00921	3.3E+06	2.5E-02	7.5E-09	1.2E+06	4.9E-02	4.2E-08

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Table 15: Amino acid sequence of sequence optimized variants of anti-Ang2 VHH 1D01

VHH ID/ SEQ ID NO:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
00039/ 124	EVQLVES GGGLVQP GGSLRLS CAASGFT FD	DYAL G	WFRQA AGKERE GVS	CIRCSD GSTYYA DSVKG	RFTISRDN SKN TVY LQMNSLR PEDTAVYYCA A	SIVPRSKLEP YEYDA	WGQ GTLV TVSS
00040/ 125	EVQLVES GGGLVQP GGSLRLS CAASGFT FD	DYAL G	WFRQA PGKERE GVS	CIRCSD GSTYYA DSVKG	RFTISRDN SKN TVY LQMNSLR PEDTAVYYCA A	SIVPRSKLEP YEYDA	WGQ GTLV TVSS
00049/ 126	EVQLVES GGGLVQP GGSLRLS CAASGFT FD	DYAL G	WFRQA AGKERE GVS	CIRCSD GSTYYA DSVKG	RFTISSDN SKN TVY LQMNSLR PEDTAVYYCA A	SIVPRSKLEP YEYDA	WGQ GTLV TVSS
00050/ 127	EVQLVES GGGLVQP GGSLRLS CAASGFT FD	DYAL G	WFRQA PGKERE GVS	CIRCSD GSTYYA DSVKG	RFTISSDN SKN TVY LQMNSLR PEDTAVYYCA A	SIVPRSKLEP YEYDA	WGQ GTLV TVSS
00051/ 128	EVQLVES GGGLVQP GGSLRLS CAASGFT FD	DYAL G	WFRQA AGKERE GVS	CIRCSG GSTYYA DSVKG	RFTISSDN SKN TVY LQMNSLR PEDTAVYYCA A	SIVPRSKLEP YEYDA	WGQ GTLV TVSS

VHH ID/ SEQ ID NO:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
00921/ 129	EVQLVES GGGLVQP GGSLRLS CAASGFT FD	DYAL G	WFRQA PGKERE GVS	CIRCSG GSTYYA DSVKG	RFTISSDNSKN TVYLQMNSLR PEDTAVYYCA A	SIVPRSKLEP YEYDA	WGQ GTLV TVSS
00925/ 130	DVQLVES GGGLVQP GGSLRLS CAASGFT FD	DYAL G	WFRQA PGKERE GVS	CIRCSG GSTYYA DSVKG	RFTISSDNSKN TVYLQMNSLR PEDTAVYYCA A	SIVPRSKLEP YEYDA	WGQ GTLV TVSS

7.2 VHH 37F02

The amino acid sequence of anti-Ang2 VHH 37F02 (see Figure 12-A) is aligned to the human germline VH3/JH consensus sequence. Residues are numbered according to Kabat, CDRs are shown in grey according to AbM definition (Oxford Molecular's AbM antibody modeling software). Residues to be mutated to their human counterpart are underlined. Potential post-translational modification sites to be tackled are boxed. The alignment shows that 37F02 contains 4 framework mutations relative to the reference germline sequence. Non-human residues at positions 60, 74, 83 and 108 are selected for substitution with their human germline counterpart. In parallel, a potential Asp isomerization site at position D₅₄G₅₅ is removed by introducing a D₅₄G substitution. A set of three cycle 1 37F02 variants carrying different combinations of human residues on these positions (Figure 12-B) is constructed and produced (Example 5; AA sequences are listed in Table 21-1).

These variants are characterized as purified protein in the human (Figure 12-1), mouse (Figure 12-2) and cyno (Figure 12-3) Ang2/Tie2 competition ELISA (Example 5.1; Example 5.2). Additionally, melting temperature (T_m) of each variant is determined in thermal shift assay (Example 6). An overview of the data can be found in Table 16. Additionally, % FR identity to the human germline is calculated according to AbM definition (Oxford Molecular's AbM antibody modeling software).

Table 16: Overview of T_m , IC_{50} (pM) in human, mouse and cyno Ang2 competition ELISA and hAng1/hAng2 IC_{50} ratios of cycle 1 sequence optimized variants of VHH 37F02

	TSA	IC ₅₀ in Ang2-Tie2 ELISA				% FR identity
VHH ID	T _m (°C) @ pH7	hAng2 (pM)	mAng2 (pM)	cAng2 (pM)	hAng1/hAng2 IC ₅₀ ratio	AbM
37F02	66.1	77	110	150	> 130,317	87.6
00044	66.9	69	91	130	n.d.	91.0
00045	71.1	120	110	160	n.d.	92.1
00046	69.8	95	83	160	n.d.	91.0

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A NNK library approach is used to knock out two potential post-translational modifications sites in CDR3: i) oxidation sensitive Met on position 100e and ii) Asp isomerization site on position D₉₅S₉₆. Since D₅₄G is tolerated (VHH 00046 and 00920; Table 16 and Table 17) no NNK approach was used to knock out this potential Asp isomerization site.

10 In the end, 3 NNK libraries containing VHH clones carrying substitutions at positions D₉₅, S₉₆ and M_{100e} to all other amino acids are screened in a hAng2/hTie2 competition AlphaScreen assay (Example 2). Briefly, periplasmic extracts containing expressed VHH are screened at 3 different dilutions (corresponding roughly to EC₂₀, EC₅₀ and EC₈₀ of the parental VHH 37F02) and changes in % inhibition at the different dilution points are compared to parental 37F02. Based on
15 the screening results and the data shown in Table 17, 8 additional cycle 2 VHH variants are constructed (based on VHH 00920 backbone) carrying different knock-out combinations of D₉₅S₉₆ and M_{100e} (Figure 11-C; AA sequences are listed in Table 19-2).

All these variants are characterized as purified protein in the human (Figure 13-1), mouse (Figure 12-2) and cyno (Figure 12-3) Ang2/Tie2 competition ELISA (Example 5.1; Example 5.2),
20 the hAng1/hTie2 competition ELISA (Example 5.3; Figure 14). Additionally, melting temperature (T_m) of each variant is determined in thermal shift assay (Example 6). An overview of the data can be found in Table 17. Additionally, % FR identity to the human germline is calculated. Affinity of VHH 00928 for human, mouse, cyno and rat Ang2 is shown in Table 18.

Table 17: Overview of T_m , IC_{50} (pM) in human, mouse and cyno Ang2 competition ELISA and hAng1/hAng2 IC_{50} ratios of cycle 2 sequence optimized variants of VHH 37F02

VHH ID	TSA	IC50 in Ang2-Tie2 ELISA			hAng1/hAng2 ratio	% FR identity
	T_m (°C) @ pH7	hAng2 (pM)	mAng2 (pM)	cAng2 (pM)		AbM
37F02	66.1	77	110	150	> 130,317	87.6
00920	73.6	130	150	230	> 79,159	92.1
00924	73.1	110	n.d.	n.d.	n.d.	91.0
00926	71.5	250	200	290	> 39,446	92.1
00927	73.6	220	190	330	> 44,668	92.1
00928	72.7	220	200	390	> 45,604	92.1
00929	69.0	150	150	250	> 65,013	92.1
00930	69.8	190	170	310	> 53,580	92.1
00931	69.4	170	150	290	> 57,677	92.1

5 n.d., not determined

Table 18: Affinity K_D of purified VHH 00928 for recombinant human, cyno, mouse and rat Ang2

	human Ang2-FLD			cyno Ang2-FLD		
	k_a (1/Ms)	k_d (1/s)	K_D (M)	k_a (1/Ms)	k_d (1/s)	K_D (M)
00928	6.2+05	4.0E-05	6.4E-11	9.7E+05	4.9E-05	5.0E-11

	mouse Ang2-FLD			rat Ang2-FLD		
	k_a (1/Ms)	k_d (1/s)	K_D (M)	k_a (1/Ms)	k_d (1/s)	K_D (M)
00928	4.2E+05	7.3E-05	1.7E-10	1.8E+05	5.4E-05	2.9E-10

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Table 19-1

VHH ID/ SEQ ID NOs:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
00044/ 131	EVQLVES GGGLVQP GGSLRLS CAASGFALD	YYAI G	WFRQA PGKERE GVS	CISSSD GITYYV DSVKG	RFTISRDN SKN TVY LQMNSLR PEDTAVYYCA T	DSGGYIDYD CMGLGYDY	WGQ GTLV TVSS
00045/ 132	EVQLVES GGGLVQP GGSLRLS CAASGFALD	YYAI G	WFRQA PGKERE GVS	CISSSD GITYYA DSVKG	RFTISRDN SKN TVY LQMNSLR PEDTAVYYCA T	DSGGYIDYD CMGLGYDY	WGQ GTLV TVSS
00046/ 133	EVQLVES GGGLVQP GGSLRLS CAASGFALD	YYAI G	WFRQA PGKERE GVS	CISSSG GITYYV DSVKG	RFTISRDN SKN TVY LQMNSLR PEDTAVYYCA T	DSGGYIDYD CMGLGYDY	WGQ GTLV TVSS

Table 19-2

VHH ID/ SEQ ID NO:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
00920/ 134	EVQLVES GGGLVQP GGSLRLS CAASGFALD	YYAI G	WFRQA PGKERE GVS	CISSSG GITYYA DSVKG	RFTISRDN SKN TVY LQMNSLR PEDTAVYYCA T	DSGGYIDYD CMGLGYDY	WGQ GTLV TVSS

VHH ID/ SEQ ID NO:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
00924/ 135	DVQLVES GGGLVQP GGSLRLS CAASGFALD	YYAI G	WFRQA PGKERE GVS	CISSSG GITYYA DSVKG	RFTISRDN SKN TVY LQMNSLR PEDTAVYYCA T	DSGGYIDYD CMGLGYDY	WGQ GTLV TVSS
00926/ 136	EVQLVES GGGLVQP GGSLRLS CAASGFALD	YYAI G	WFRQA PGKERE GVS	CISSSG GITYYA DSVKG	RFTISRDN SKN TVY LQMNSLR PEDTAVYYCA T	DSGGYIDYD CQGLGYDY	WGQ GTLV TVSS
00927/ 137	EVQLVES GGGLVQP GGSLRLS CAASGFALD	YYAI G	WFRQA PGKERE GVS	CISSSG GITYYA DSVKG	RFTISRDN SKN TVY LQMNSLR PEDTAVYYCA T	DSGGYIDYD CRGLGYDY	WGQ GTLV TVSS
00928/ 138	EVQLVES GGGLVQP GGSLRLS CAASGFALD	YYAI G	WFRQA PGKERE GVS	CISSSG GITYYA DSVKG	RFTISRDN SKN TVY LQMNSLR PEDTAVYYCA T	DSGGYIDYD CSGLGYDY	WGQ GTLV TVSS
00929/ 139	EVQLVES GGGLVQP GGSLRLS CAASGFALD	YYAI G	WFRQA PGKERE GVS	CISSSG GITYYA DSVKG	RFTISRDN SKN TVY LQMNSLR PEDTAVYYCA T	ESGGYIDYD CQGLGYDY	WGQ GTLV TVSS
00930/ 140	EVQLVES GGGLVQP GGSLRLS CAASGFALD	YYAI G	WFRQA PGKERE GVS	CISSSG GITYYA DSVKG	RFTISRDN SKN TVY LQMNSLR PEDTAVYYCA T	ESGGYIDYD CRGLGYDY	WGQ GTLV TVSS

VHH ID/ SEQ ID NO:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
00931/ 141	EVQLVES GGGLVQP GGSLRLS CAASGFA LD	YYAI G	WFRQA PGKERE GVS	CISSSG GITYYA DSVKG	RFTISRDN SKN TVYLQMNSLR PEDTAVYYCA T	ESGGYIDYD CSGLGYDY	WGQ GTLV TVSS

7.3 VHH 28D10

The amino acid sequence of anti-Ang2 VHH 28D10 (see Figure 15-A) is aligned to the human germline VH3/JH consensus sequence. Residues are numbered according to Kabat, CDRs are shown in grey according to AbM definition (Oxford Molecular's AbM antibody modeling software). Residues to be mutated to their human counterpart are underlined. Potential post-translational modification sites to be tackled are boxed. The alignment shows that 28D10 contains 5 framework mutations relative to the reference germline sequence. Non-human residues at positions 14, 71, 74, 83 and 108 are selected for substitution with their human germline counterpart. In parallel, a potential Asp isomerization site at position D₅₄G₅₅ is removed by introducing a D₅₄G substitution. The free cystein at position 50 was removed by substitution with Ala, Thr or Ser. In the end, a set of eleven cycle 1 28D10 variants carrying different combinations of human residues on these positions is constructed and produced (see Figure 15-B; AA sequences are listed in Table 24-1).

These variants are characterized as purified protein in the human (Figure 16-1), mouse (Figure 16-2) and cyno (Figure 16-3) Ang2/Tie2 competition ELISA (Example 5.1; Example 5.2), the hAng1/hTie2 competition ELISA (Example 5.3; Figure 17). Additionally, melting temperature (T_m) of each variant is determined in thermal shift assay (Example 6). An overview of the data can be found in Table 20. Additionally, % FR identity to the human germline is calculated.

Table 20: Overview of T_m , IC_{50} (nM) in human, mouse and cyno Ang2 competition ELISA and hAng1/hAng2 IC_{50} ratios of cycle 1 sequence optimized variants of VHH 28D10

VHH ID	TSA	IC50 in Ang2-Tie2 ELISA			hAng1/hAng2 ratio	% FR identity
	Tm (°C) @ pH7	hAng2 (nM)	mAng2 (nM)	cAng2 (nM)		AbM
28D10	66.1	1.8	5.7	2.1	> 5,675	86.5
00025	63.2	2.1	4.9	1.7	n.d.	87.6
00026	68.2	1.0	2.6	1.1	n.d.	87.6
00027	61.1	0.7	2.0	0.7	> 14,878	87.6
00041	62.3	0.6	1.7	0.9	n.d.	89.9
00042	61.9	0.7	1.9	0.8	> 15,476	91.0
00043	65.7	9.5	29.2	12.6	n.d.	91.0
00048	63.2	0.6	2.1	1.0	n.d.	87.6
00052	61.1	1.0	2.1	0.8	n.d.	89.9
00053	64.8	10.7	36.7	13.8	n.d.	91.0
00054	65.7	9.5	22.9	11.7	n.d.	92.1
00055	63.6	1.8	4.6	2.0	n.d.	87.6

n.d., not determined

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An additional set of variants (cycle 2) is created to explore the affinity maturation substitution on position A₂₄V and to further explore C₅₀X–S₅₃X variants (Table 21; Figure 15-C; AA sequences are listed in Table 23-4-2). These variants are characterized as purified protein in the human (Figure 18-1), mouse (Figure 18-2) and cyno (Figure 18-3) Ang2/Tie2 competition ELISA (Example 5.1; Example 5.2), the hAng1/hTie2 competition ELISA (Example 5.3; Figure 19). Additionally, melting temperature (T_m) of each variant is determined in thermal shift assay (Example 6).

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Table 21: Overview of T_m , IC_{50} (nM) in human, mouse and cyno Ang2 competition ELISA and hAng1/hAng2 IC_{50} ratios of cycle 2 sequence optimized variants of VHH 28D10

VHH ID	TSA	IC50 in Ang2-Tie2 ELISA			hAng1/hAng2 ratio	% FR identity
	Tm (°C) @ pH7	hAng2 (nM)	mAng2 (nM)	cAng2 (nM)		AbM
28D10	66.1	1.8	5.7	2.1	> 5,675	86.5
00898	66.1	1.2	n.d.	n.d.	> 8,279	87.6
00899	61.9	0.9	n.d.	n.d.	> 11,749	87.6
00900	64.3	0.2	n.d.	n.d.	> 42,855	86.5
00901	67.3	1.2	n.d.	n.d.	> 8,054	87.6
00902	66.1	1.3	n.d.	n.d.	> 7,907	87.6
00919	67.3	0.9	1.8	0.7	> 11,212	91.0
00923	67.7	0.7	n.d.	n.d.	n.d.	89.9

n.d., not determined

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In parallel, a NNK library approach is used to knock out two post-translational modifications sites in CDR2: two sequential Asp isomerization sites on position $D_{52a}S_{53}$ and $D_{54}G_{55}$. Since $D_{54}G$ is tolerated (Example 6; Table 20) no NNK approach was used to knock out this potential Asp isomerization site. In the end, 2 NNK libraries containing VHH clones carrying substitutions at positions D_{52a} and S_{53} to all other amino acids are screened in a hAng2/hTie2 competition AlphaScreen assay (Example 2). Briefly, periplasmic extracts containing expressed VHH are screened at 3 different dilutions (corresponding roughly to EC_{20} , EC_{50} and EC_{80} of the reference 00902) and changes in % inhibition at the different dilution points are compared to reference 00902. Based on the screening results and the data shown in Table 21, 7 additional VHH cycle 3 variants are constructed (based on 00908 backbone) (see Figure 15-D). The final aim is to construct VHH variants that retain or show increased potency, increased thermostability and have relevant PTM sites knocked out compared to VHH 28D10. (AA sequences are listed in Table 24-3). These variants are characterized as purified protein in the human (Figure 20-1), mouse (Figure 20-2) and cyno (Figure 20-3) Ang2/Tie2 competition ELISA (Example 5.1; Example 5.2), the hAng1/hTie2 competition ELISA (Example 5.3). Additionally, melting

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temperature (T_m) of each variant is determined in thermal shift assay (Example 6). An overview of the data can be found in Table 22. Additionally, % FR identity to the human germline is calculated. The most optimal sequence changes were finally applied to a non-affinity matured variant VHH 00956 (Figure 15-D). Affinity of VHH 00919, 00938 and 00956 for human, mouse, cyno and rat Ang2 is shown in Table 23.

Table 22: Overview of T_m , IC_{50} (nM) in human, mouse and cyno Ang2 competition ELISA and hAng1/hAng2 IC_{50} ratios of cycle 3 sequence optimized variants of VHH 28D10

10

VHH ID	TSA	IC50 in Ang2/Tie2 ELISA			hAng1/hAng2 IC_{50} ratio	HUVEC survival	% FR identity
	T_m @ pH 7.0 (°C)	hAng2 (pM)	mAng2 (pM)	cAng2 (pM)		IC_{50} (nM)	AbM
00027	61.1	672	1,975	728	> 14,878	n.d.	87.6
00908	67.3	45	85	79	> 192,014	n.d.	91.0
00932	70.5	49	38	54	> 205,747	n.d.	89.9
00933	70.5	56	62	71	> 179,887	n.d.	91.0
00934	67.1	64	74	71	> 156,675	n.d.	91.0
00935	68.6	68	78	69	> 146,218	n.d.	91.0
00936	73.9	45	42	60	> 223,872	n.d.	89.9
00937	72.0	54	52	85	> 186,209	n.d.	89.9
00938	73.9	50	55	91	> 201,064	4.3	89.9
00956	68.0	1,300	2,200	830	> 7,727	6.8	91.0

n.d. not determined

Table 23: Affinity K_D of purified VHHs 00919, 00938 and 00956 for recombinant human, cyno, mouse and rat Ang2

	human Ang2-FLD			cyno Ang2-FLD		
	k_a (1/Ms)	k_d (1/s)	K_D (M)	k_a (1/Ms)	k_d (1/s)	K_D (M)
00919	9.5E+05	1.5E-03	1.6E-09	2.3E+06	1.2E-03	5.4E-10
00938	1.6E+06	2.8E-05	1.7E-11	2.6E+06	2.2E-05	8.7E-12
00956	1.3E+06	1.5E-03	1.2E-09	1.7E+06	1.3E-03	7.2E-10

5

	mouse Ang2-FLD			rat Ang2-FLD		
	k_a (1/Ms)	k_d (1/s)	K_D (M)	k_a (1/Ms)	k_d (1/s)	K_D (M)
00919	1.3E+06	3.9E-03	3.0E-09	5.0E+05	5.0E-03	1.0E-08
00938	1.1E+06	5.6E-05	5.0E-11	5.1E+05	7.2E-05	1.4E-10
00956	9.8E+05	3.9E-03	4.0E-09	4.2E+05	5.2E-03	1.3E-08

Table 24-1

VHH ID/ SEQ ID NO:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
00025/ 142	EVQLVES GGGLVQA GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	TIRDSD GSTYYA DSVKG	RFTISSDNDKN TVYLMNSLK PEDTAVYYCA A	VPAGRLRFG EQWYPLYEY DA	WGQ GTLV TVSS

VHH ID/ SEQ ID NO:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
00026/ 143	EVQLVES GGGLVQA GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	AIRDSD GSTYYA DSVKG	RFTISSDNDKN TVYLMNSLK PEDTAVYYCA A	VPAGRLRFG EQWYPLYEY DA	WGQ GTLV TVSS
00027/ 144	EVQLVES GGGLVQA GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	SIRDND GSTYYA DSVKG	RFTISSDNDKN TVYLMNSLK PEDTAVYYCA A	VPAGRLRFG EQWYPLYEY DA	WGQ GTLV TVSS
00041/ 145	EVQLVES GGGLVQP GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	SIRDND GSTYYA DSVKG	RFTISSDNAKN TVYLMNSLR PEDTAVYYCA A	VPAGRLRFG EQWYPLYEY DA	WGQ GTLV TVSS
00042/ 146	EVQLVES GGGLVQP GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	SIRDND GSTYYA DSVKG	RFTISSDNSKN TVYLMNSLR PEDTAVYYCA A	VPAGRLRFG EQWYPLYEY DA	WGQ GTLV TVSS
00043/ 147	EVQLVES GGGLVQP GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	SIRDND GSTYYA DSVKG	RFTISRDNAKN TVYLMNSLR PEDTAVYYCA A	VPAGRLRFG EQWYPLYEY DA	WGQ GTLV TVSS
00048/ 148	EVQLVES GGGLVQA GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	SIRDSD GSTYYA DSVKG	RFTISSDNDKN TVYLMNSLK PEDTAVYYCA A	VPAGRLRFG EQWYPLYEY DA	WGQ GTLV TVSS

VHH ID/ SEQ ID NO:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
00052/ 149	EVQLVES GGGLVQP GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	SIRDND GSTYYA DSVKG	RFTISSDNDKN TVYLQMNSLR PEDTAVYYCA A	VPAGRLRFG EQWYPLYEY DA	WGQ GTLV TVSS
00053/ 150	EVQLVES GGGLVQP GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	SIRDND GSTYYA DSVKG	RFTISRDNNDKN TVYLQMNSLR PEDTAVYYCA A	VPAGRLRFG EQWYPLYEY DA	WGQ GTLV TVSS
00054/ 151	EVQLVES GGGLVQP GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	SIRDND GSTYYA DSVKG	RFTISRDNNSKN TVYLQMNSLR PEDTAVYYCA A	VPAGRLRFG EQWYPLYEY DA	WGQ GTLV TVSS
00055/ 152	EVQLVES GGGLVQA GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	SIRDNG GSTYYA DSVKG	RFTISSDNDKN TVYLQMNSLK PEDTAVYYCA A	VPAGRLRFG EQWYPLYEY DA	WGQ GTLV TVSS

Table 24-2

VHH ID/ SEQ ID NO:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
00898/ 153	EVQLVES GGGLVQA GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	AIRDND GSTYYA DSVKG	RFTISSDNDKN TVYLMNSLK PEDTAVYYCA A	VPAGRLRFG EQWYPLYEY DA	WGQ GTLV TVSS
00899/ 154	EVQLVES GGGLVQA GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	SIRDIDG STYYAD SVKG	RFTISSDNDKN TVYLMNSLK PEDTAVYYCA A	VPAGRLRFG EQWYPLYEY DA	WGQ GTLV TVSS
00900/ 155	EVQLVES GGGLVQA GGSLRLS CAVSGFTL D	DYAI G	WFRQA PGKERE GVS	SIRDND GSTYYA DSVKG	RFTISSDNDKN TVYLMNSLK PEDTAVYYCA A	VPAGRLRFG EQWYPLYEY DA	WGQ GTLV TVSS
00901/ 156	EVQLVES GGGLVQA GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	AIRDSD GSTYYA DSVKG	RFTISSDNDKN TVYLMNSLK PEDTAVYYCA A	VPAGRLRFG EQWYPLYEY DA	WGQ GTLV TVSS
00902/ 157	EVQLVES GGGLVQA GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	AIRDSD GSTYYA DSVKG	RFTISSDNDKN TVYLMNSLK PEDTAVYYCA A	VPAGRLRFG EQWYPLYEY DA	WGQ GTLV TVSS

Table 24-3

VHH ID/ SEQ ID NO:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
00919/ 158	EVQLVES GGGLVQP GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	AIRDNG GSTYYA DSVKG	RFTISSDNSKN TVYLMNSLR PEDTAVYYCA A	VPAGRLRFG EQWYPLYEY DA	WGQ GTLV TVSS
00923/ 159	DVQLVES GGGLVQP GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	AIRDNG GSTYYA DSVKG	RFTISSDNSKN TVYLMNSLR PEDTAVYYCA A	VPAGRLRFG EQWYPLYEY DA	WGQ GTLV TVSS
00932/ 160	EVQLVES GGGLVQP GGSLRLS CAVSGITL D	DYAI G	WFRQA PGKERE GVS	SIRDNG GSTYYA DSVKG	RFTISSDNSKN TVYLMNSLR PEDTAVYYCA A	VPAGRLRYG EQWYPIYEY DA	WGQ GTLV TVSS
00933/ 161	EVQLVES GGGLVQP GGSLRLS CAASGITL D	DYAI G	WFRQA PGKERE GVS	AIRDNG GSTYYA DSVKG	RFTISSDNSKN TVYLMNSLR PEDTAVYYCA A	VPAGRLRYG EQWYPIYEY DA	WGQ GTLV TVSS
00934/ 162	EVQLVES GGGLVQP GGSLRLS CAASGITL D	DYAI G	WFRQA PGKERE GVS	AIRESG GSTYYA DSVKG	RFTISSDNSKN TVYLMNSLR PEDTAVYYCA A	VPAGRLRYG EQWYPIYEY DA	WGQ GTLV TVSS

VHH ID/ SEQ ID NO:	FR1	CDR1	FR2	CDR2	FR3	CDR3	FR4
00935/ 163	EVQLVES GGGLVQP GGSLRLS CAASGITL D	DYAI G	WFRQA PGKERE GVS	AIRSSG GSTYYA DSVKG	RFTISSDNSKN TVYLMNSLR PEDTAVYYCA A	VPAGRLRYG EQWYPIY EYDA	WGQ GTLV TVSS
00936/ 164	EVQLVES GGGLVQP GGSLRLS CAVSGITL D	DYAI G	WFRQA PGKERE GVS	AIRDNG GSTYYA DSVKG	RFTISSDNSKN TVYLMNSLR PEDTAVYYCA A	VPAGRLRYG EQWYPIY EYDA	WGQ GTLV TVSS
00937/ 165	EVQLVES GGGLVQP GGSLRLS CAVSGITL D	DYAI G	WFRQA PGKERE GVS	AIRESG GSTYYA DSVKG	RFTISSDNSKN TVYLMNSLR PEDTAVYYCA A	VPAGRLRYG EQWYPIY EYDA	WGQ GTLV TVSS
00938/ 166	EVQLVES GGGLVQP GGSLRLS CAVSGITL D	DYAI G	WFRQA PGKERE GVS	AIRSSG GSTYYA DSVKG	RFTISSDNSKN TVYLMNSLR PEDTAVYYCA A	VPAGRLRYG EQWYPIY EYDA	WGQ GTLV TVSS
00956/ 167	EVQLVES GGGLVQP GGSLRLS CAASGFTL D	DYAI G	WFRQA PGKERE GVS	AIRSSG GSTYYA DSVKG	RFTISSDNSKN TVYLMNSLR PEDTAVYYCA A	VPAGRLRFG EQWYPLY EYDA	WGQ GTLV TVSS

Claims:

1. An Ang2-binding molecule comprising an immunoglobulin single variable domain, wherein said immunoglobulin single variable domain comprises three complementarity determining regions CDR1, CDR2 and CDR3, wherein CDR1 has an amino acid sequence shown in SEQ ID NO: 168, CDR2 has an amino acid sequence shown in SEQ ID NO: 171 and CDR3 has an amino acid sequence shown in SEQ ID NO: 175.
2. The Ang2-binding molecule according to claim 1, wherein said immunoglobulin single variable domain is a VHH or a domain antibody.
3. The Ang2-binding molecule according to claim 1 or claim 2, wherein said immunoglobulin single variable domain is a VHH.
4. The Ang2-binding molecule according to any one of claims 1 to 3, wherein said immunoglobulin single variable domain has a sequence consisting of SEQ ID NO: 166.
5. An Ang2-binding molecule consisting of the immunoglobulin single variable domain as set out in any one of claims 1 to 4.
6. The Ang2-binding molecule according to claim 4 wherein said immunoglobulin single variable domain has a modification or exchange on its N terminus, wherein said modification is a deletion of its first amino acid and said exchange is a replacement of its first amino acid by another amino acid.
7. An expression vector comprising a nucleic acid molecule encoding the Ang2-binding molecule according to any one of claims 1 to 6, wherein said nucleic acid molecule is operably linked to a heterologous promoter, enhancer, or terminator sequence.
8. A host cell carrying one or more expression vector according to claim 7.
9. A method for producing the Ang2-binding molecule according to any one of claims 1 to 6, comprising the steps of:
 - transfecting a host cell with one or more said expression vector according to claim 7,
 - culturing said host cell, and
 - recovering and purifying said Ang2-binding molecule.
10. A pharmaceutical composition comprising, as the active ingredient, one or more said Ang2-binding molecule according to any one of claims 1 to 6, and at least a

physiologically acceptable carrier.

11. The pharmaceutical composition according to claim 10, further comprising one or more additional therapeutic agent.
12. The pharmaceutical composition according to claim 11, wherein the therapeutic agent is selected from chemotherapeutic agents, therapeutically active compounds that inhibit angiogenesis, signal transduction pathway inhibitors, and hormonal therapy agents.
13. The pharmaceutical composition according to claim 12, wherein the chemotherapeutic agents are selected from DNA damaging agents, anti-mitotic drugs in cancer cells, and taxol.
14. The pharmaceutical composition according to claim 12 or 13, wherein the therapeutically active compounds that inhibit angiogenesis are selected from antiangiogenic drugs, VEGF inhibitors, VEGF receptor inhibitors, avastin, nitedanib, and sunitinib.
15. The pharmaceutical composition according to any one of claims 12 to 14, wherein the signal induction pathway inhibitors are selected from mTOR inhibitors, and temsirolimus.
16. The pharmaceutical composition according to any one of claims 12 to 15, wherein the hormonal therapy agents include tamoxifen.
17. The Ang-2 binding molecule according to any one of claims 1 to 6, or the pharmaceutical composition according to any one of claims 10 to 16, when used for the treatment of cancer or a cancerous disease.
18. A method of treating cancer or a cancerous disease comprising administering a therapeutically effective amount of the Ang2-binding molecule according to any one of claims 1 to 6, or the pharmaceutical composition according to any one of claims 10 to 16 to a subject in need thereof.
19. Use of the Ang2-binding molecule according to any one of claims 1 to 6 for the manufacture of a medicament for the treatment of cancer or a cancerous disease.
20. The Ang-2 binding molecule or pharmaceutical composition when used according to claim 17, the method according to claim 18, or the use according to claim 19, wherein

the cancer or cancerous disease is selected from breast cancer, renal cell carcinoma, ovarian cancer and pancreatic cancer.

Boehringer Ingelheim International GmbH

Patent Attorneys for the Applicant/Nominated Person

SPRUSON & FERGUSON

2013241769 09 Mar 2017

Fig. 1-1D

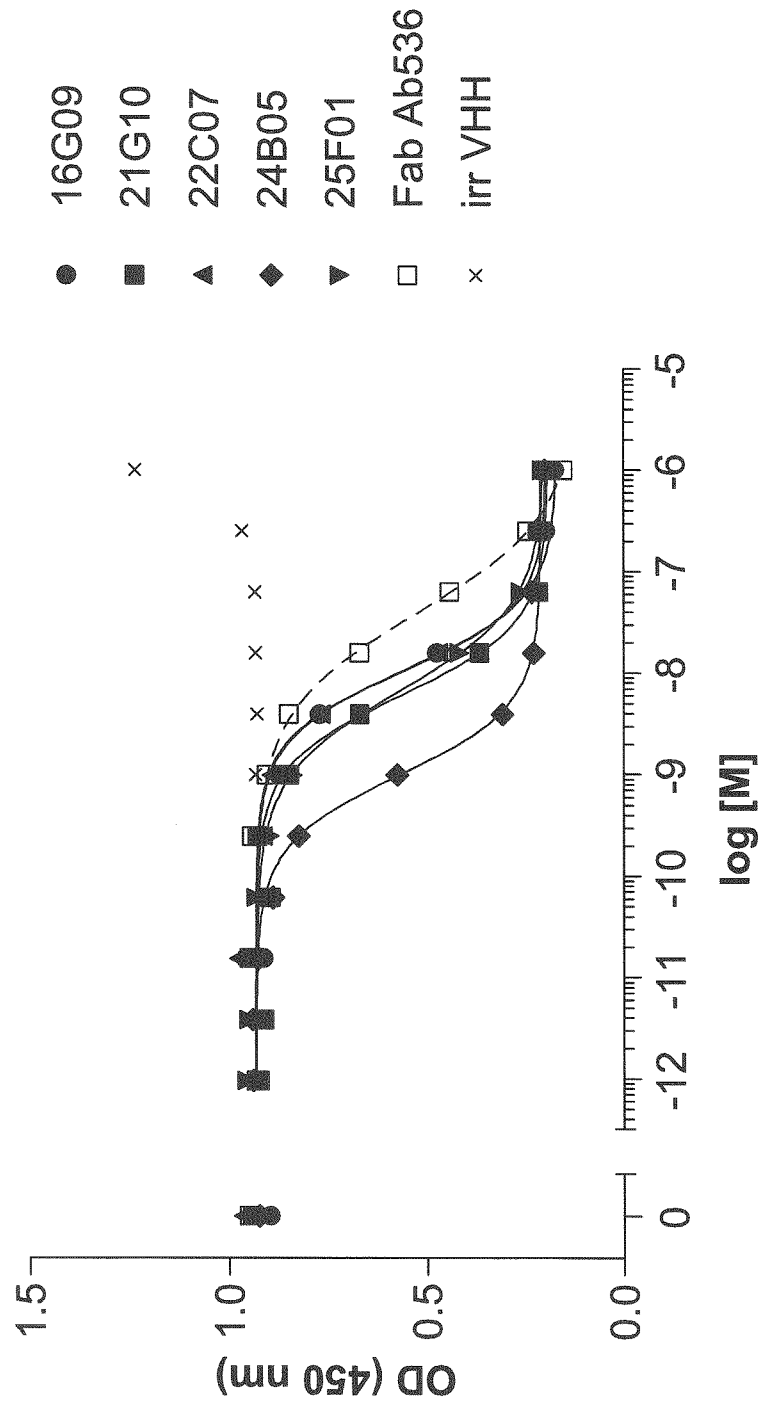


Fig. 1-2B

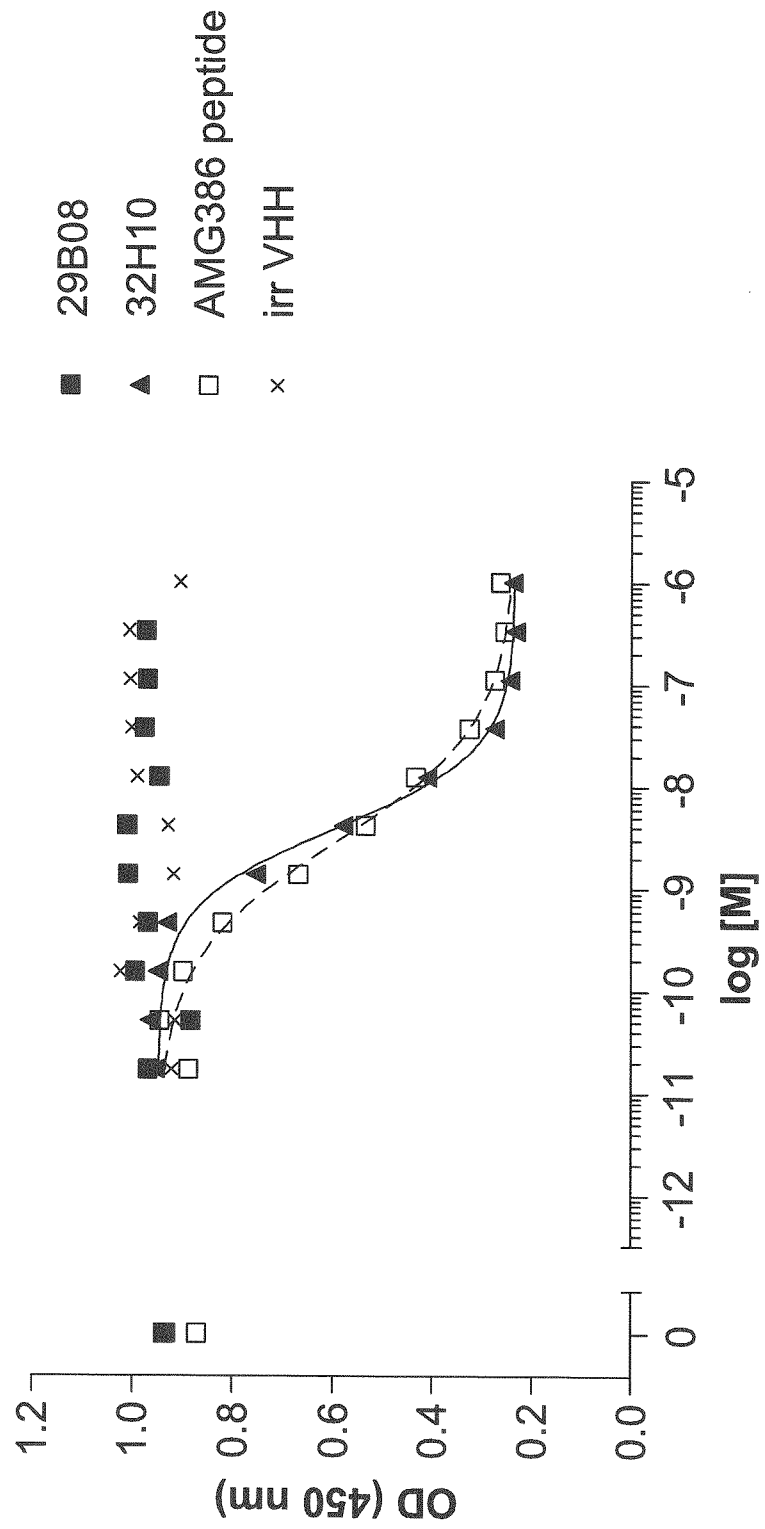


Fig. 1-2C

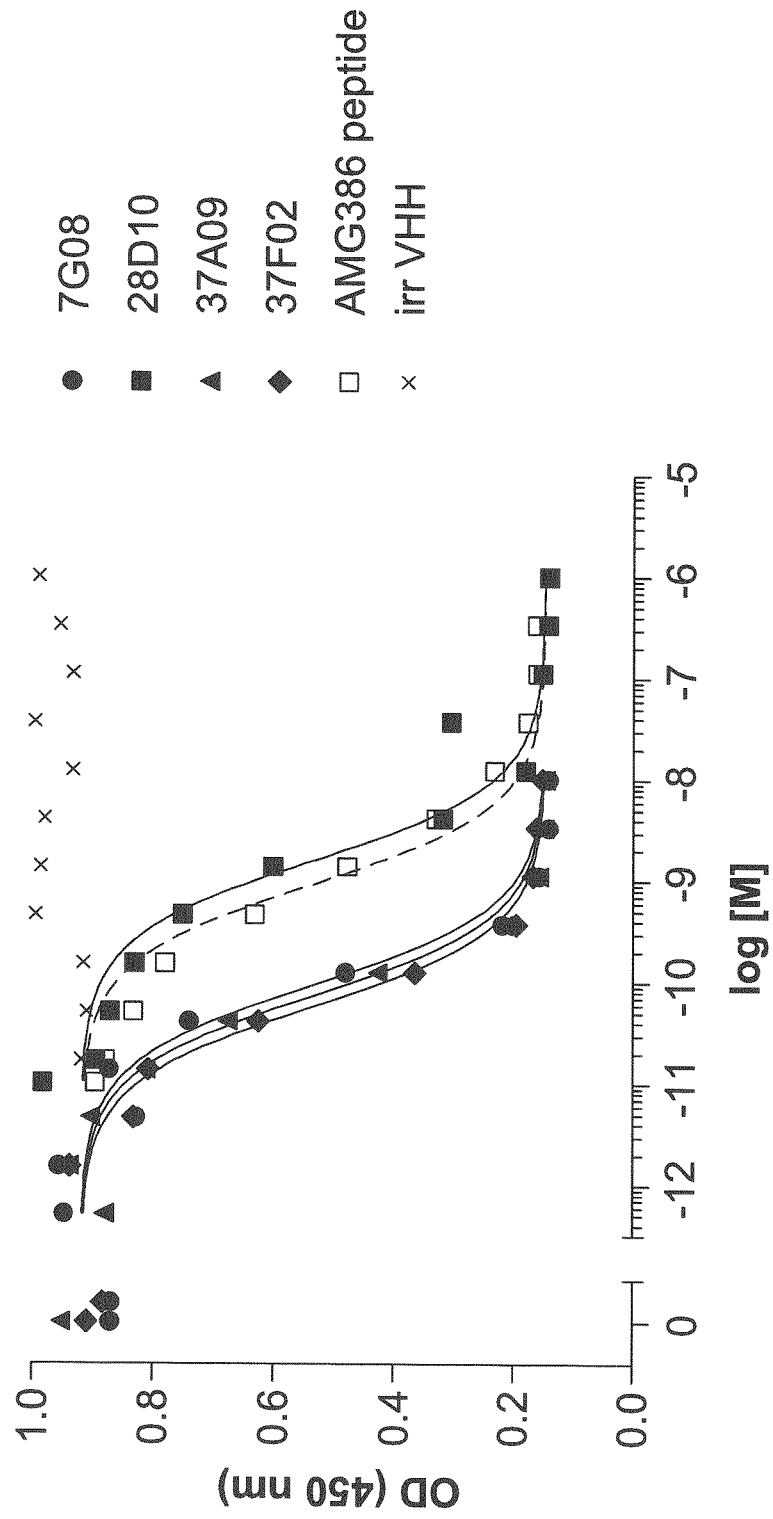


Fig. 2-1B

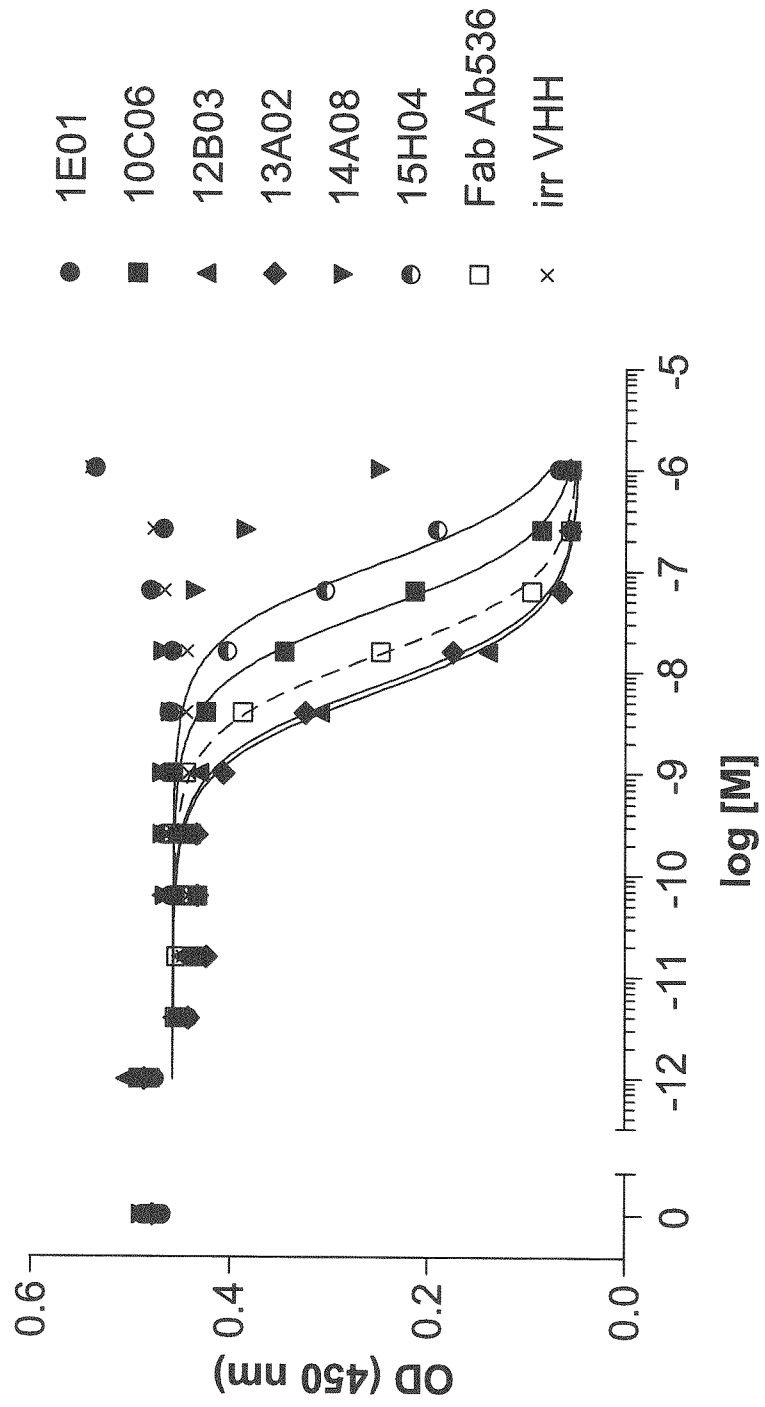


Fig. 2-2B

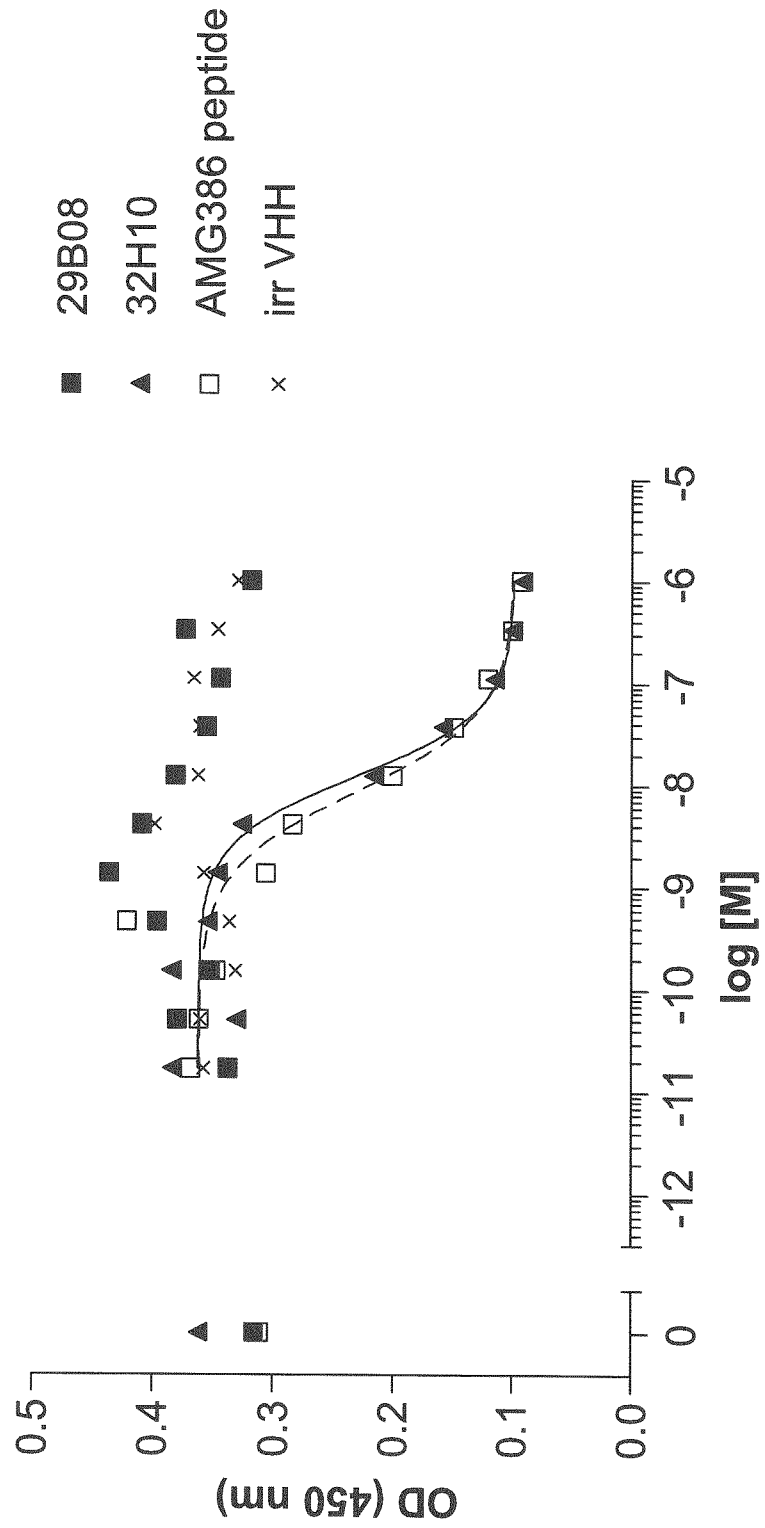


Fig. 2-2C

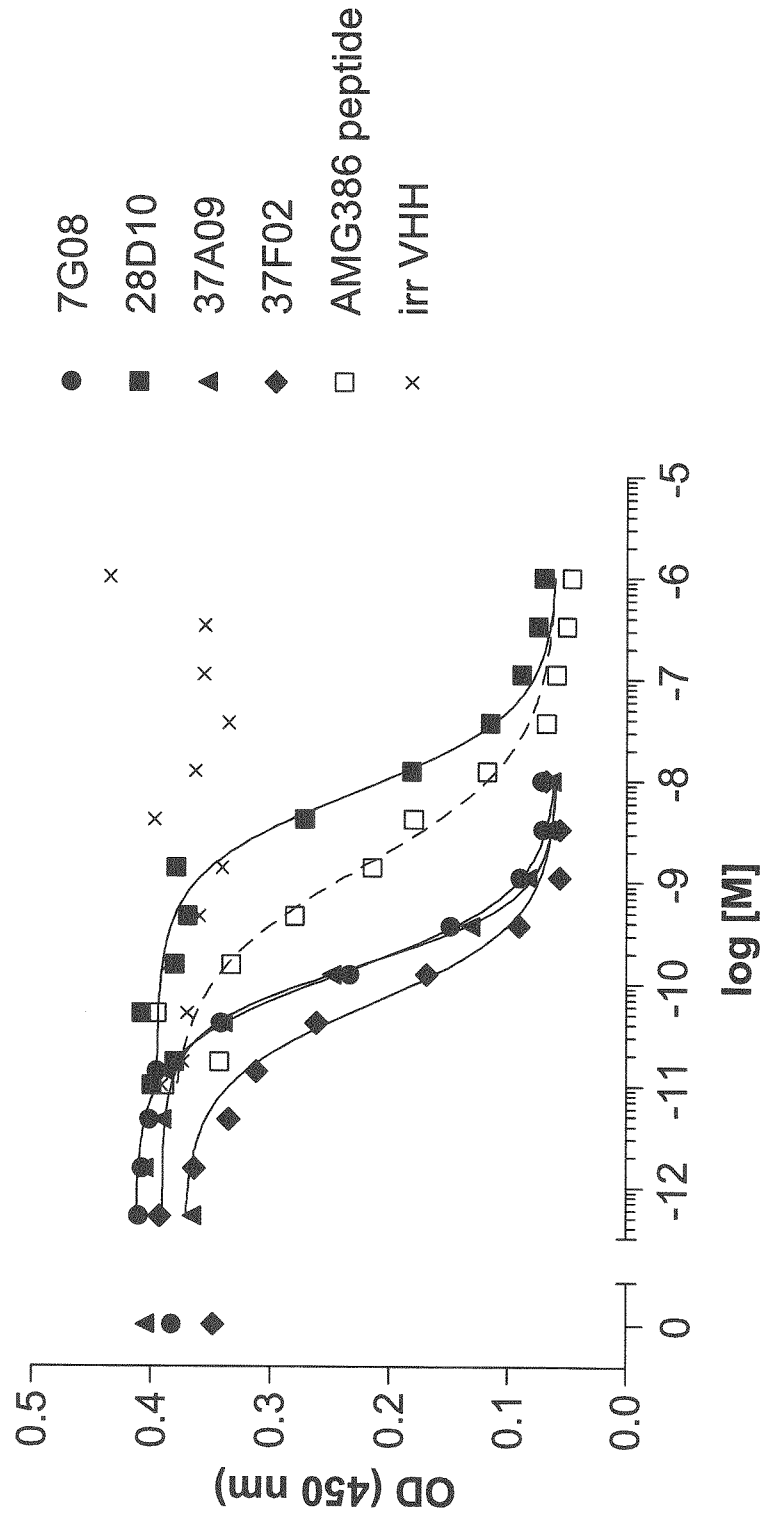


Fig. 3A

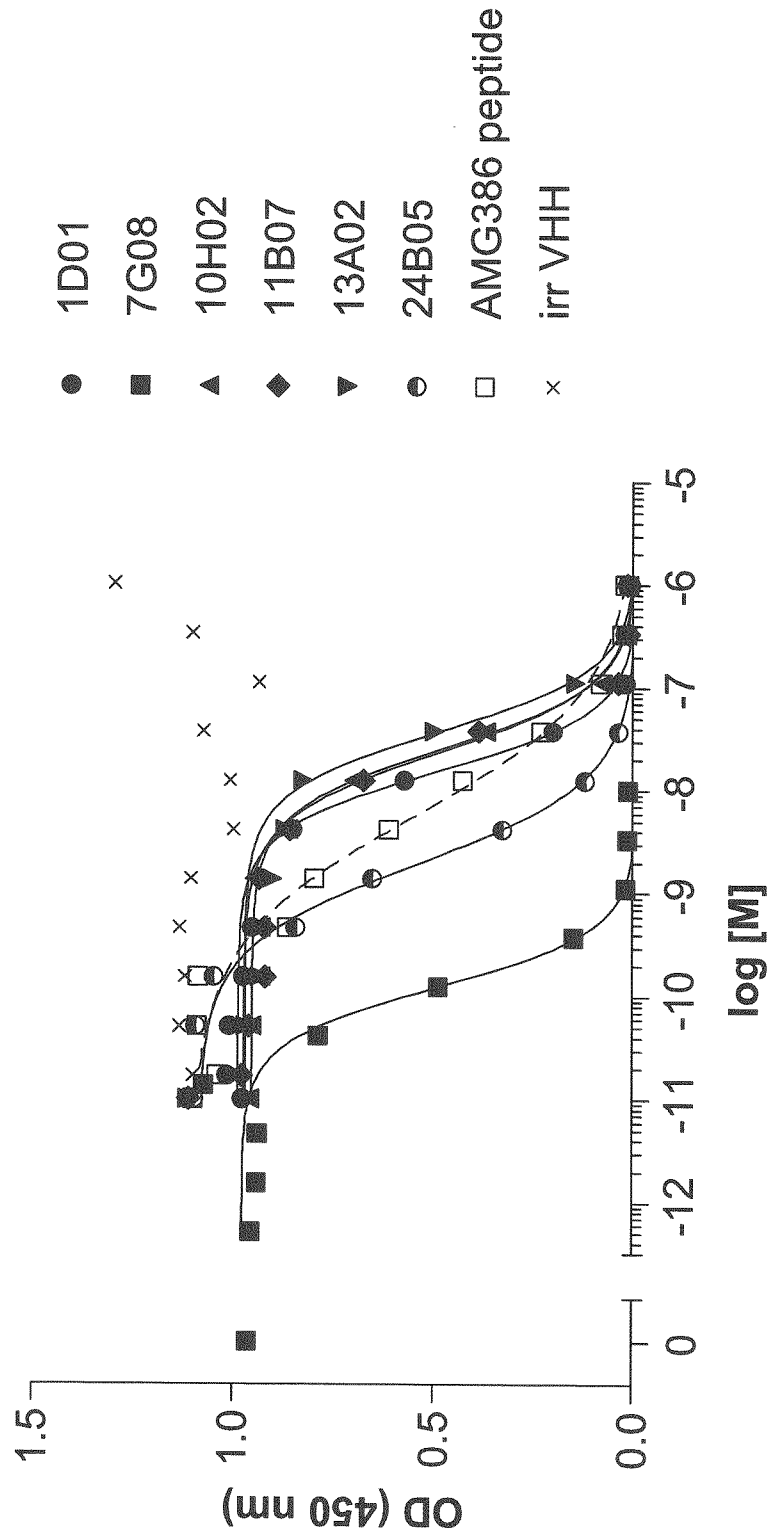


Fig. 3B

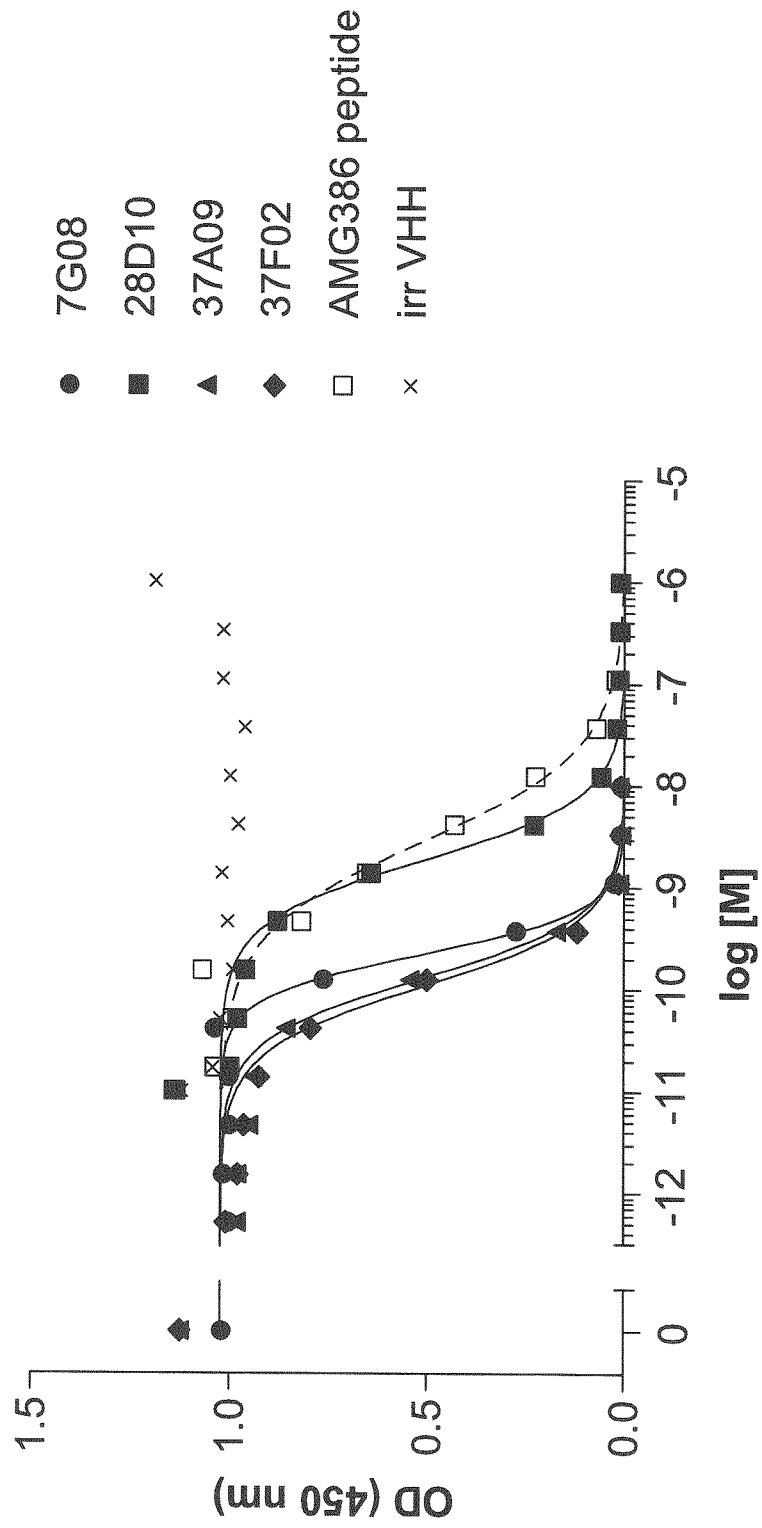


Fig. 4A

1D01

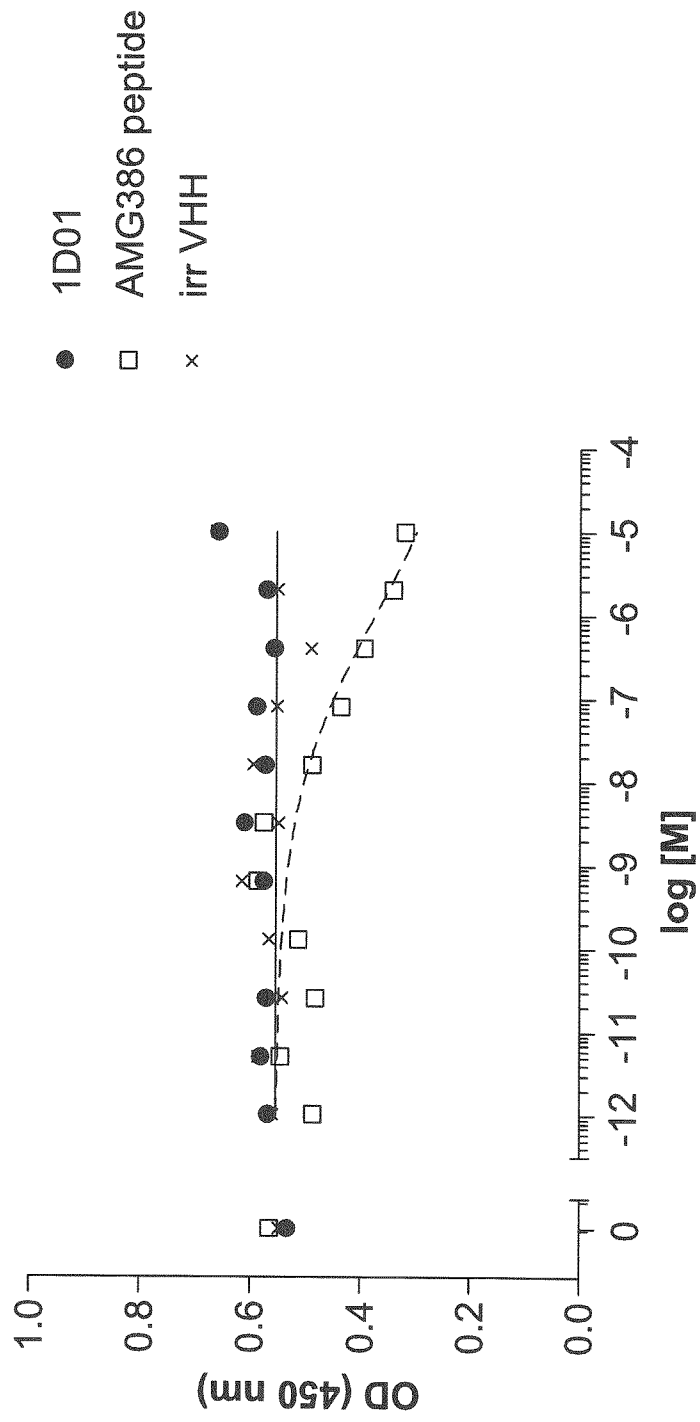


Fig. 4B

7G08

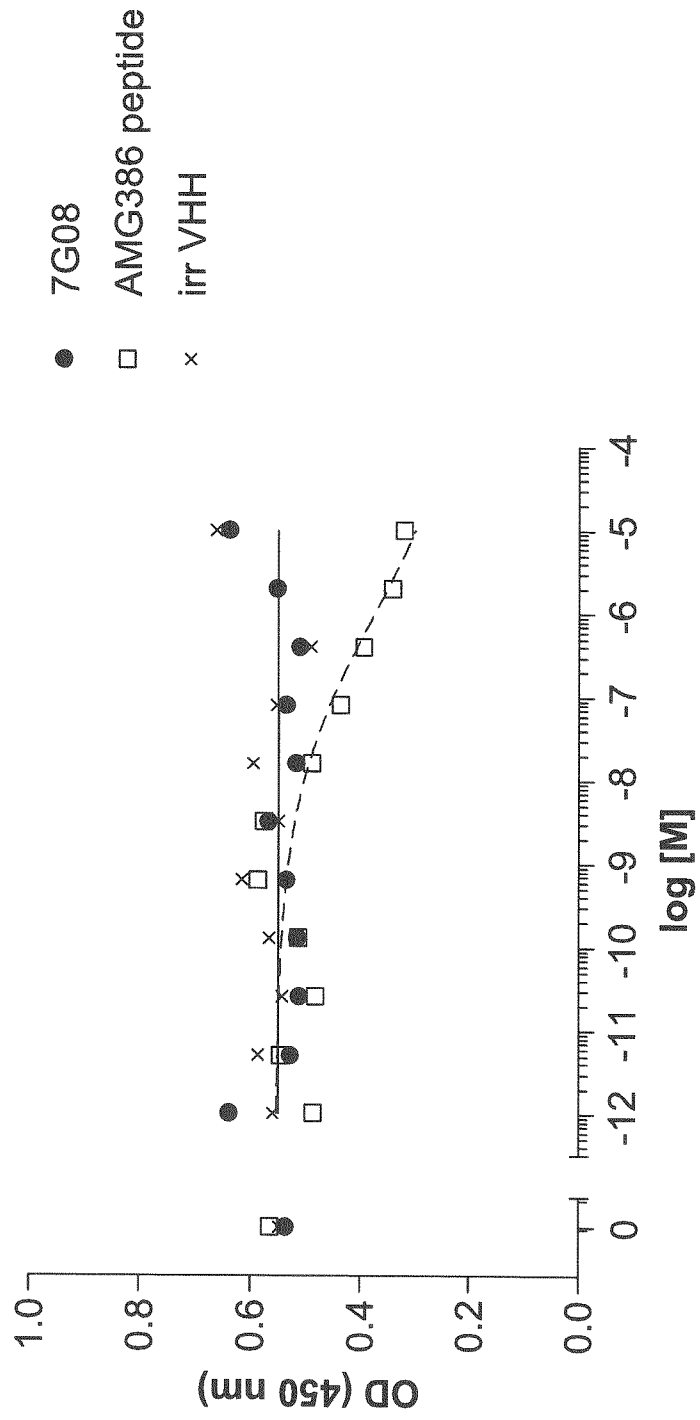


Fig. 4C

10H02

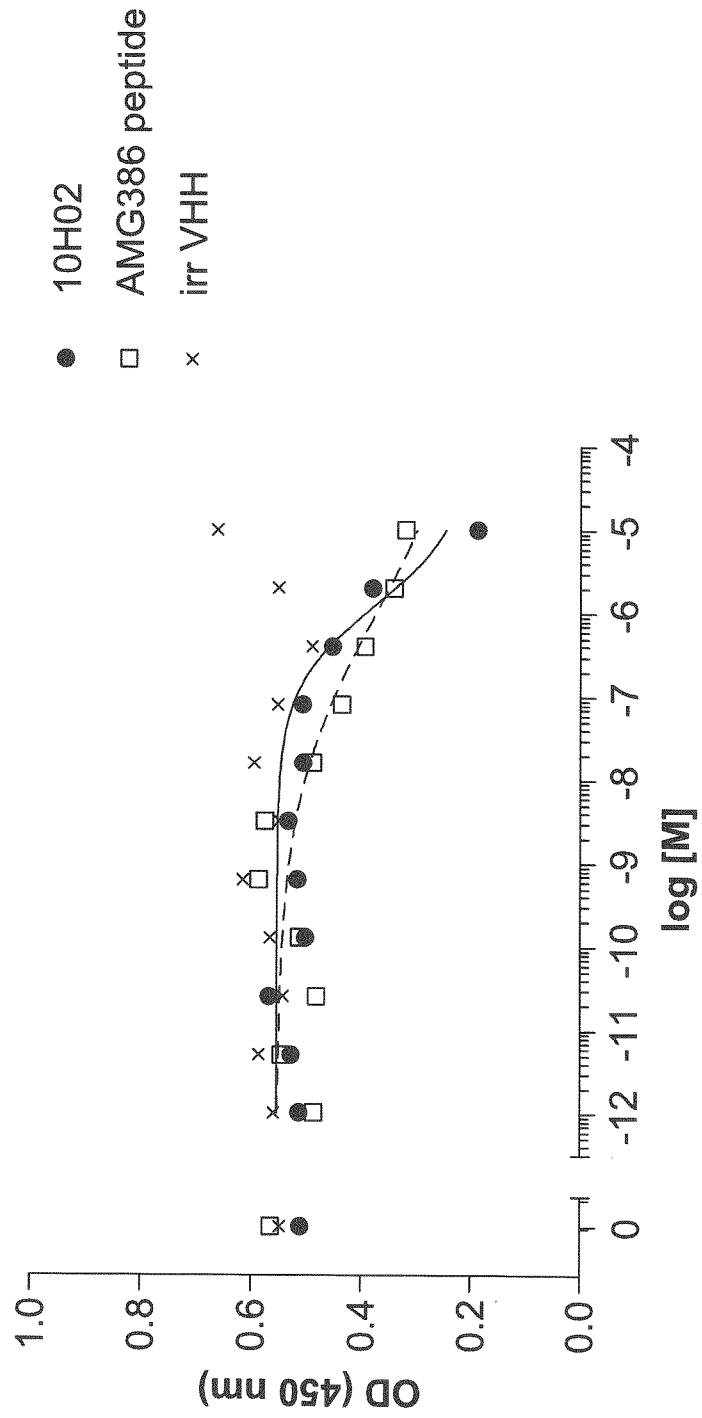


Fig. 4D

11B07

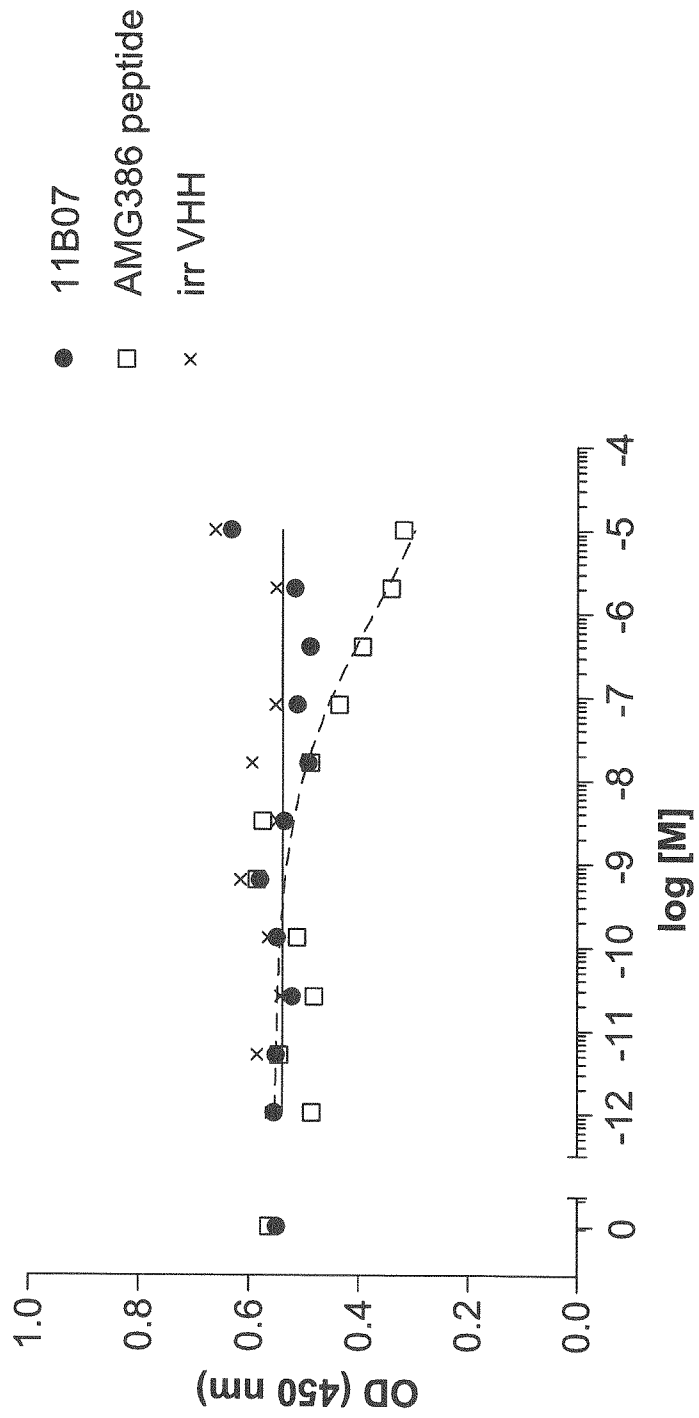


Fig. 4E

13A02

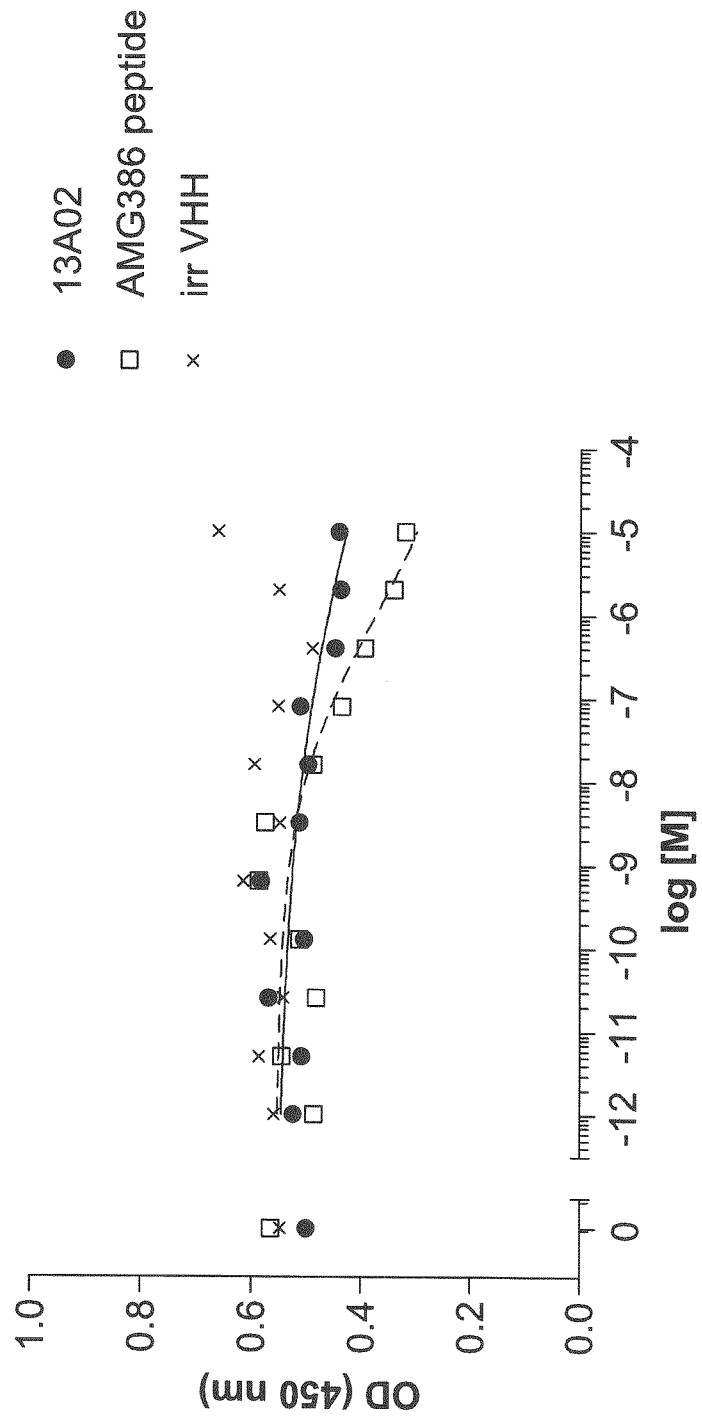


Fig. 4F

24B05

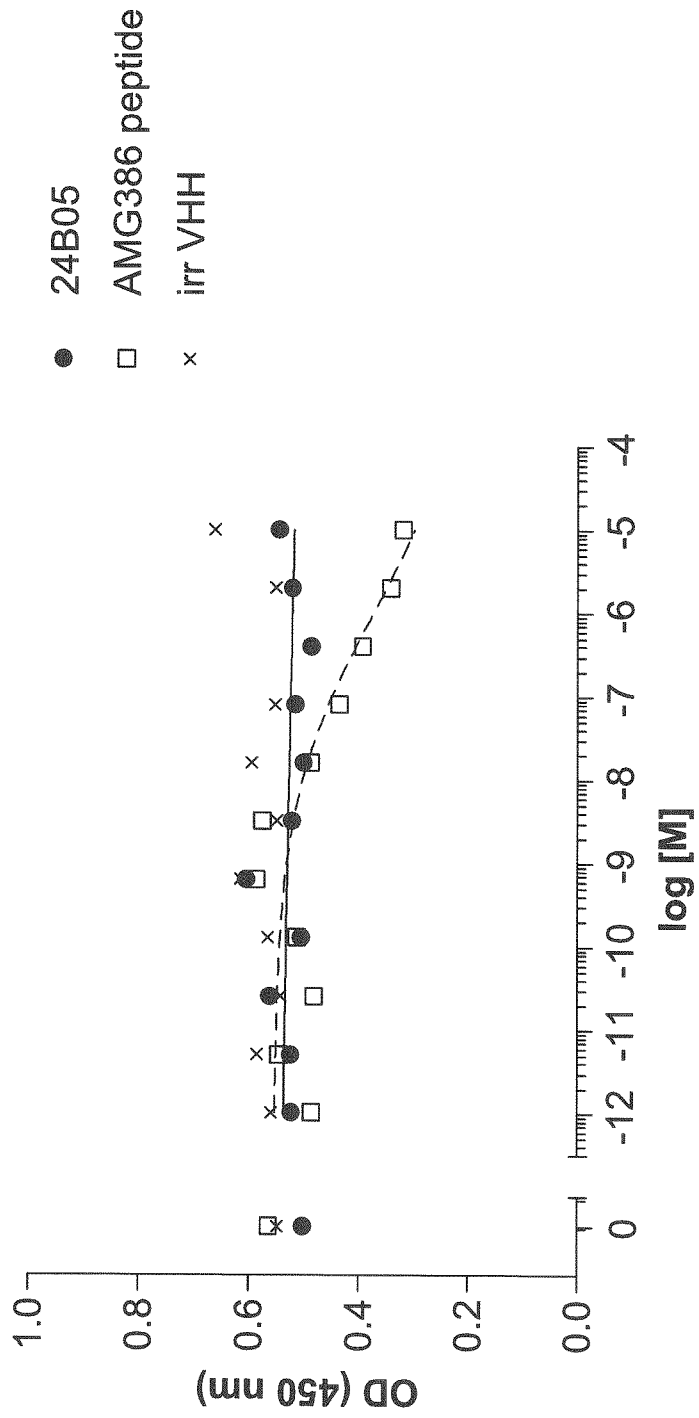


Fig. 4G

28D10

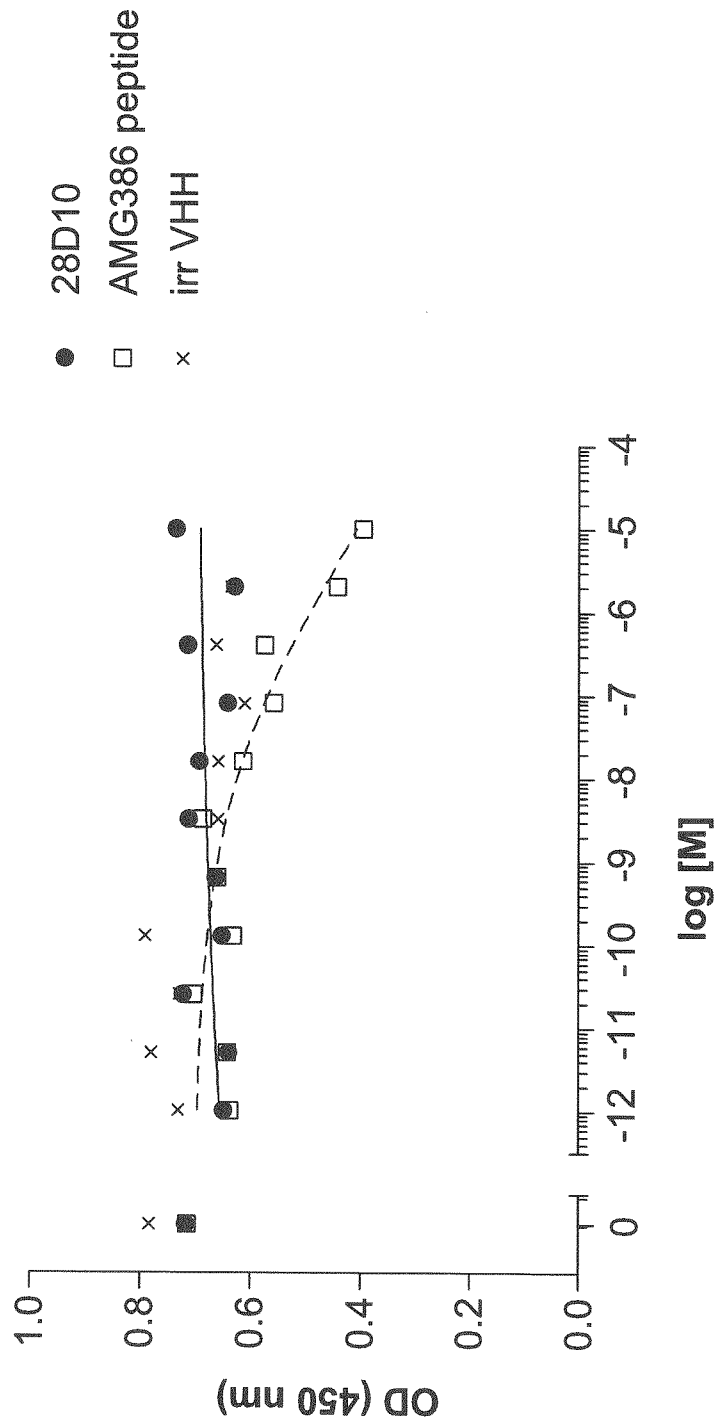


Fig. 4H

37A09

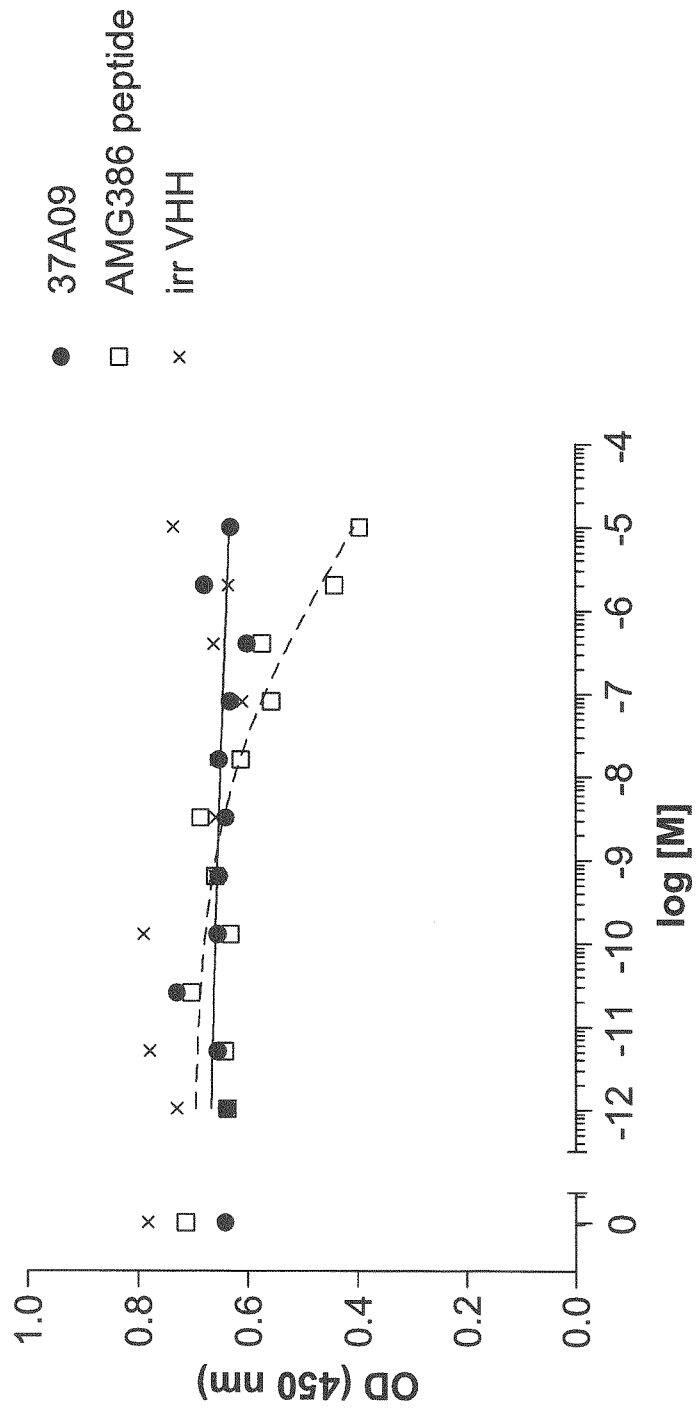


Fig. 4I

37F02

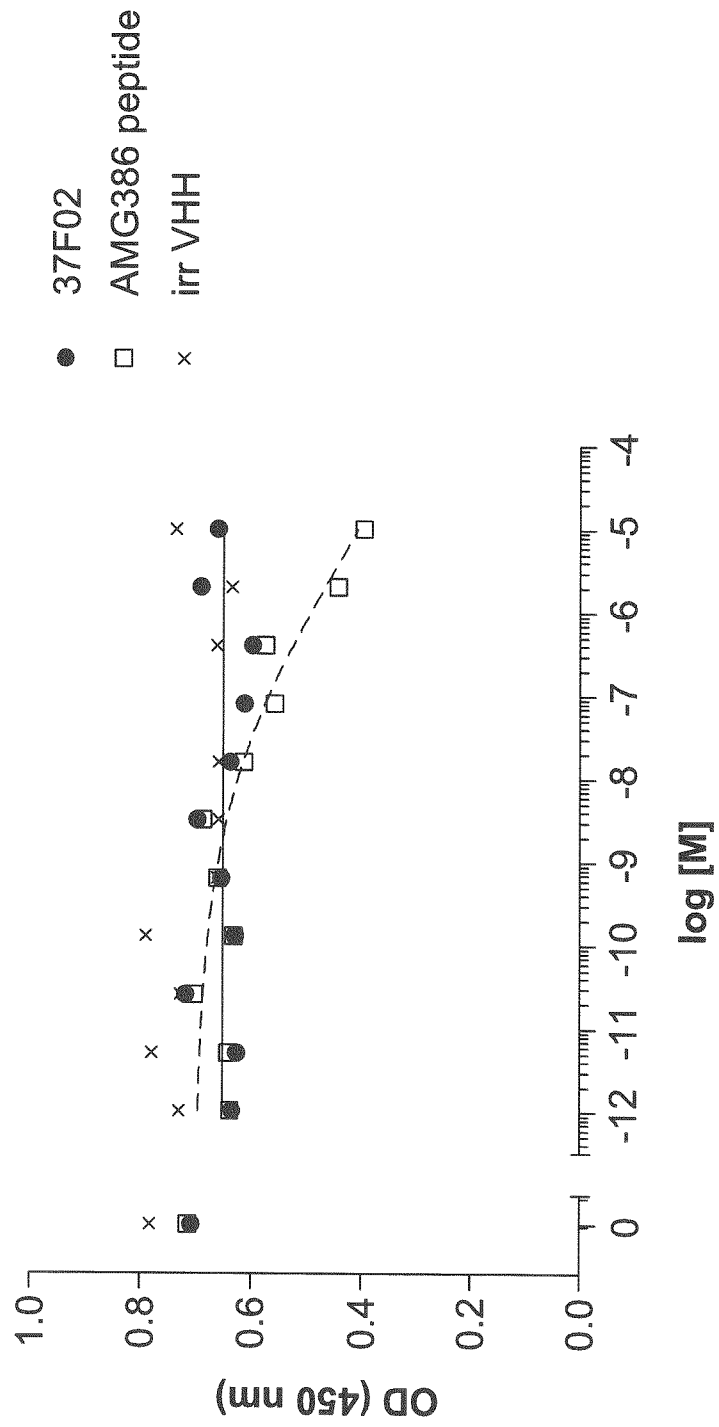


Fig. 6C

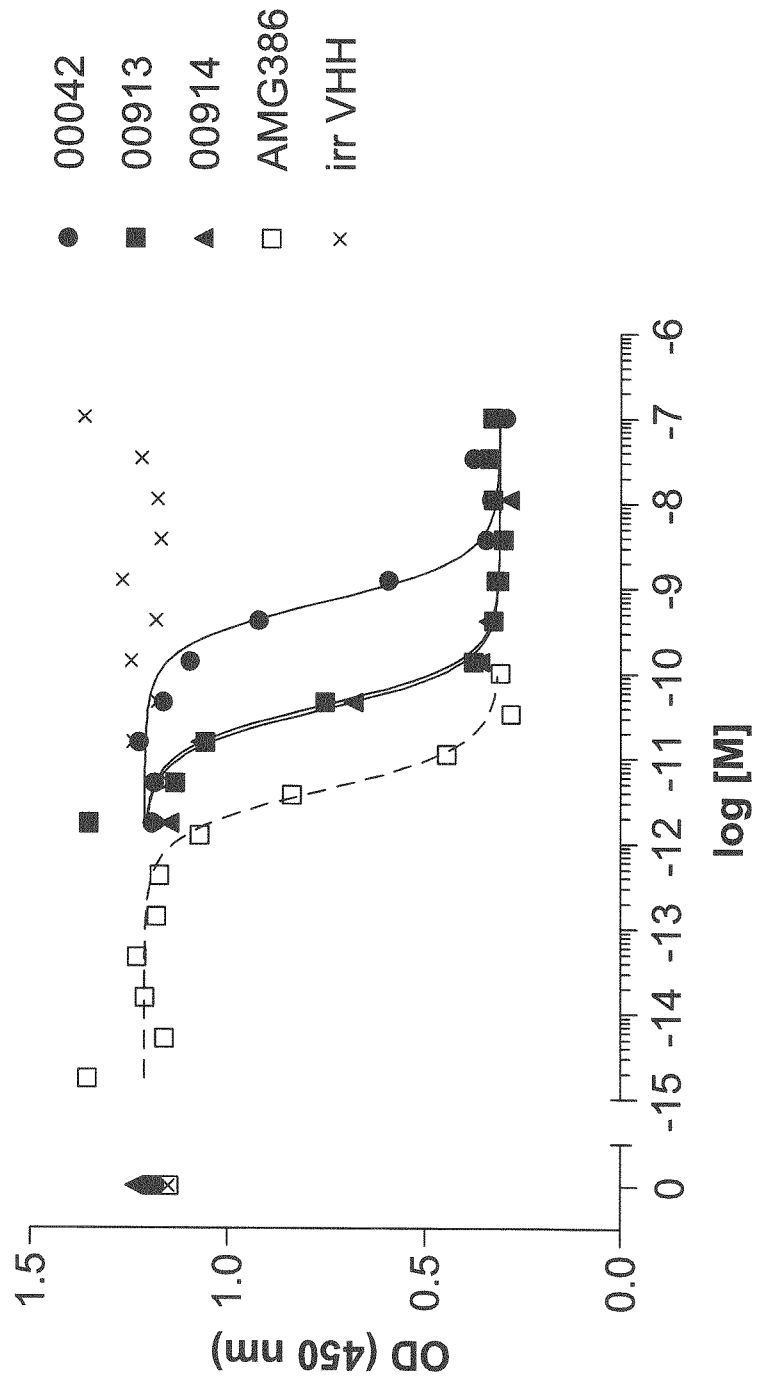


Fig. 7B

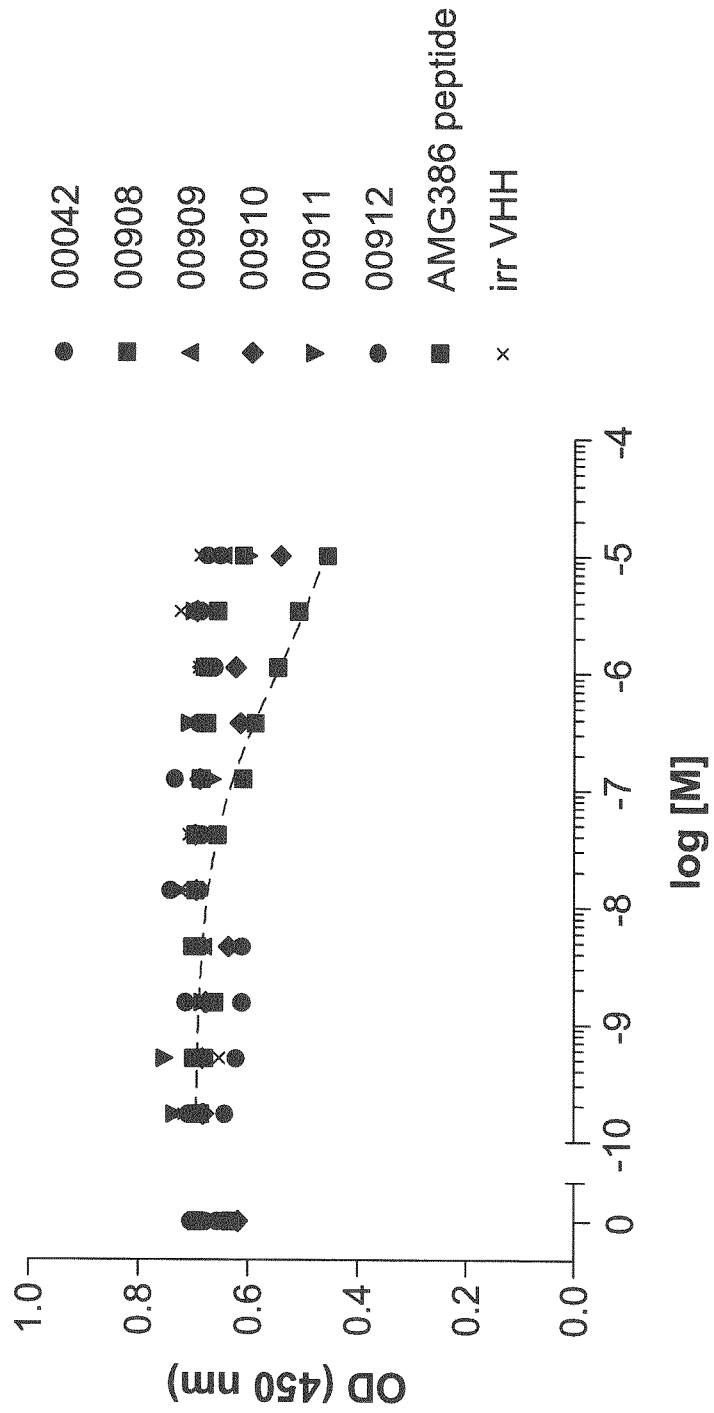


Fig. 7C

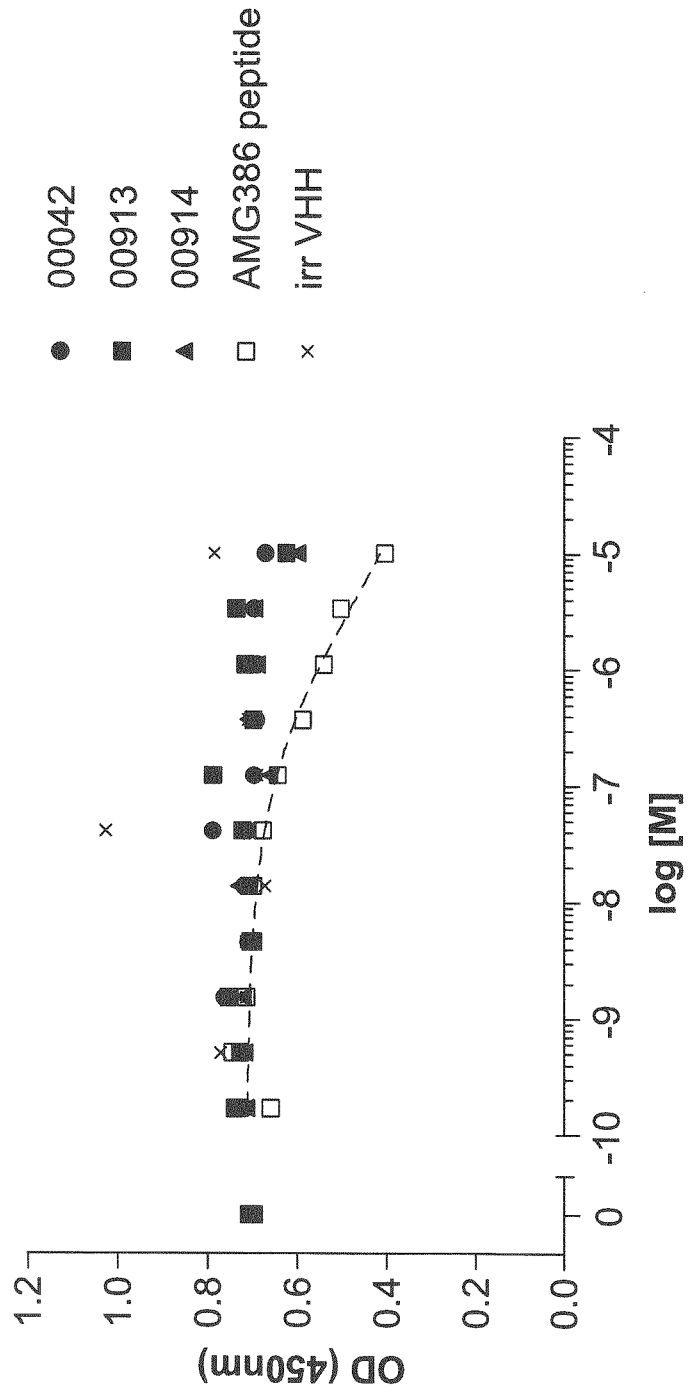


Fig. 8A

Kabat#	10	20	30	40	50	60
hVH3-JHcons	:					
1D01	: EVQLVESGGGLVQPGGSLRLSCAAG FTFSSYAMS WVRQAPGKGLEWVSA ISSN GGSTYYA					
	: <u>A</u> DD .. LG .F... <u>A</u> ..ER.G... C . RCSD 					
Kabat#	70	80	90	100	110	
hVH3-JHcons	:abc..... abcdefg.....					
1D01	: DSVKGRFTISRDN S KNTLYLQMN S LR A EDTAVYY C AR-----WGQGTLLVTVSS					
	: <u>S</u> .. <u>A</u> ...V..... <u>K</u> P..... ASIVPRSKLEPYEYDA <u>Q</u>					

Fig. 8B

```

Kabat#           : .....|.....|.....|.....|.....|.....|.....|.....|.....|.....|
hVH3-JHcons     : EVQLVESGGGLVQPGGSLRLSCAASGFTFSYAMSWVRQAPGKGLEWVSAISSNNGGSTYYA
1D01            : .....A.....A.....DD..LG.F...A..ER.G..C.RCSD.....
00039           : .....A.....A.....DD..LG.F...A..ER.G..C.RCSD.....
00040           : .....A.....A.....DD..LG.F...A..ER.G..C.RCSD.....
00049           : .....A.....A.....DD..LG.F...A..ER.G..C.RCSD.....
00050           : .....A.....A.....DD..LG.F...A..ER.G..C.RCSD.....
00051           : .....A.....A.....DD..LG.F...A..ER.G..C.RCSD.....
00921           : .....A.....A.....DD..LG.F...A..ER.G..C.RCS.....
00925           : .....A.....A.....DD..LG.F...A..ER.G..C.RCS.....

Kabat#           : .....|.....|.....|.....|.....|.....|.....|.....|.....|.....|
hVH3-JHcons     : DSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYFCAR-----WGQGLTVTVSS
1D01            : .....S..A..V.....V.....KP.....ASIVPRSKLEPEYDA.....Q.....
00039           : .....S..A..V.....V.....P.....ASIVPRSKLEPEYDA.....
00040           : .....S..A..V.....V.....P.....ASIVPRSKLEPEYDA.....
00049           : .....S..A..V.....V.....P.....ASIVPRSKLEPEYDA.....
00050           : .....S..A..V.....V.....P.....ASIVPRSKLEPEYDA.....
00051           : .....S..A..V.....V.....P.....ASIVPRSKLEPEYDA.....
00921           : .....S..A..V.....V.....P.....ASIVPRSKLEPEYDA.....
00925           : .....S..A..V.....V.....P.....ASIVPRSKLEPEYDA.....
    
```


Fig. 9-1B

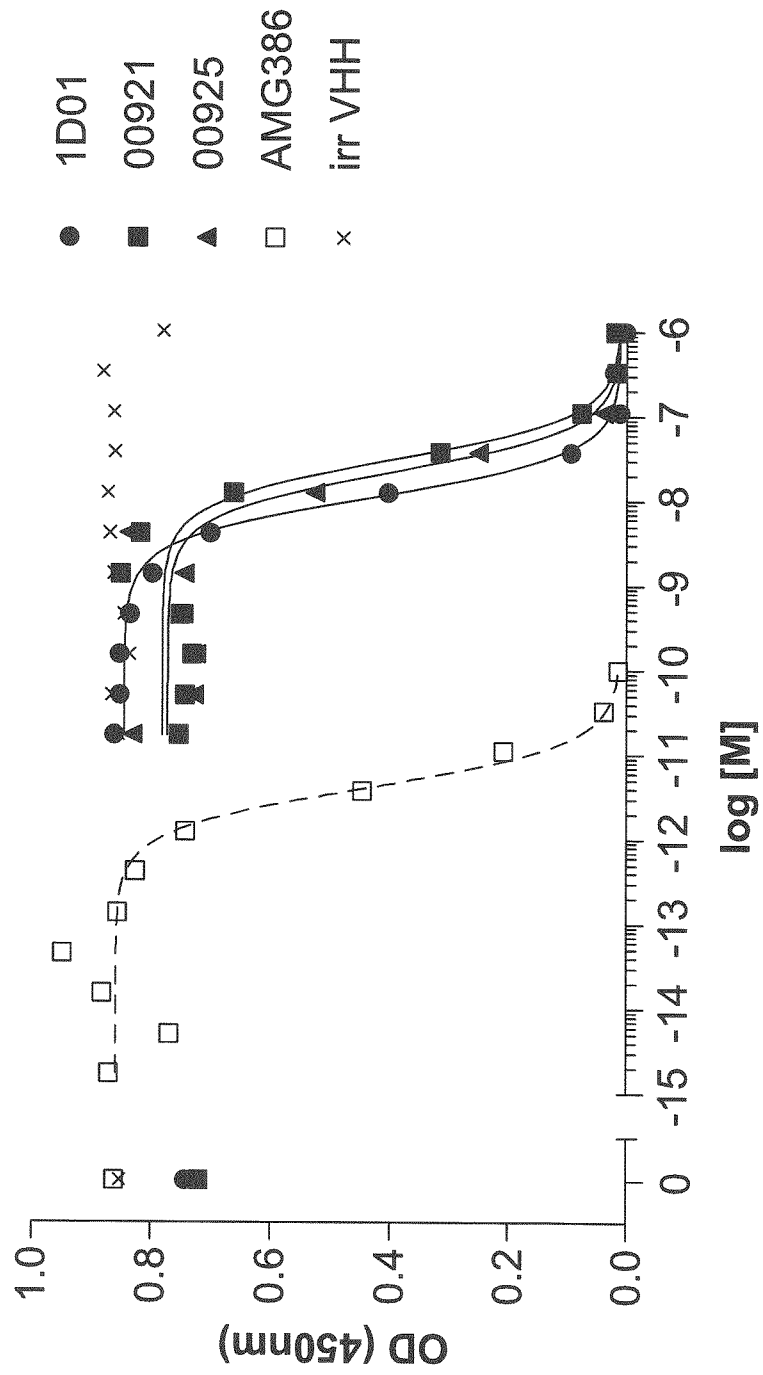


Fig. 9-2B

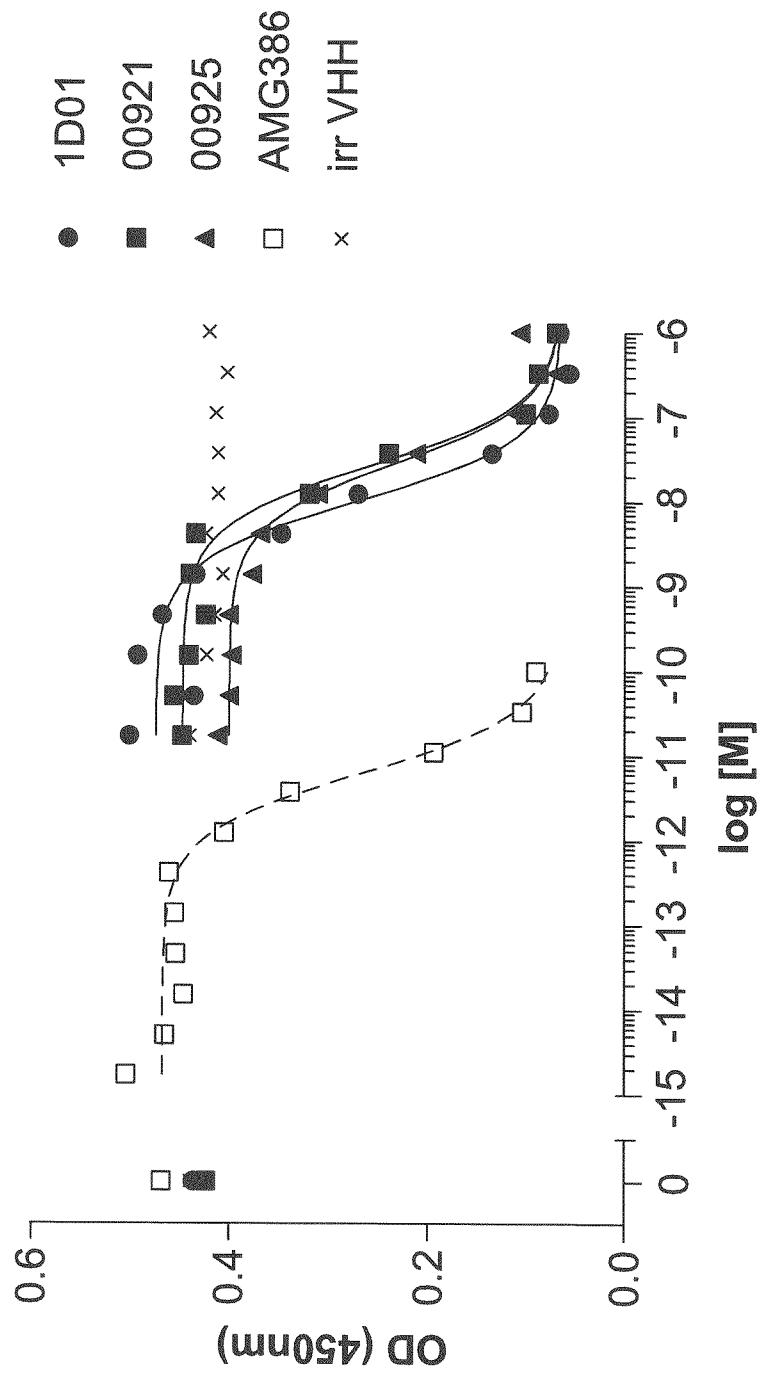


Fig. 9-3B

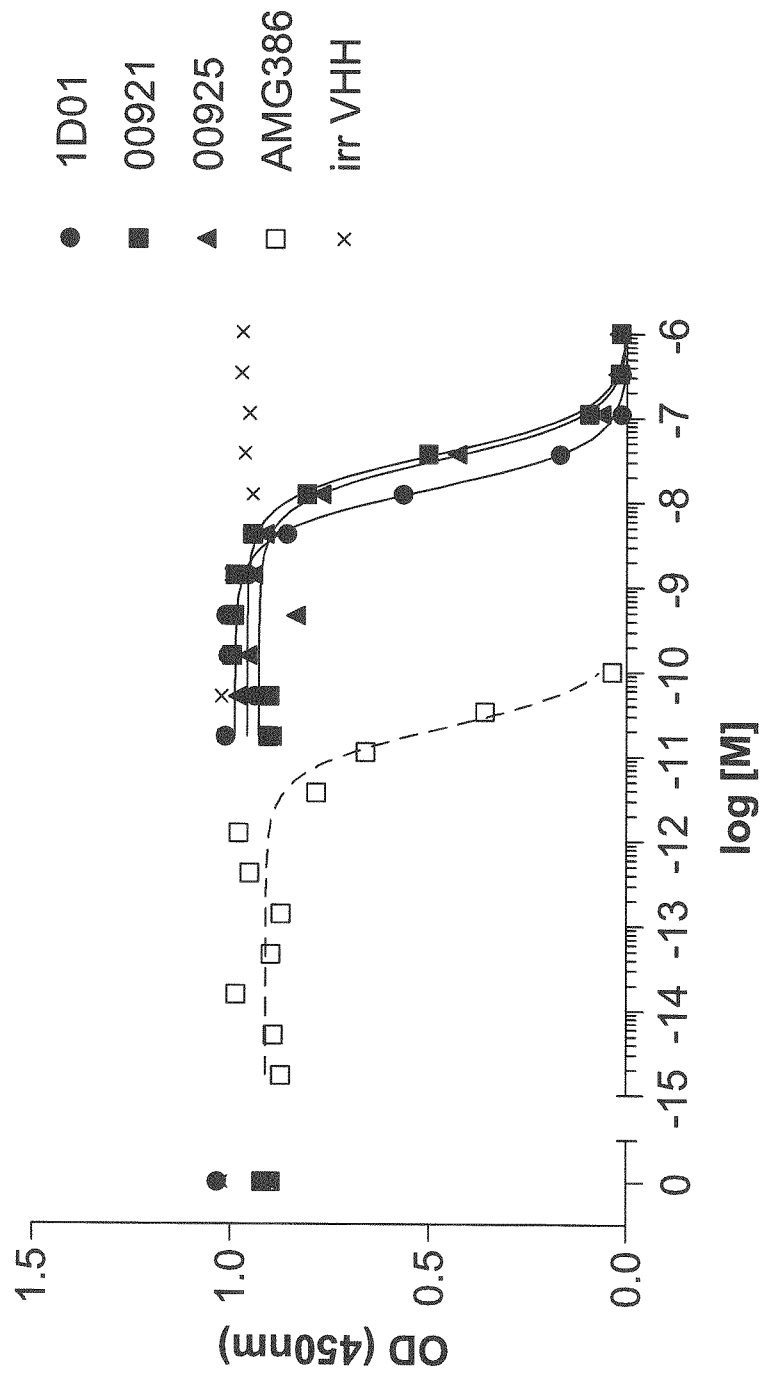


Fig. 10

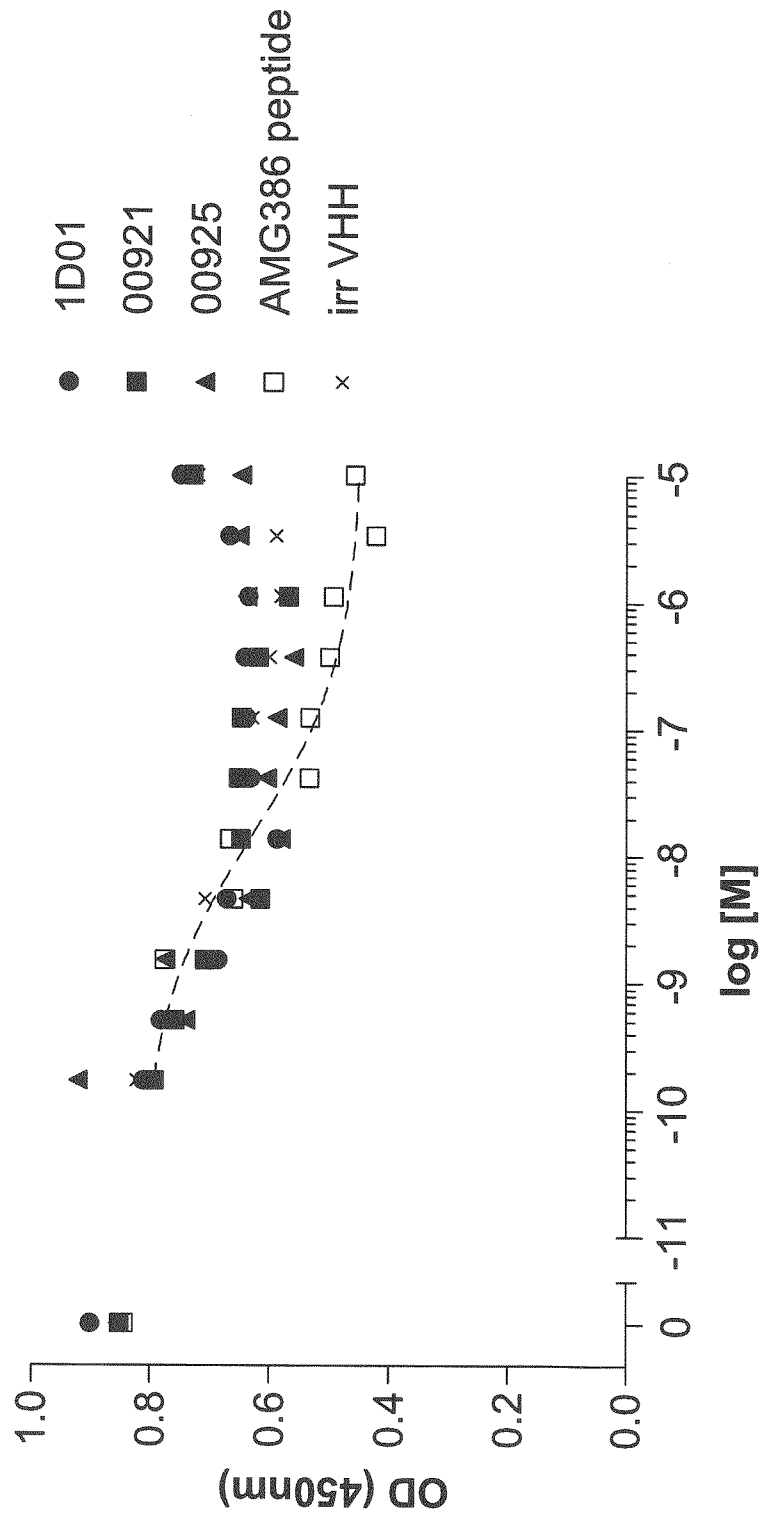


Fig. 11A

Kabat#	10	20	30	40	50	60
hVH3-JHcons	:					
37F02	: EVQLVESGGGLVQPGGSLRLSCAAS FTFSSYAMS WVRQAPGKGLEWVS AISSNNGG STYYA					
	: ALDY ... IG .F..... ER.G.C ... SD . I V					
Kabat#	70	80	90	100	110	
hVH3-JHcons	:abc..... abcdefghi.....					
37F02	: DSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYC AR ----- WGQ GLVTVSS					
	: A V KP TDSGGYIDYDCMGLGYD Y..... Q					

Fig. 11C

```

Kabat#           : .....|.....|.....|.....|.....|.....|.....|.....|.....|.....|
hVH3-JHcons     : EVQLVESGGGLVQPGGSLRLSCAAGFTFSYAMSWVRQAPGKGLEWVSAISSNGGSIYYA
37F02           : .....|.....|.....|.....|.....|.....|.....|.....|.....|.....|
00920           : .....|.....|.....|.....|.....|.....|.....|.....|.....|.....|
00924           : D.....|.....|.....|.....|.....|.....|.....|.....|.....|.....|
00926           : .....|.....|.....|.....|.....|.....|.....|.....|.....|.....|
00927           : .....|.....|.....|.....|.....|.....|.....|.....|.....|.....|
00928           : .....|.....|.....|.....|.....|.....|.....|.....|.....|.....|
00929           : .....|.....|.....|.....|.....|.....|.....|.....|.....|.....|
00930           : .....|.....|.....|.....|.....|.....|.....|.....|.....|.....|
00931           : .....|.....|.....|.....|.....|.....|.....|.....|.....|.....|

Kabat#           : .....|.....|.....|.....|.....|.....|.....|.....|.....|.....|
hVH3-JHcons     : DSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAR-----WGQGTLLVTVSS
37F02           : .....|.....|.....|.....|.....|.....|.....|.....|.....|.....|
00920           : .....|.....|.....|.....|.....|.....|.....|.....|.....|.....|
00924           : .....|.....|.....|.....|.....|.....|.....|.....|.....|.....|
00926           : .....|.....|.....|.....|.....|.....|.....|.....|.....|.....|
00927           : .....|.....|.....|.....|.....|.....|.....|.....|.....|.....|
00928           : .....|.....|.....|.....|.....|.....|.....|.....|.....|.....|
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00930           : .....|.....|.....|.....|.....|.....|.....|.....|.....|.....|
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Fig. 12-1

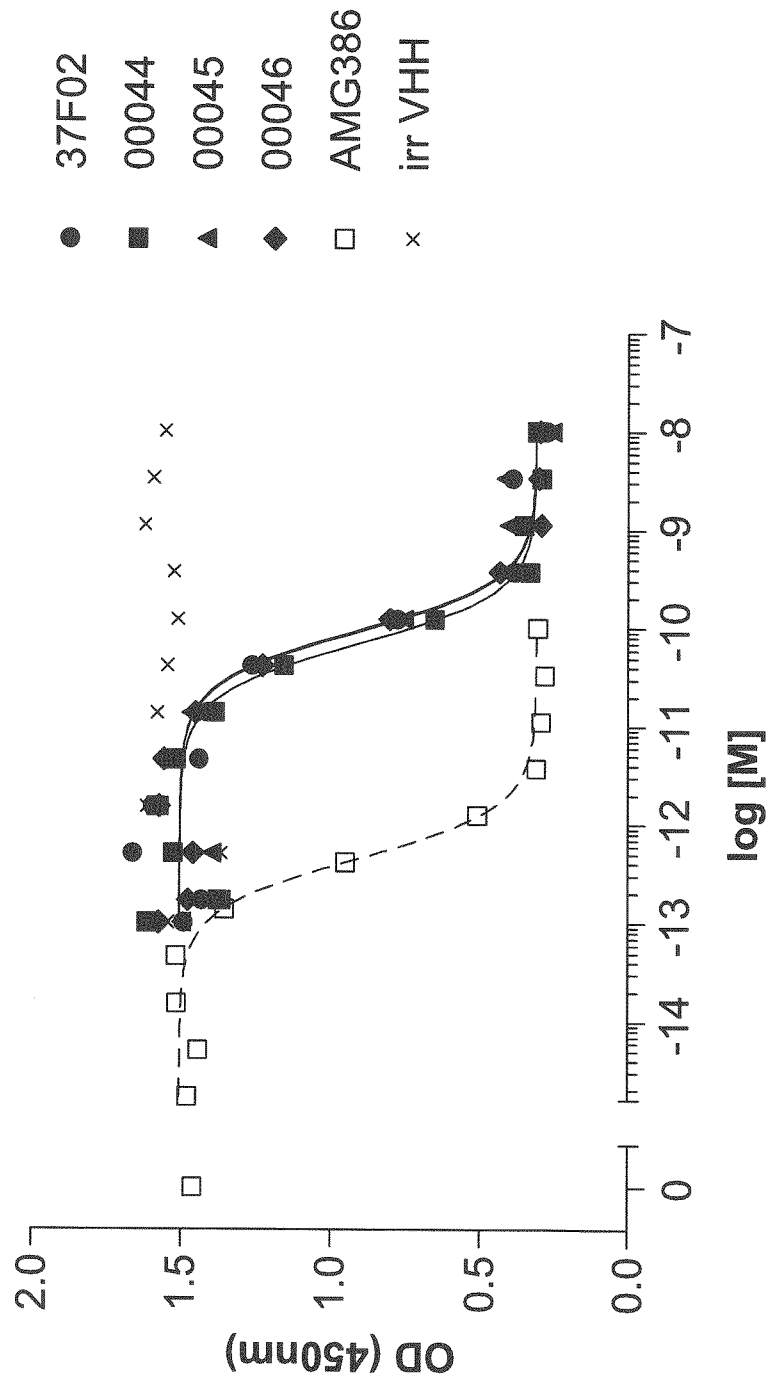


Fig. 12-2

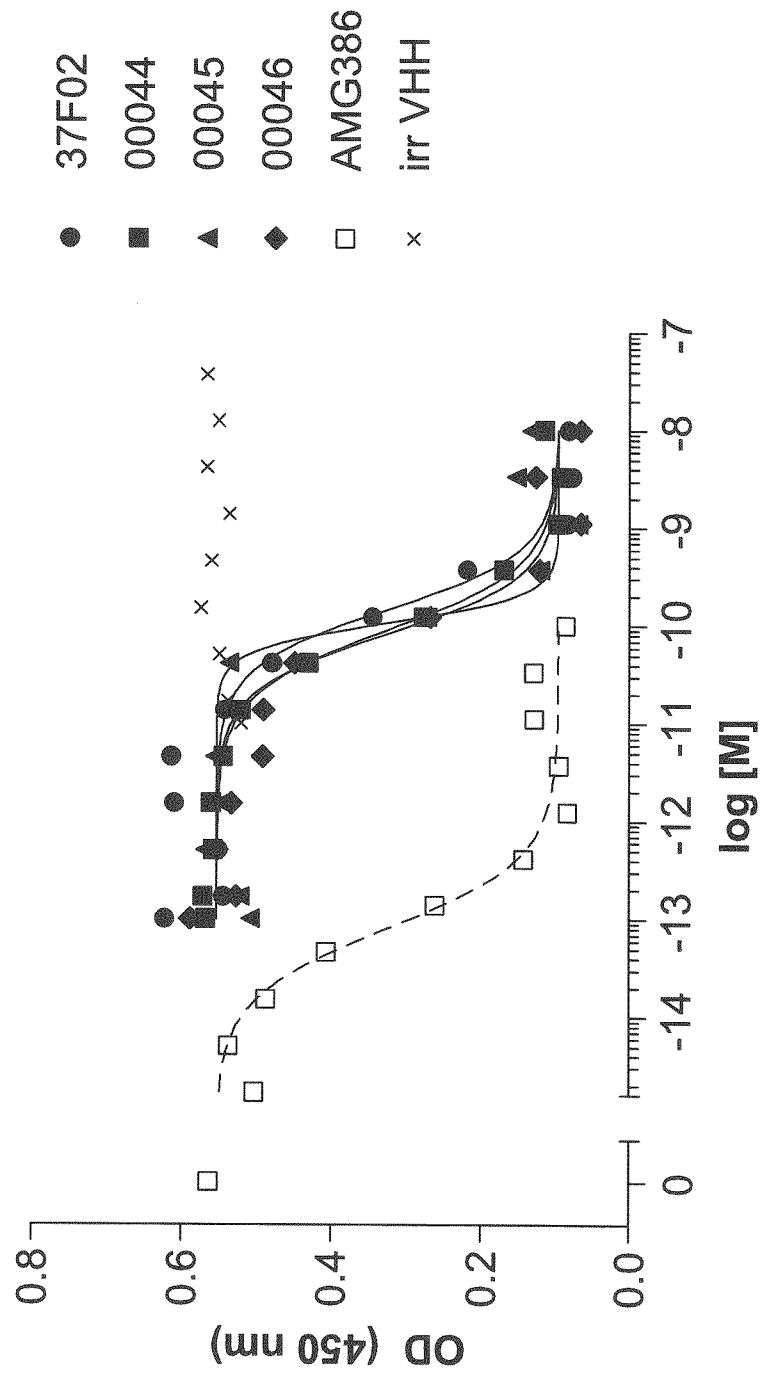


Fig. 12-3

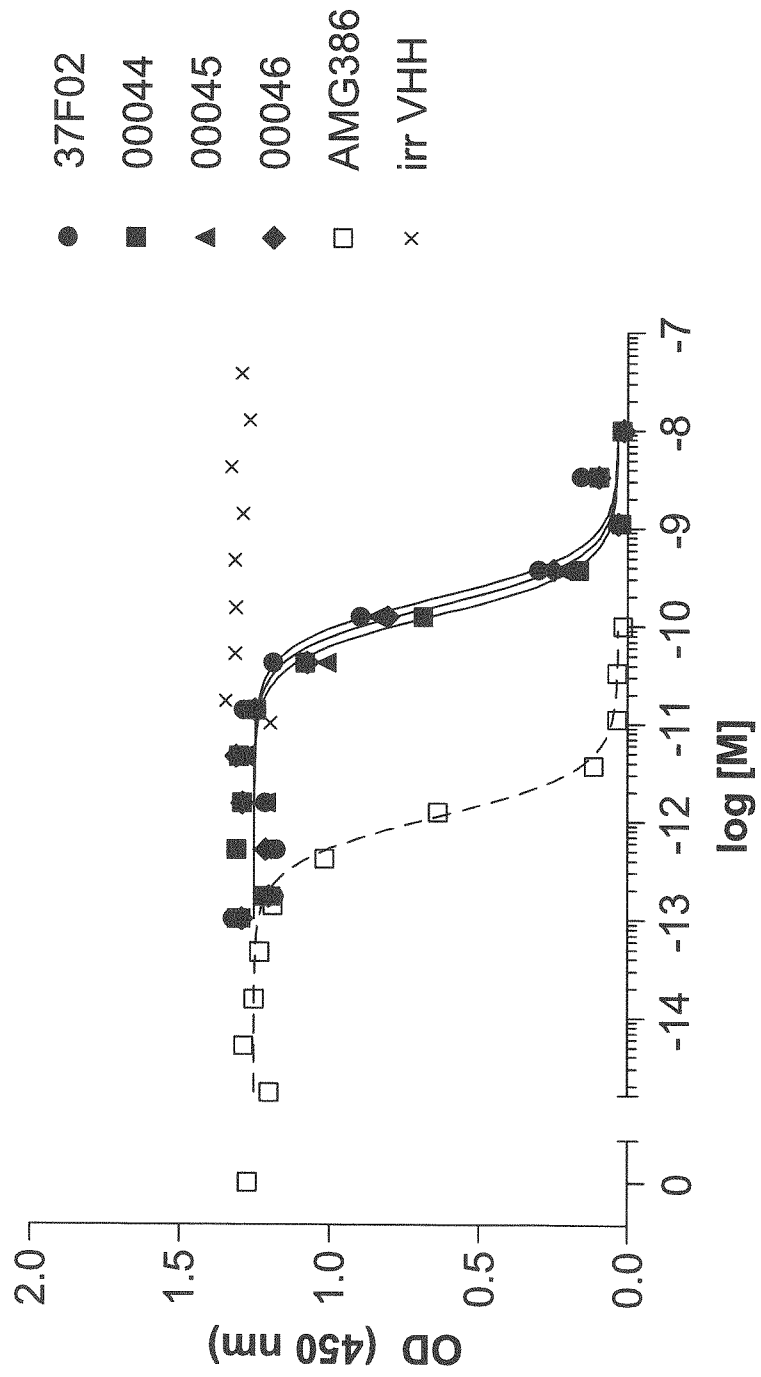


Fig. 13-1B

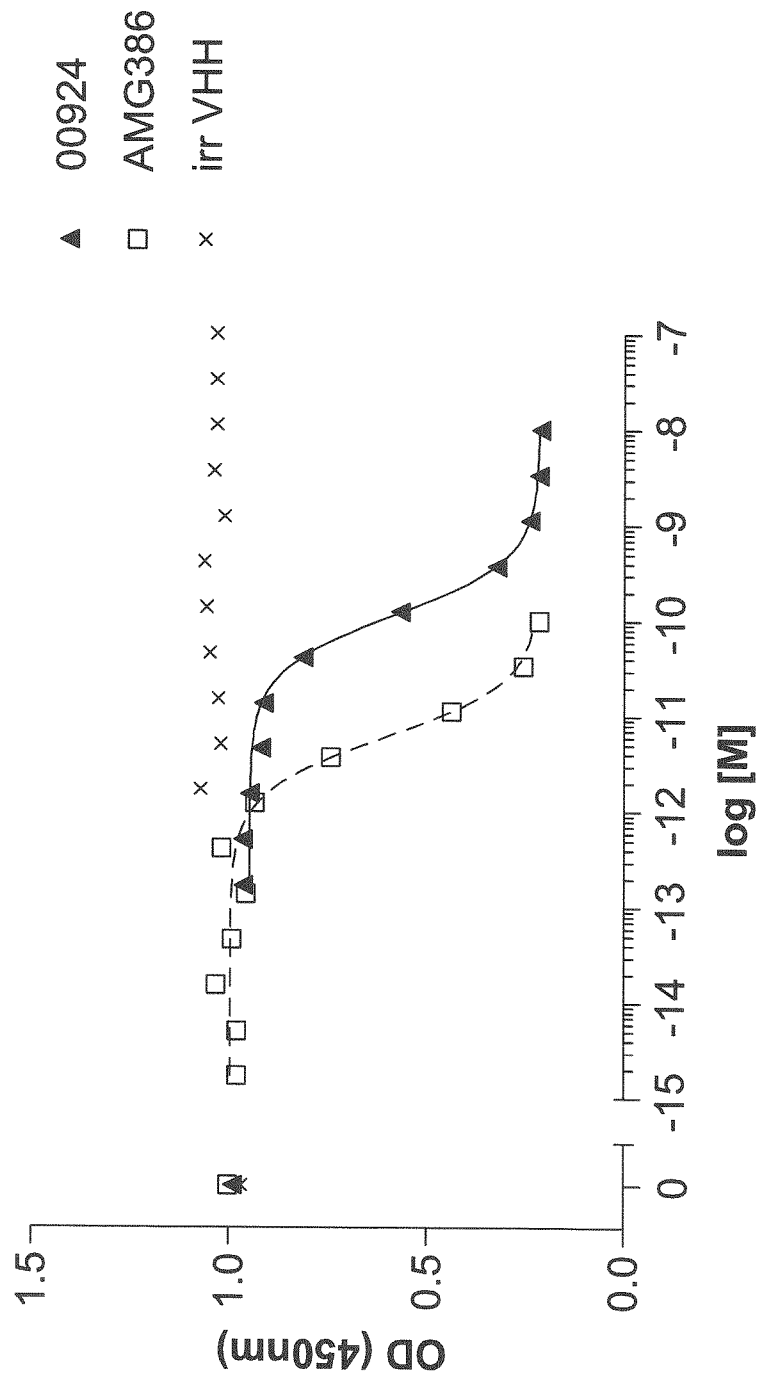


Fig. 13-2

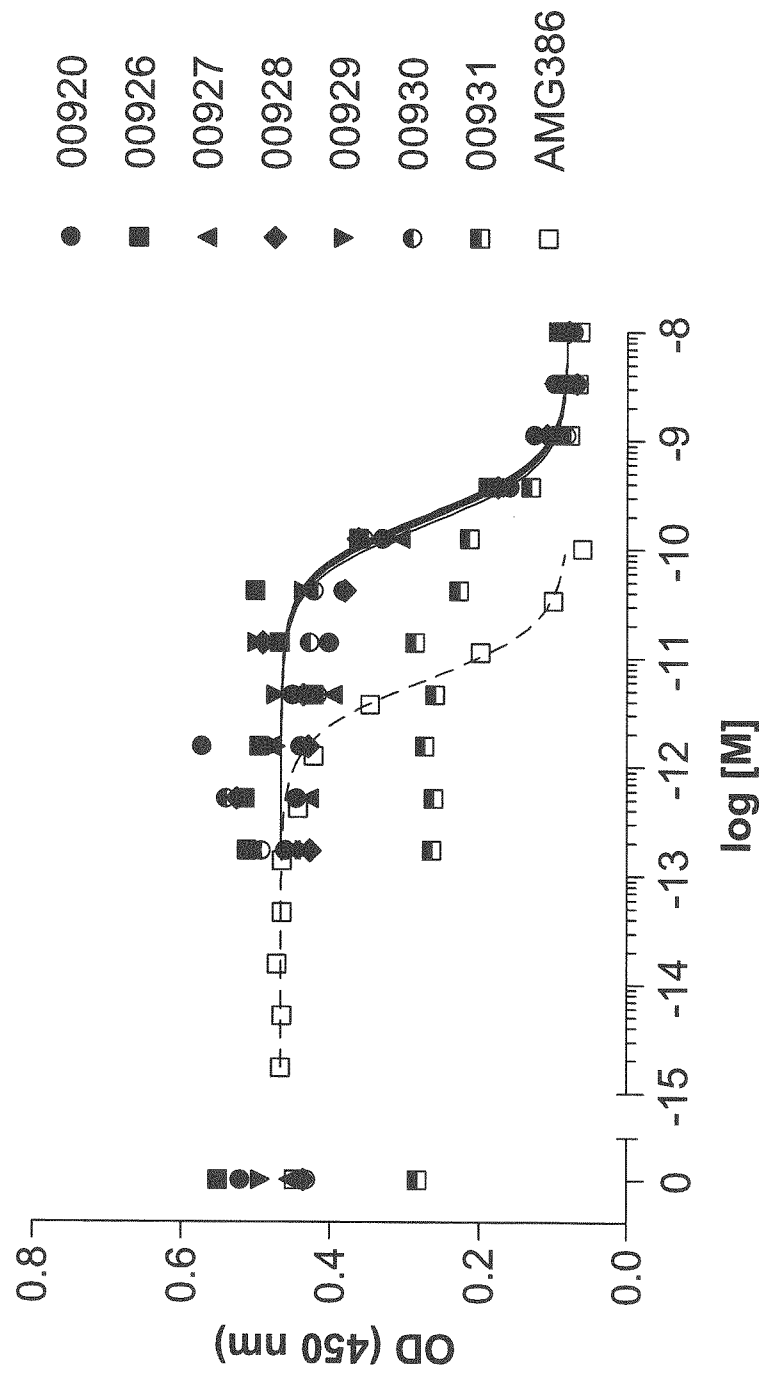


Fig. 13-3

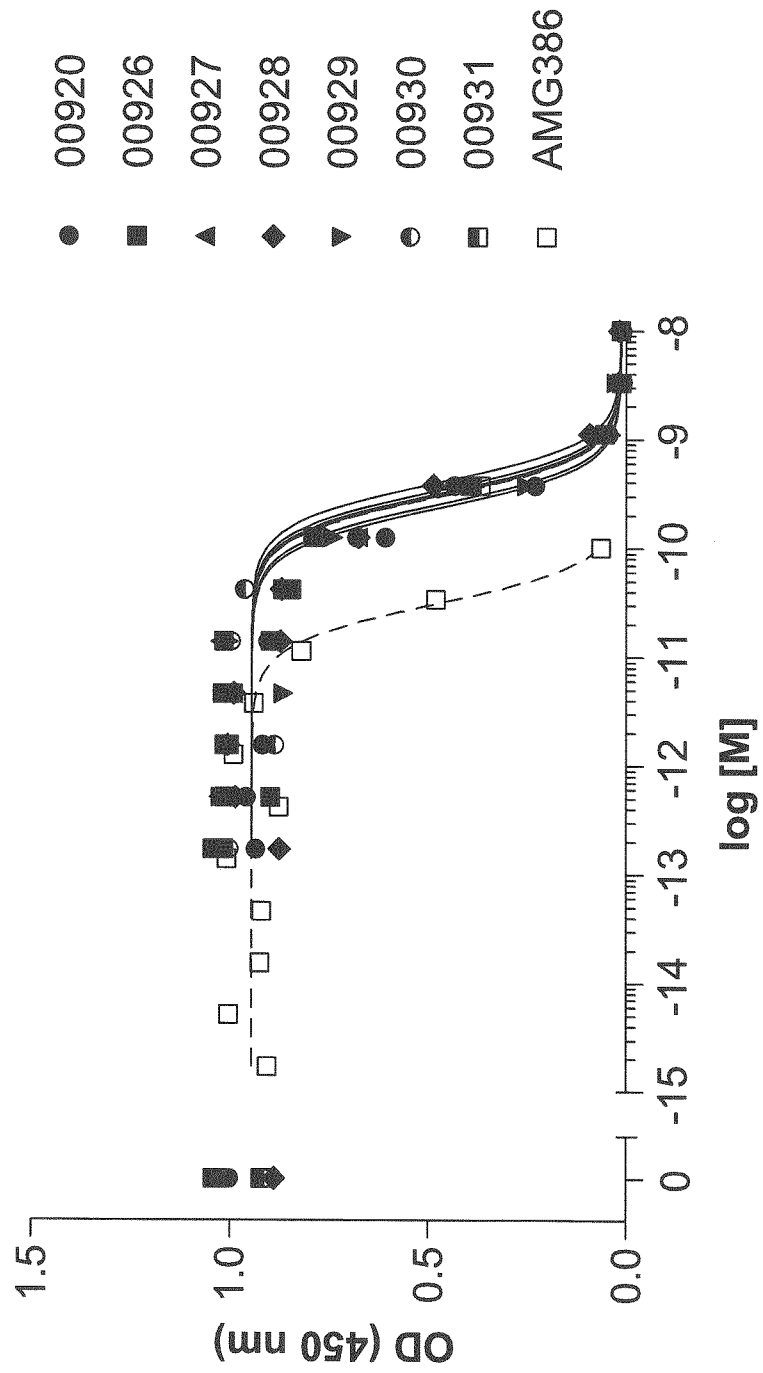


Fig. 14

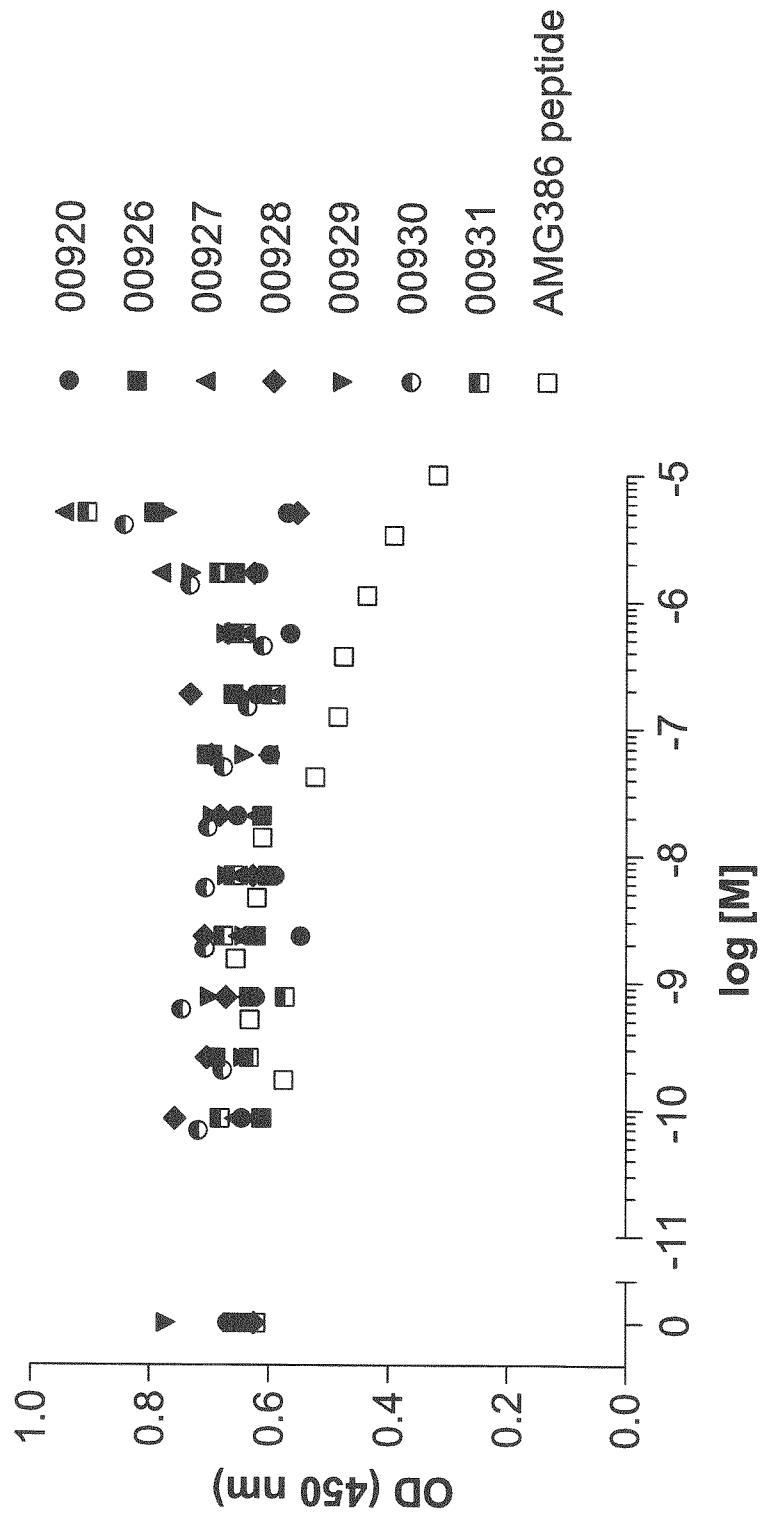


Fig. 15A

```

Kabat#           : .....|.....|.....|.....|.....|.....|.....|.....|.....|
hVH3-JHcons     : EVQLVESGGGLVQPGGSLRLSCAASGFTFSYAMSWVRQAPGKGLEWVSAISSNGGSTYYA
28D10          : .....A.....LDY...IG.F.....ER.G...[C].RpSD[.]......
                :
Kabat#           : .....|.....|..abc.....|.....|.....|abcdefghijkl.....|....
hVH3-JHcons     : DSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAR-----WGQGLLVTVSS
28D10          : .....S..D...V.....KP.....AVPAGRLRFGEQWYPLYEYDA.....Q.....

```


Fig. 15B (continued)

```

Kabat#           70           80           90           100          110
hVH3-JHcons : .....|.....|..abc.....|.....|.....|abcdefghijk|.....|....
                DSVKGRFTISRDN SKNTLYLQMN SLRAEDTAVYYCAR-----WGQGTLLVTVSS
28D10 : .....S..D...V.....KP.....AVPAGRLRFGEQWYPLYEYDA.....Q.....
00025 : .....S..D...V.....KP.....AVPAGRLRFGEQWYPLYEYDA.....
00026 : .....S..D...V.....KP.....AVPAGRLRFGEQWYPLYEYDA.....
00027 : .....S..D...V.....KP.....AVPAGRLRFGEQWYPLYEYDA.....
00041 : .....S..A...V.....P.....AVPAGRLRFGEQWYPLYEYDA.....
00042 : .....S.....V.....P.....AVPAGRLRFGEQWYPLYEYDA.....
00043 : .....S.....A...V.....P.....AVPAGRLRFGEQWYPLYEYDA.....
00048 : .....S..D...V.....KP.....AVPAGRLRFGEQWYPLYEYDA.....
00052 : .....S..D...V.....P.....AVPAGRLRFGEQWYPLYEYDA.....
00053 : .....S.....D...V.....P.....AVPAGRLRFGEQWYPLYEYDA.....
00054 : .....S.....V.....P.....AVPAGRLRFGEQWYPLYEYDA.....
00055 : .....S..D...V.....KP.....AVPAGRLRFGEQWYPLYEYDA.....

```


Fig. 15D

Kabat#	10	20	30	40	50	60
hVH3-JHcons	:	:	:	:	:	:
28D10	: EVQLVESGGGLVQPGGSLRLS	CAASGFTFSYAMS	WVRQAPGKGL	EWVSA	ISSNNGG	STYYA
00932	:A.....	LDY..IG.F.....	ER.G..C.RDSD
00933	:	V..I.LDD..IG.F.....	ER.G..S.RD
00934	:	I.LDD..IG.F.....	ER.G..RES
00935	:	I.LDD..IG.F.....	ER.G..R.S
00936	:	V..I.LDD..IG.F.....	ER.G..RD
00937	:	V..I.LDD..IG.F.....	ER.G..RES
00938	:	V..I.LDD..IG.F.....	ER.G..R.S
00956	:	LDD..IG.F.....	ER.G..R.S
Kabat#	70	80	90	100	110	
hVH3-JHcons	:	:	:	:	:	
28D10	: DSVKGRFTISRDN	SKNTLYLQMN	SLRAEDTAVYY	CAR-----	WGQGLVTVSS	
00932	:S.D..V.....KP.....	AVPAGRLRFGEQWYPLIYEYDAQ.....	
00933	:	V.....P.....	AVPAGRLRYGEQWYPIYEYDA	
00934	:	V.....P.....	AVPAGRLRYGEQWYPIYEYDA	
00935	:	V.....P.....	AVPAGRLRYGEQWYPIYEYDA	
00936	:	V.....P.....	AVPAGRLRYGEQWYPIYEYDA	
00937	:	V.....P.....	AVPAGRLRYGEQWYPIYEYDA	
00938	:	V.....P.....	AVPAGRLRYGEQWYPIYEYDA	
00956	:	V.....P.....	AVPAGRLRFGEQWYPLIYEYDA	

Fig. 16-1A

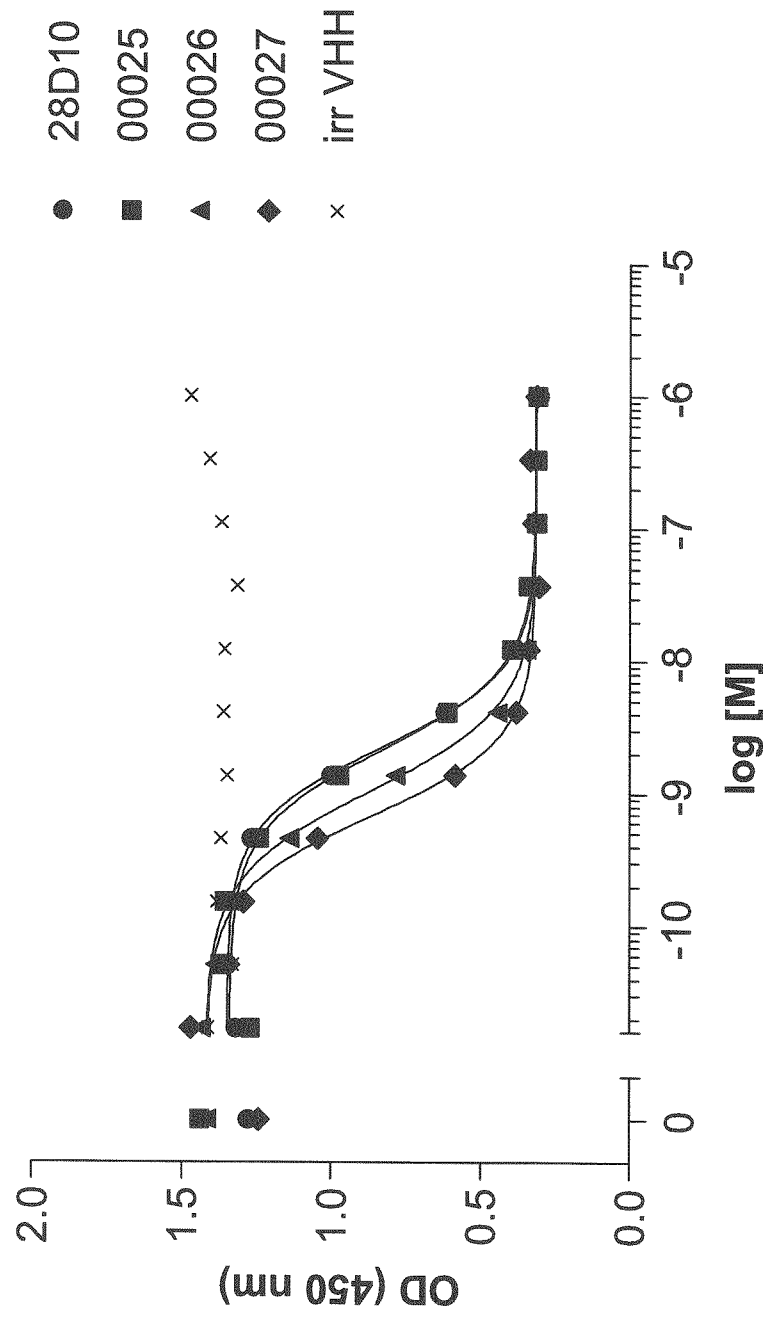


Fig. 16-1C

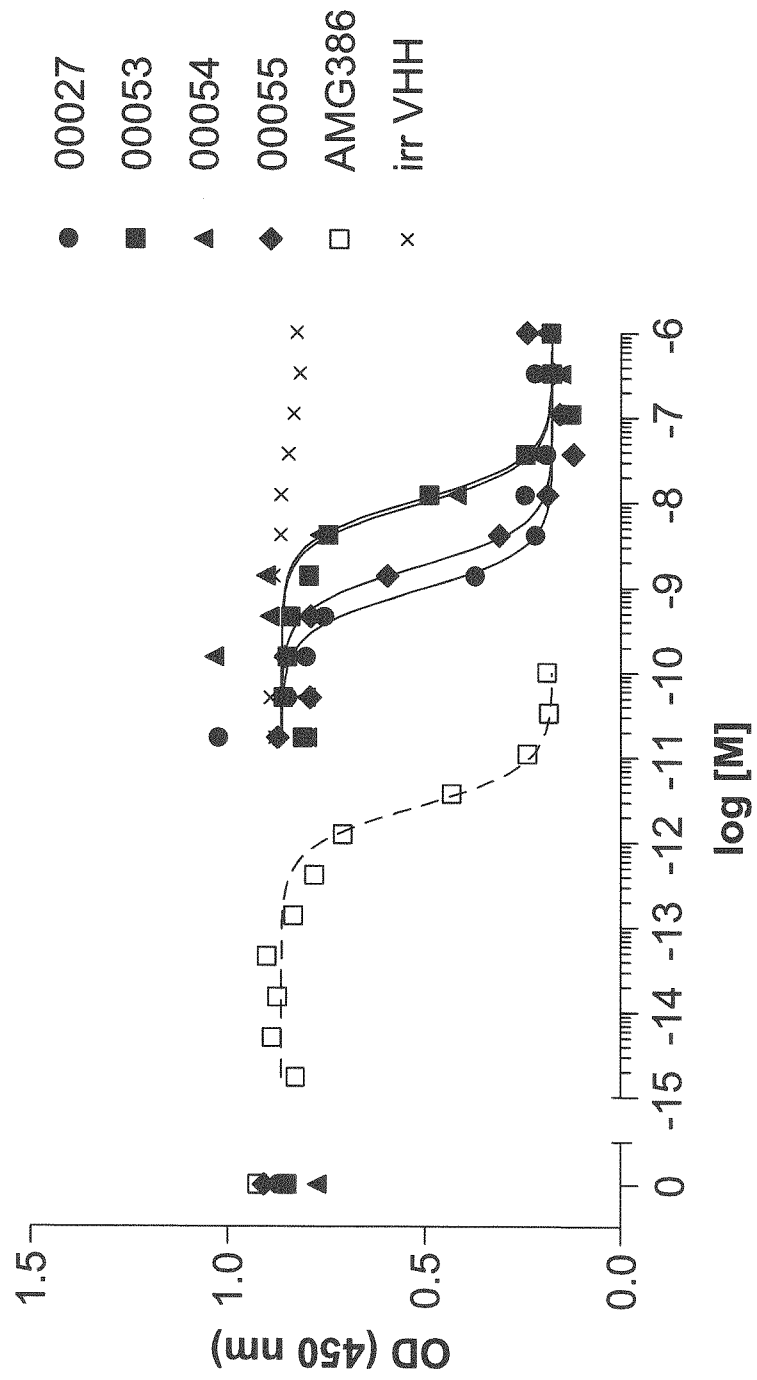


Fig. 16-2A

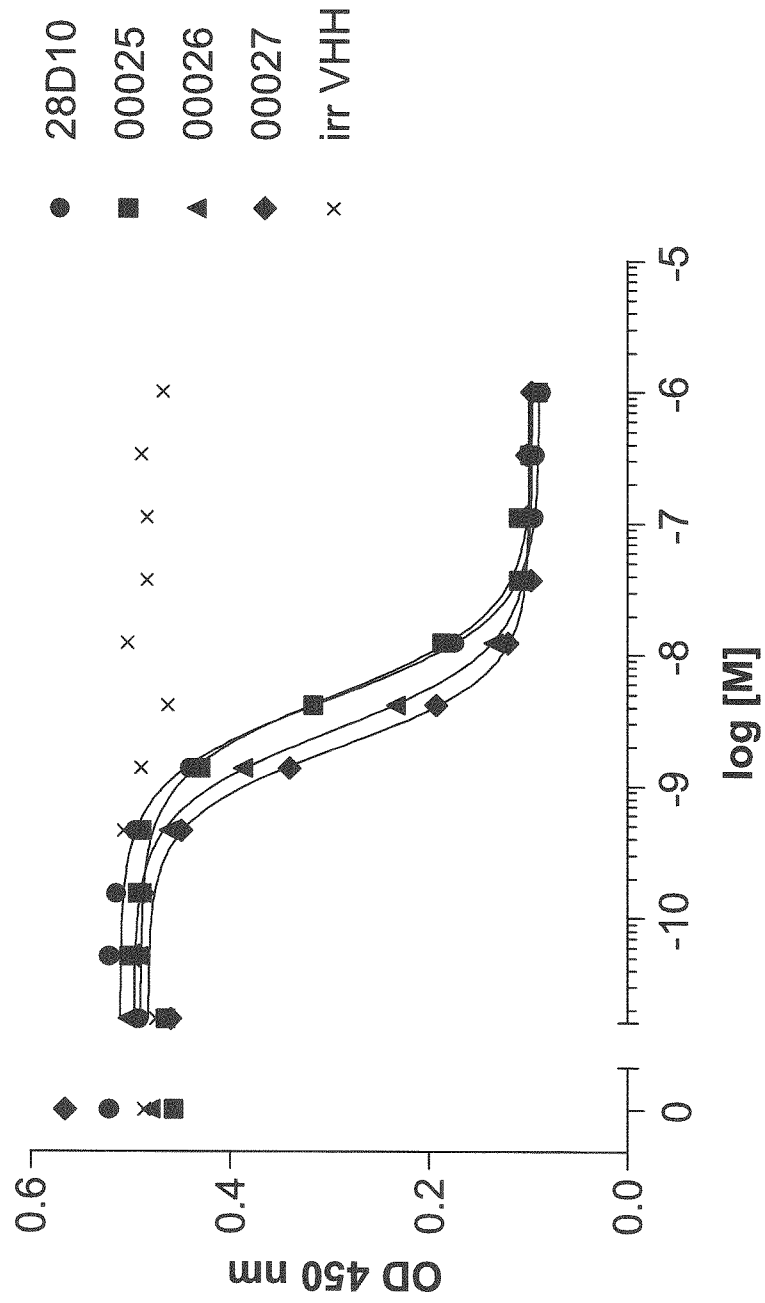


Fig. 16-2C

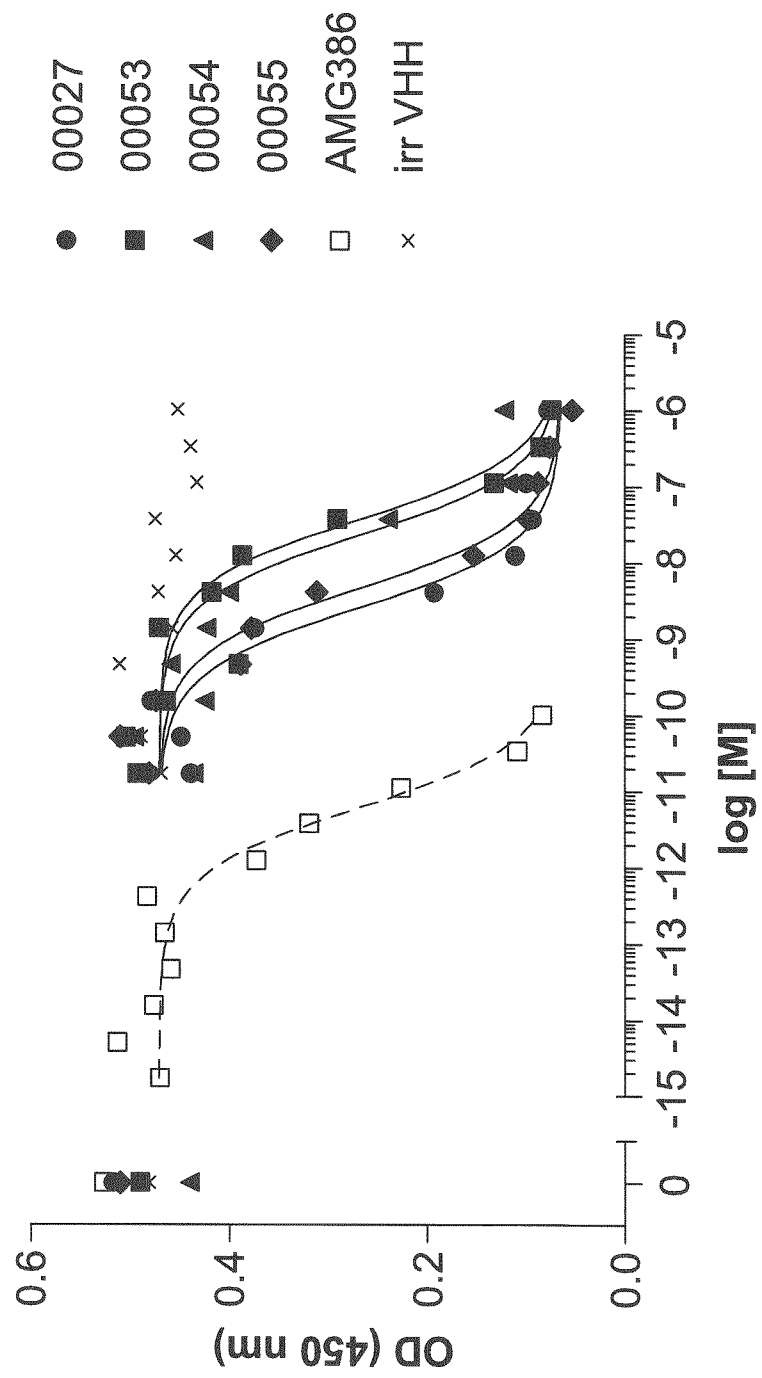


Fig. 16-3A

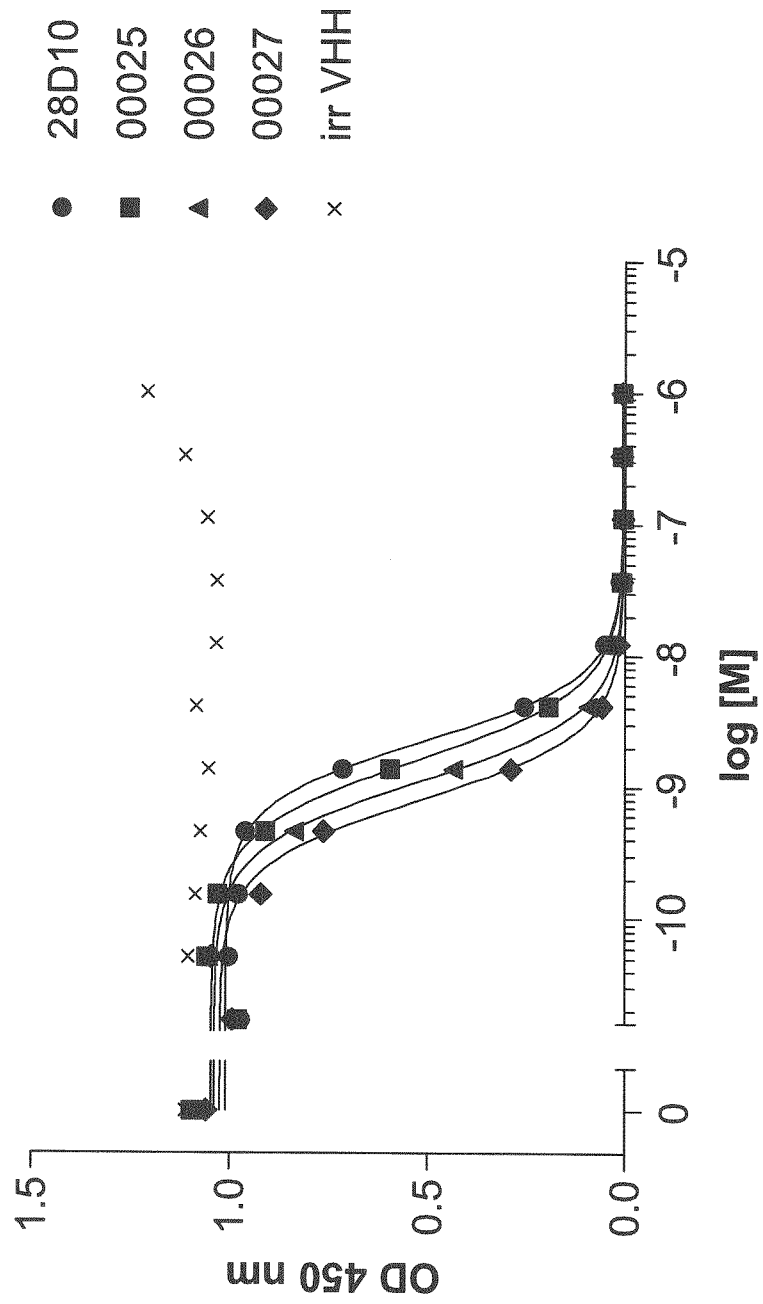


Fig. 16-3C

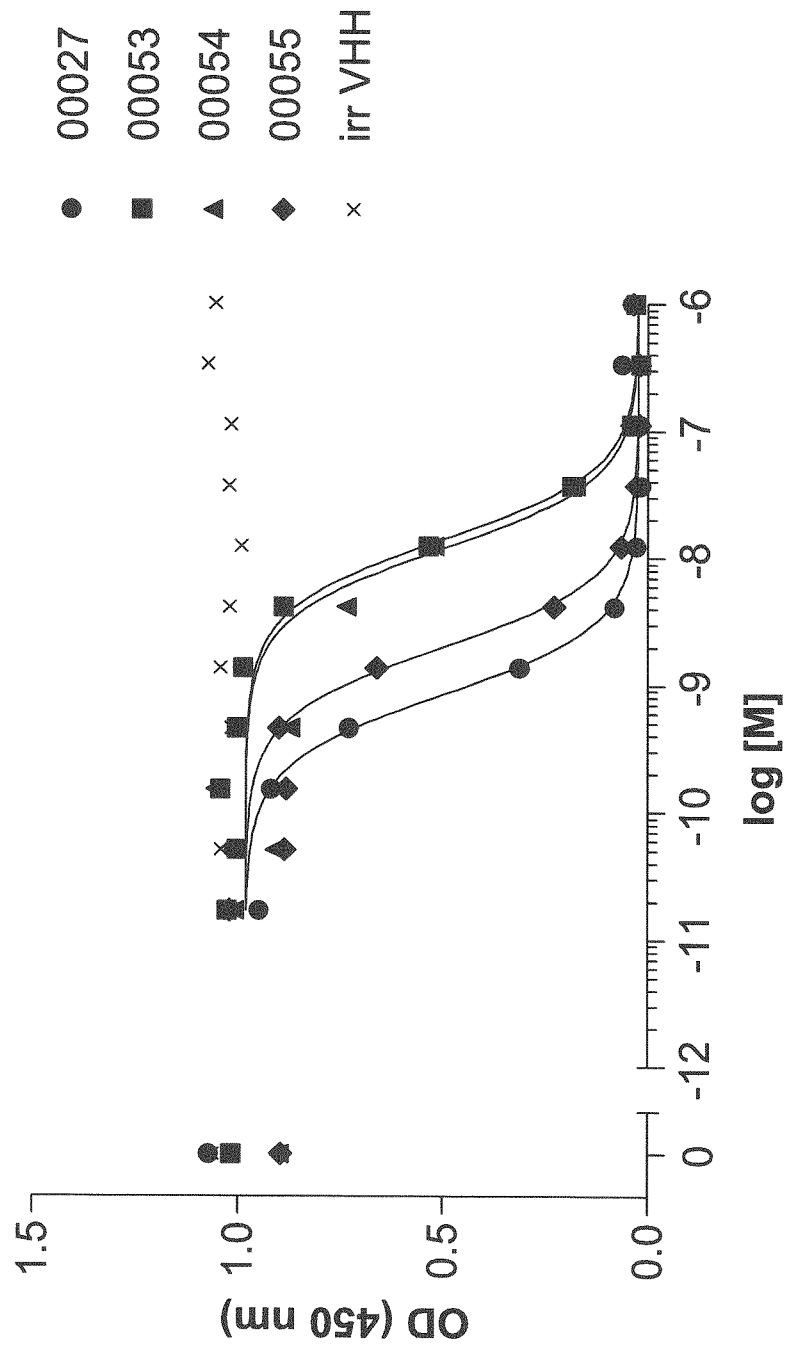


Fig. 17A

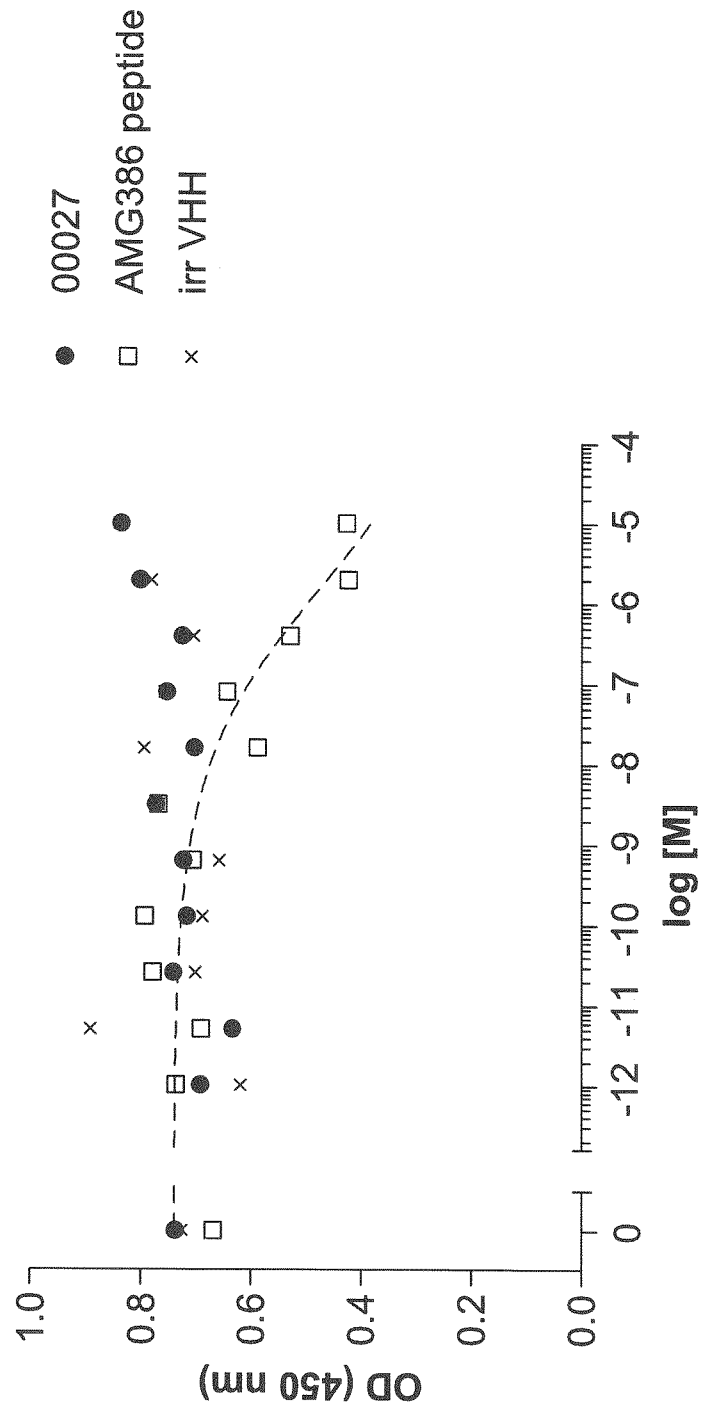


Fig. 17B

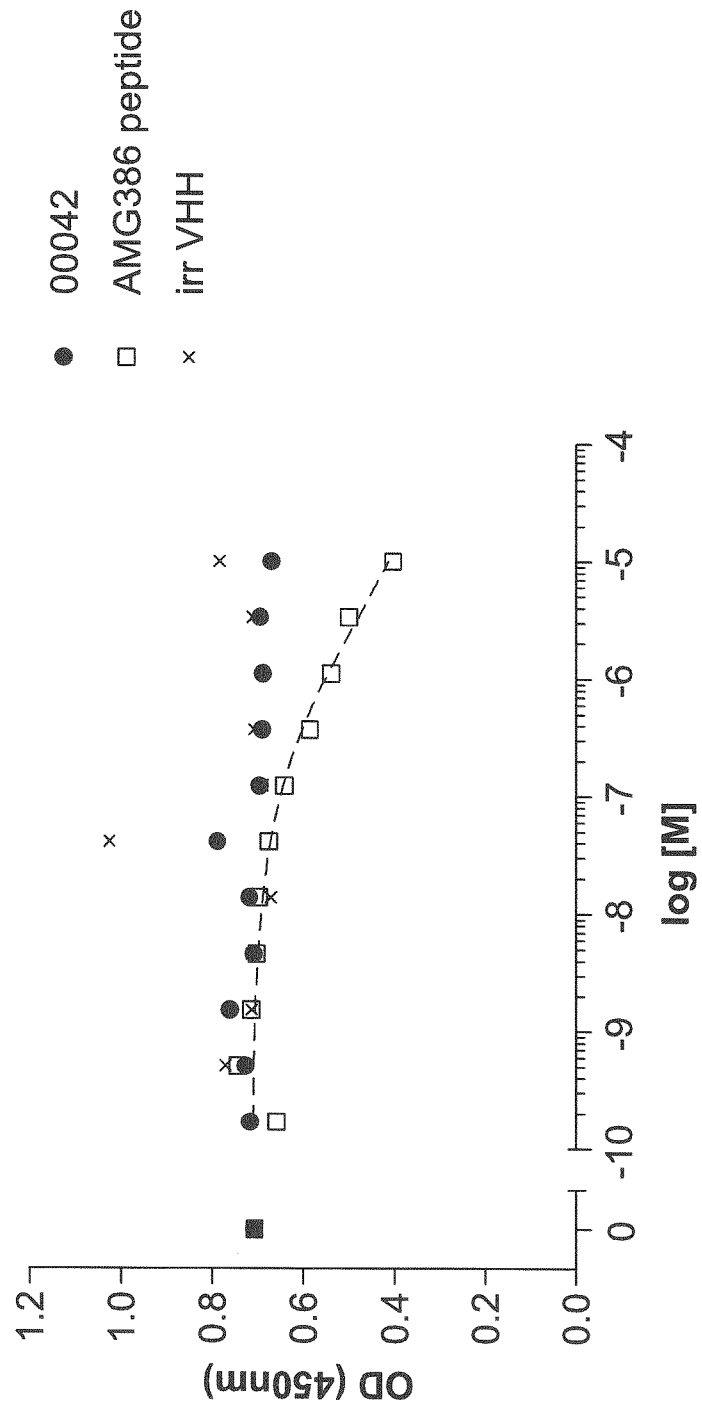


Fig. 18-1B

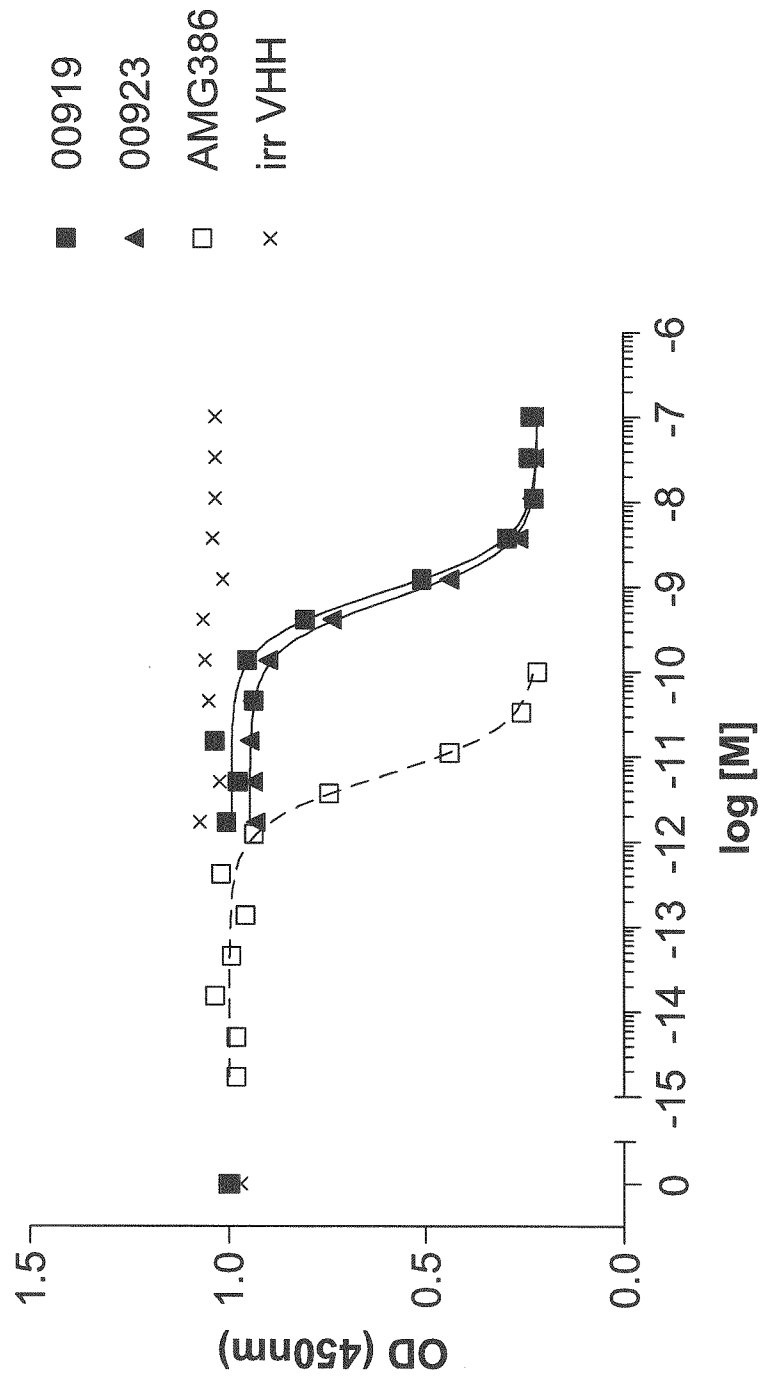


Fig. 18-2

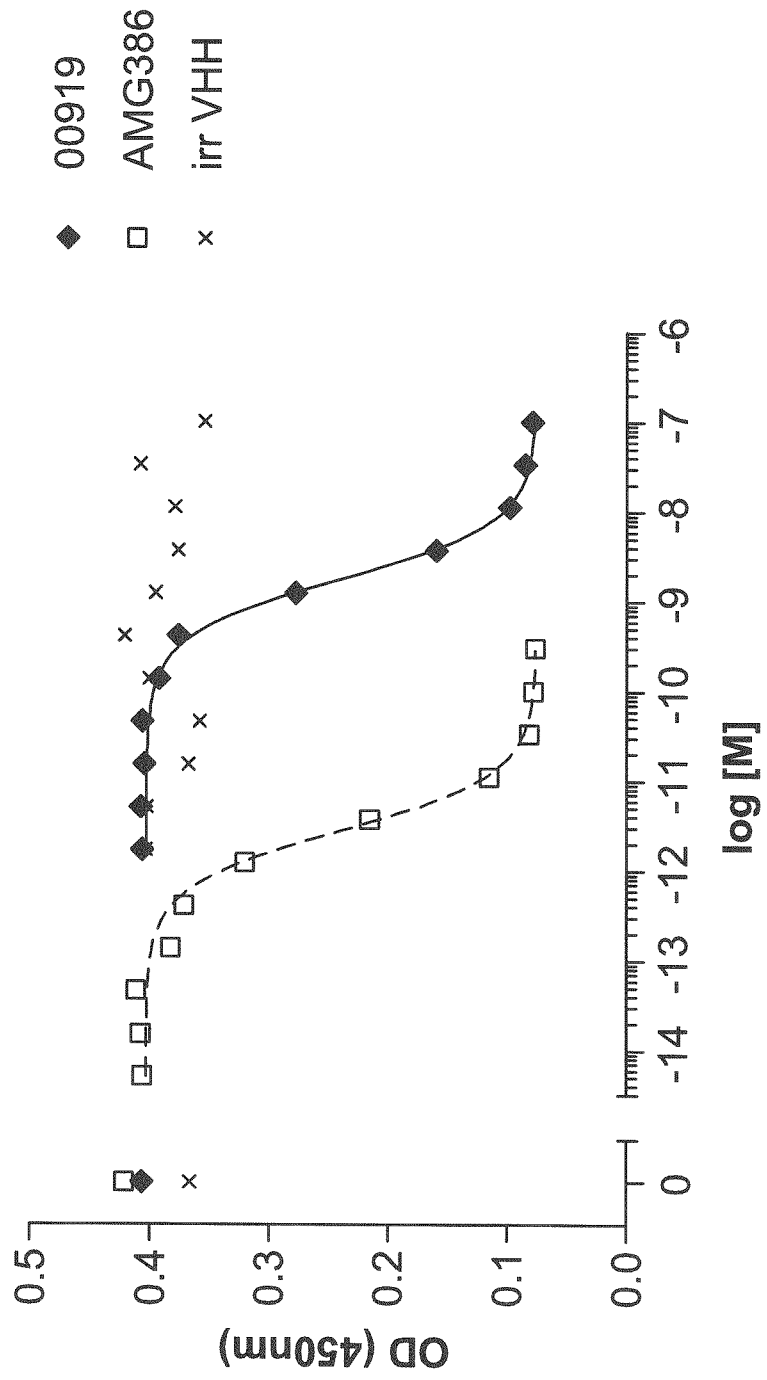


Fig. 18-3

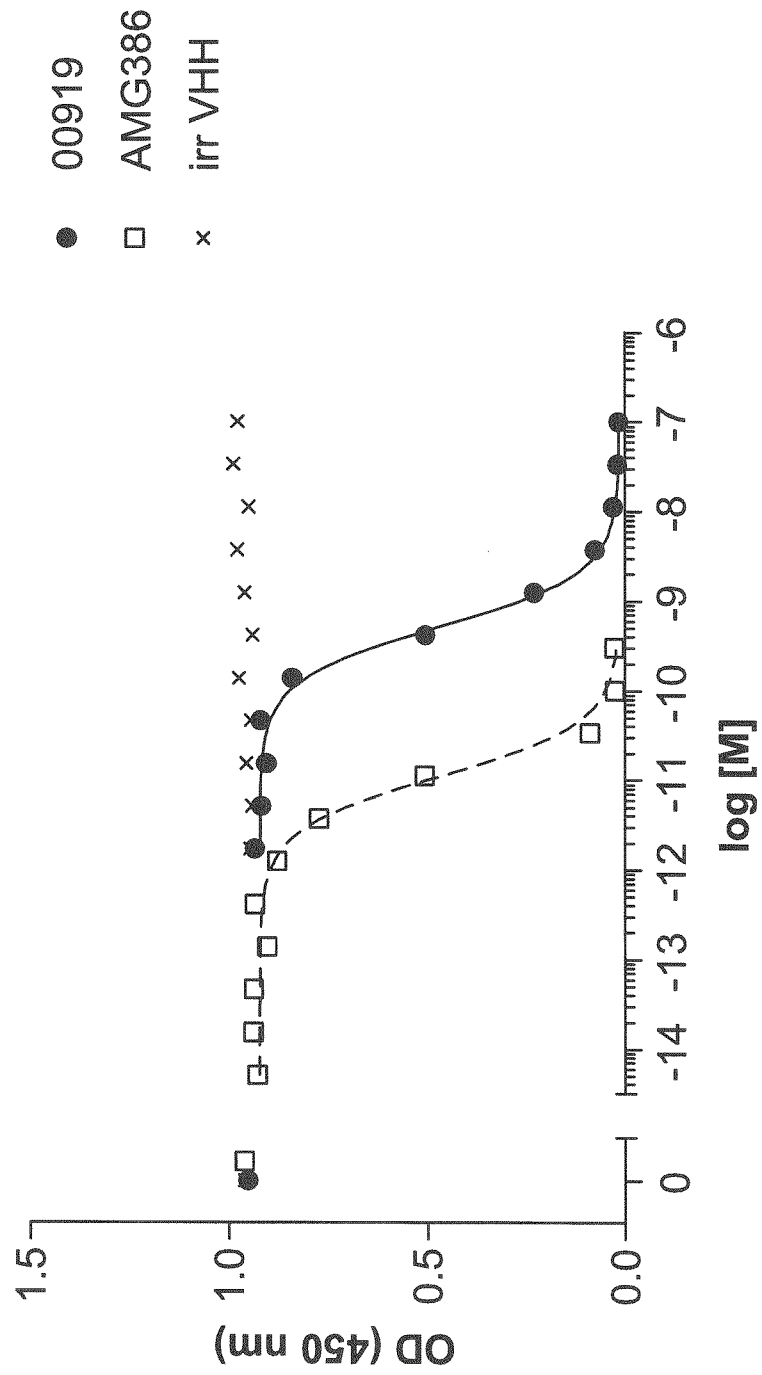


Fig. 20-1B

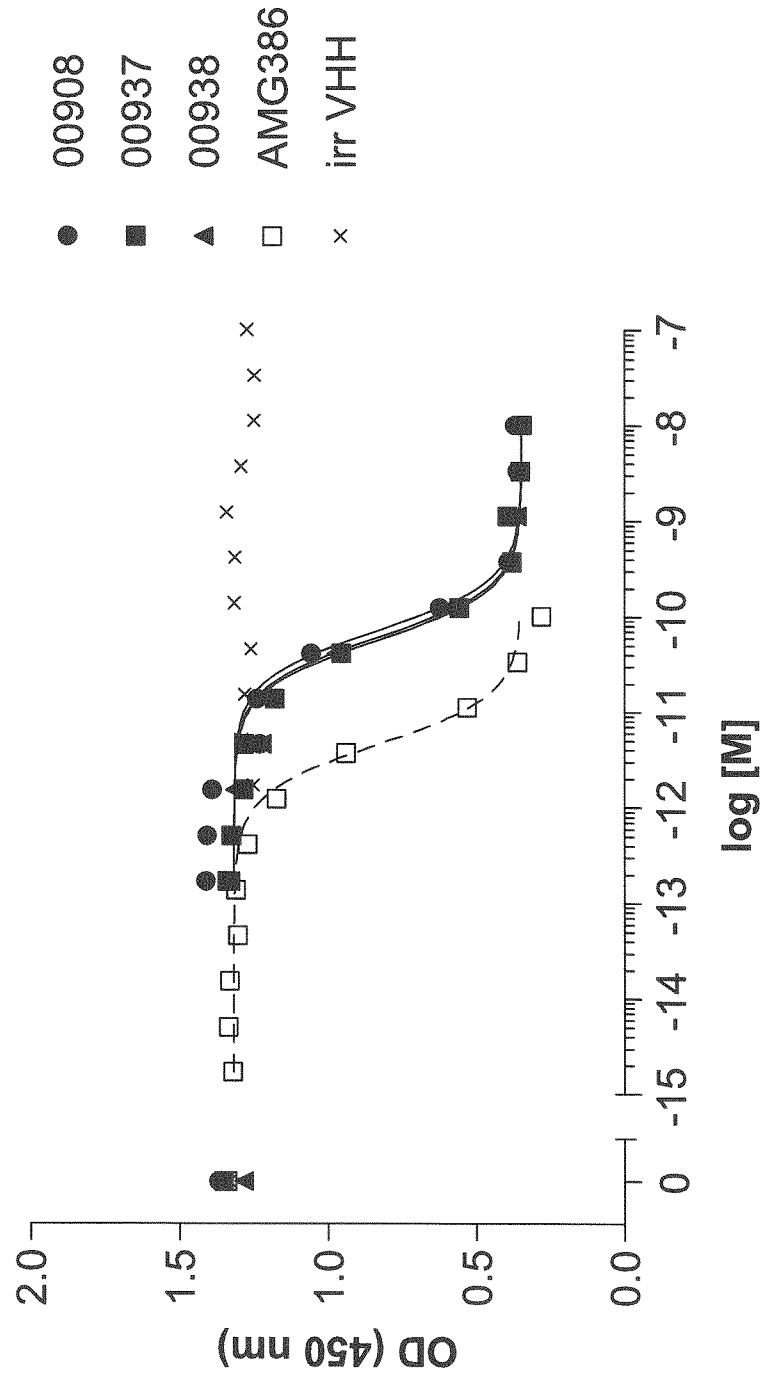


Fig. 20-1C

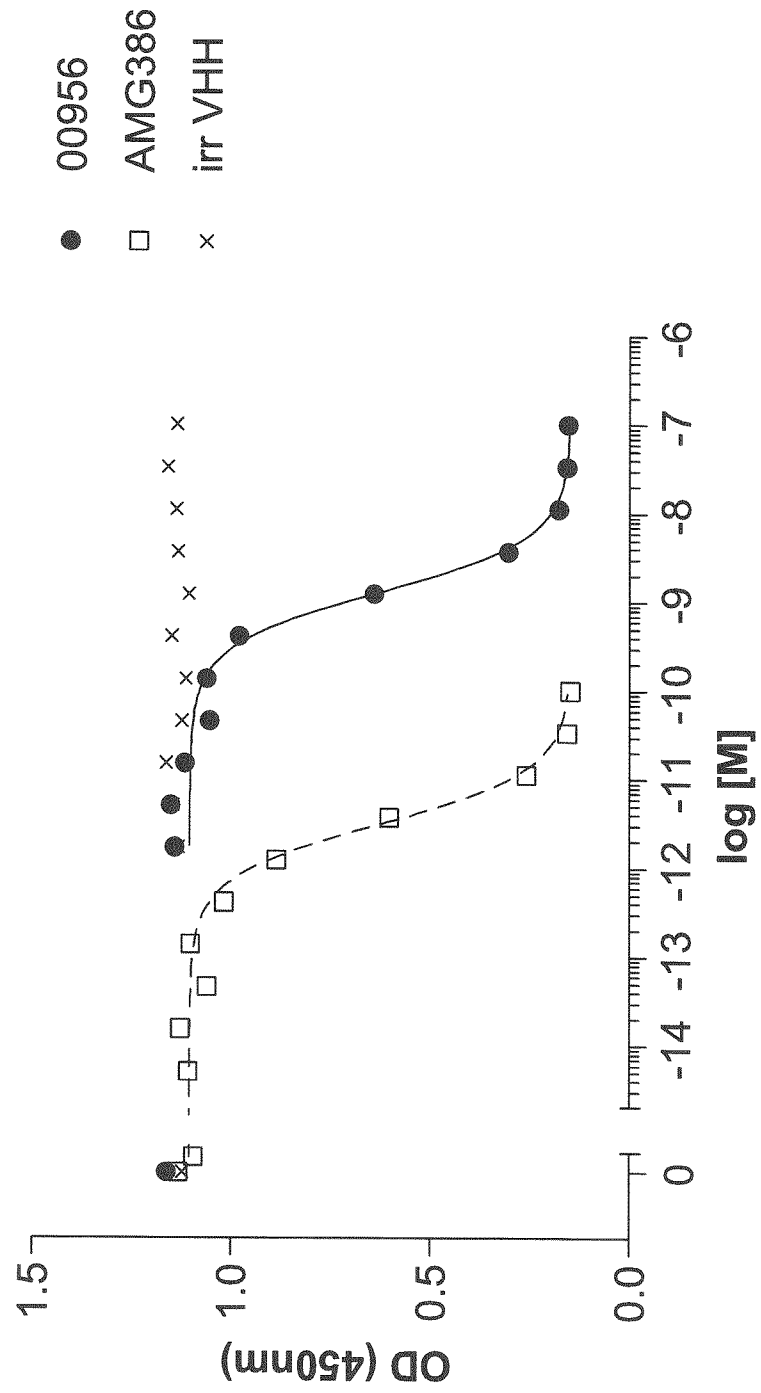


Fig. 20-2B

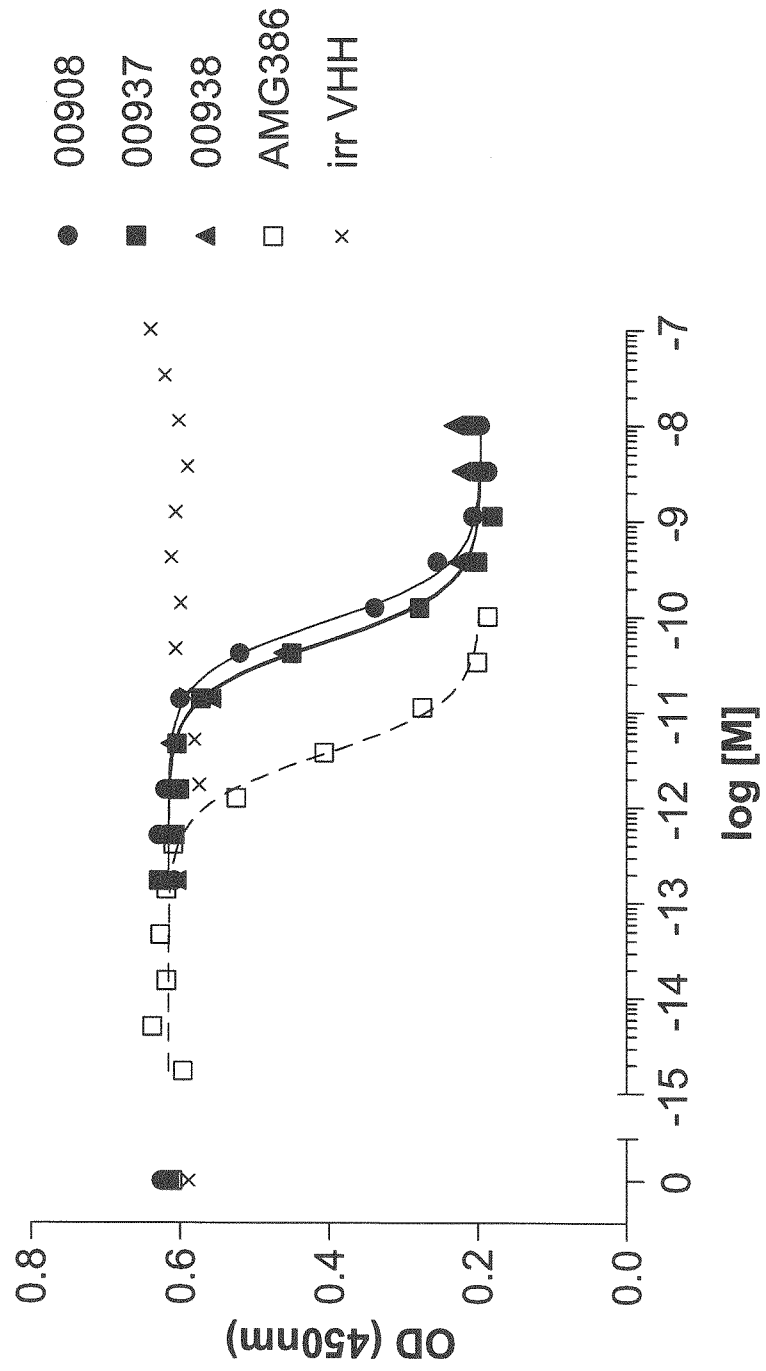


Fig. 20-2C

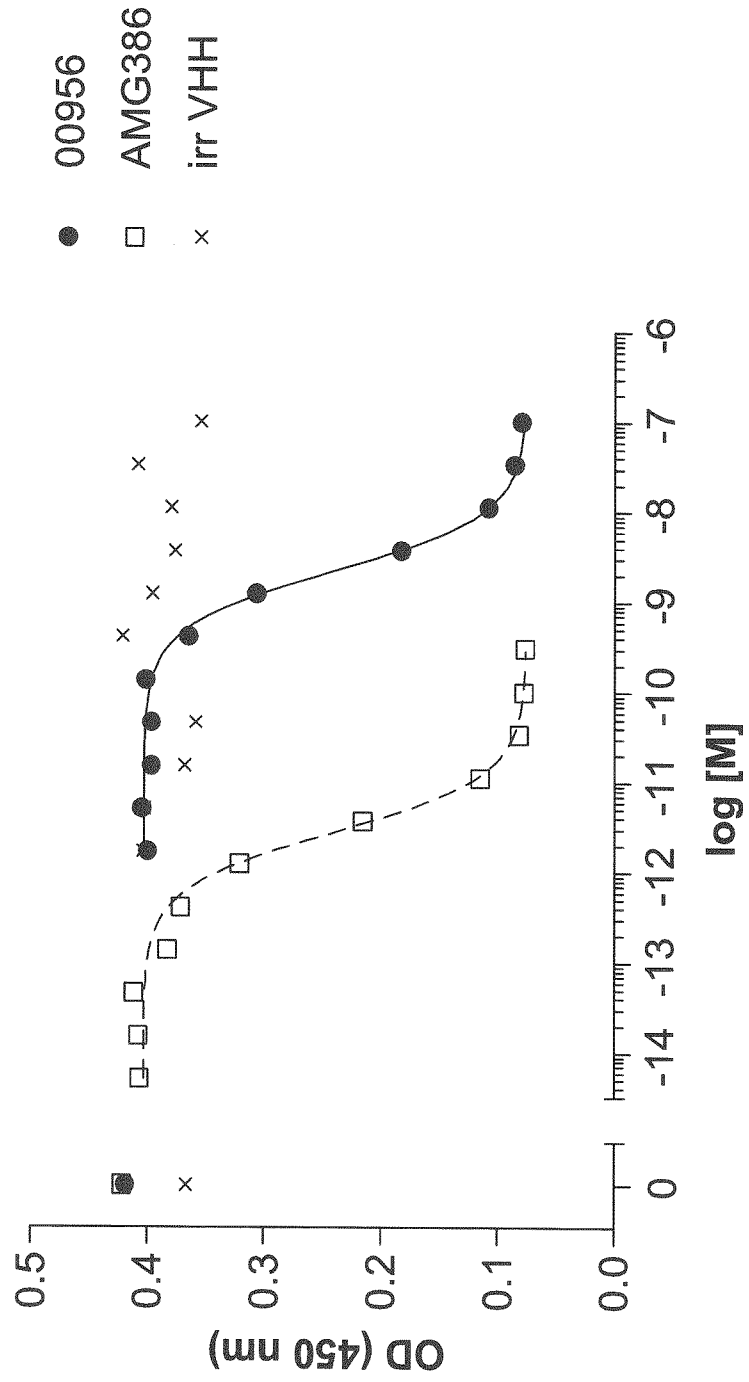


Fig. 20-3A

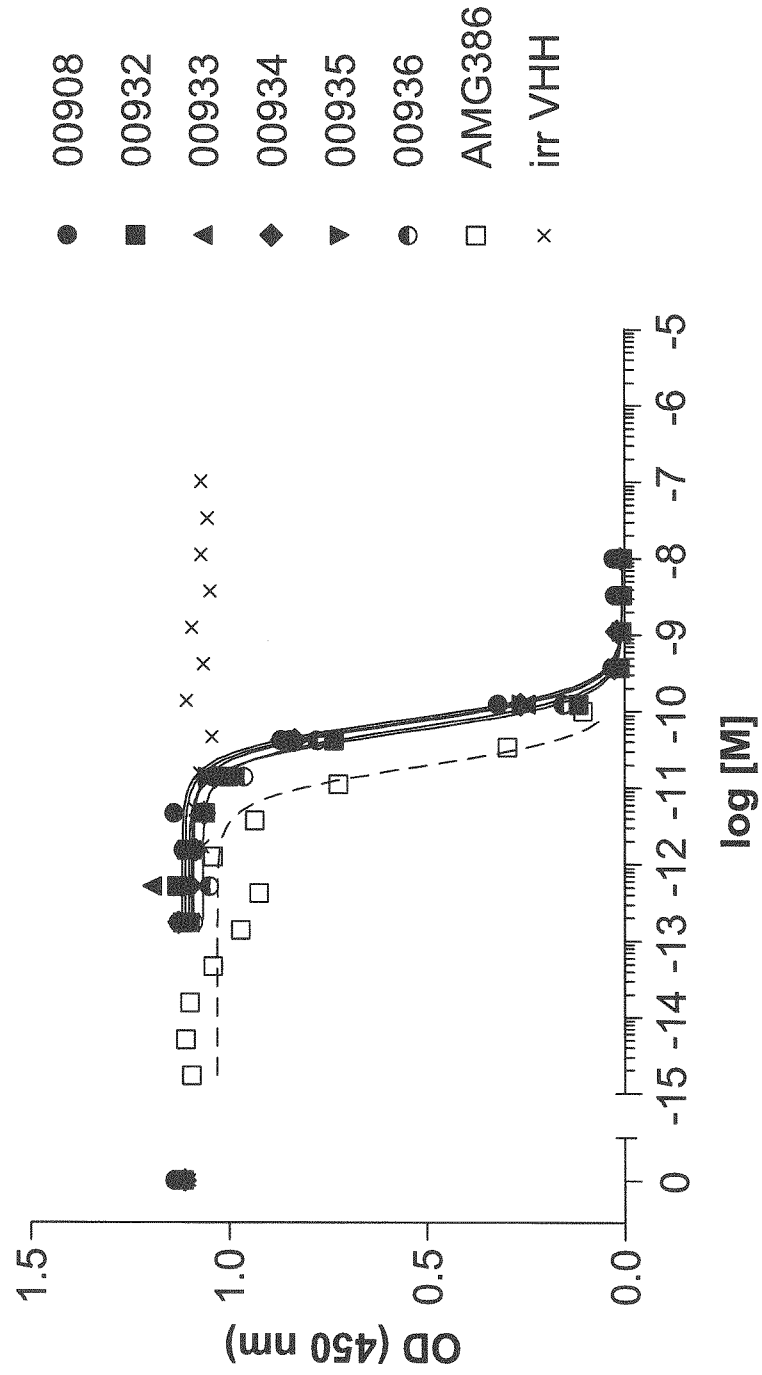


Fig. 20-3B

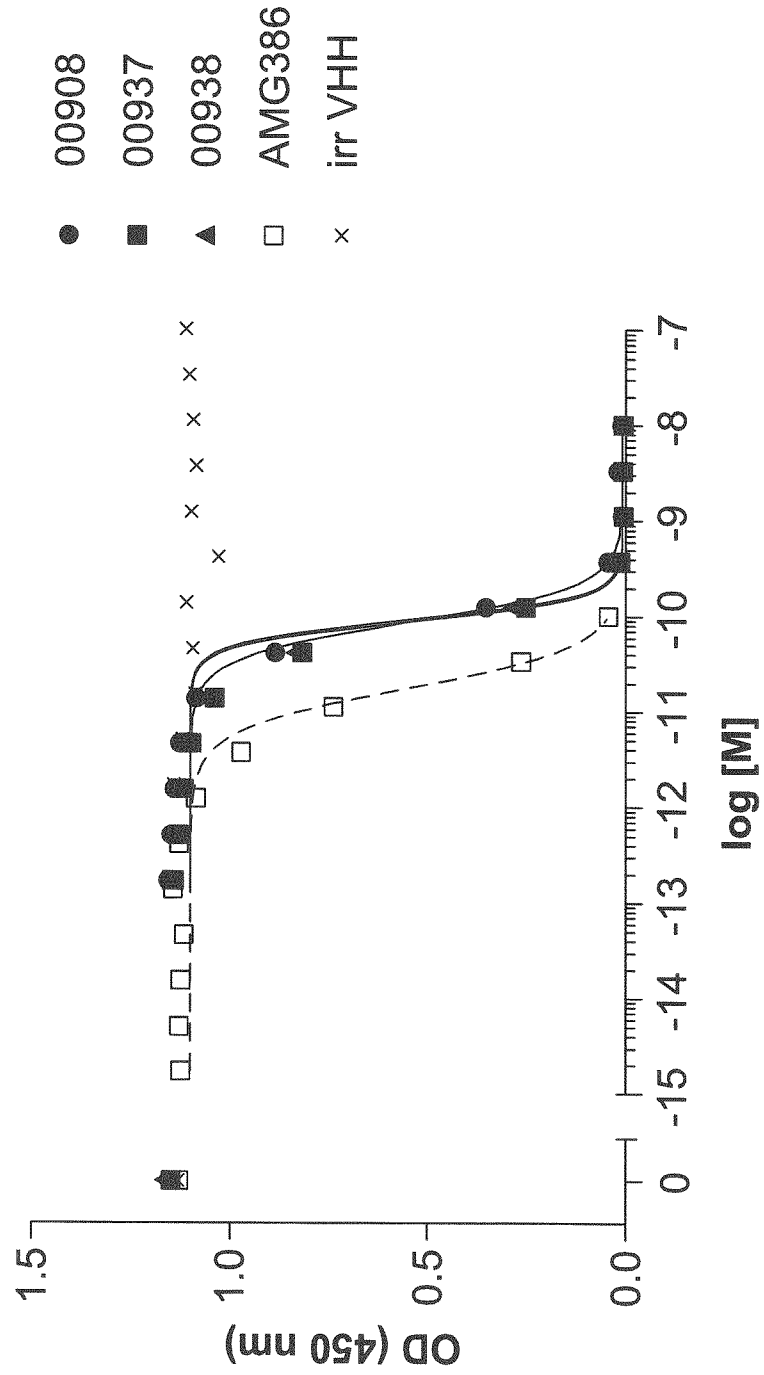
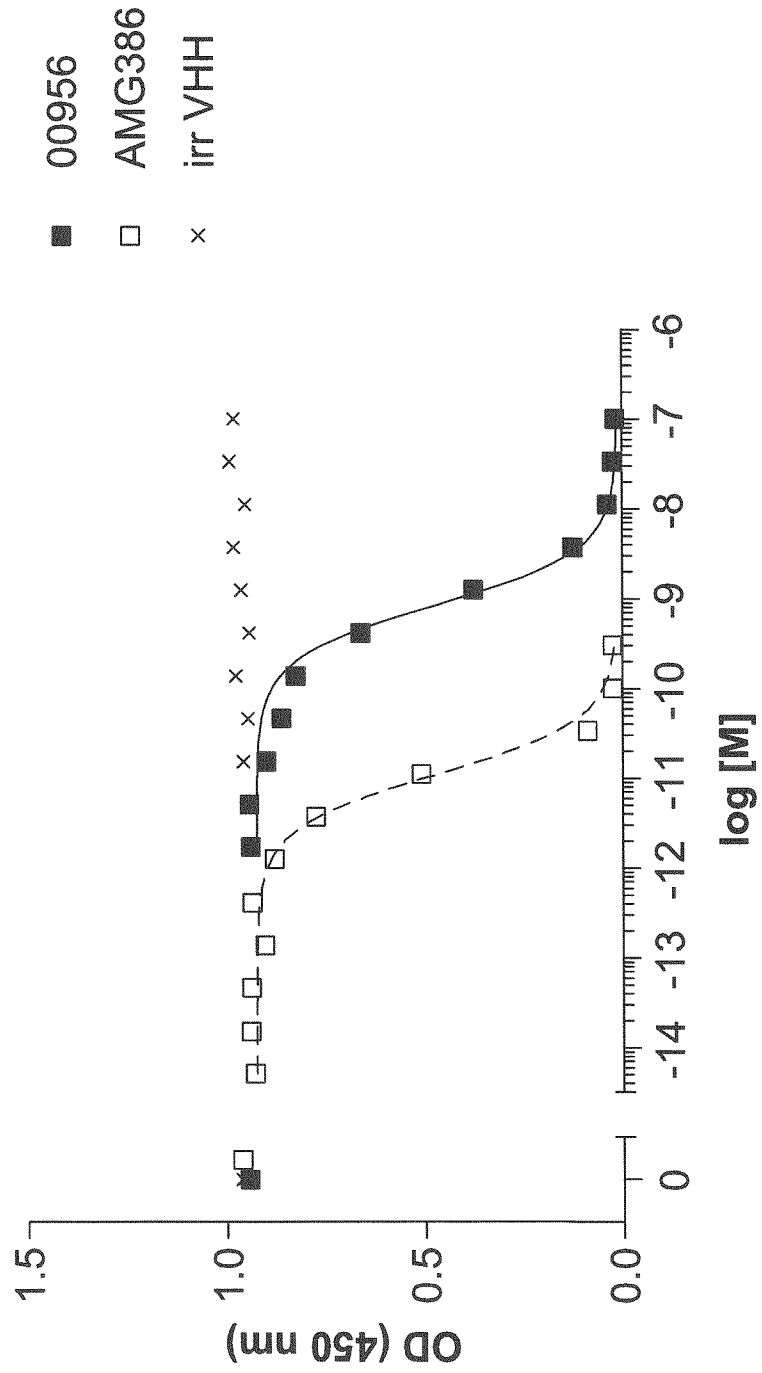


Fig. 20-3C



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35 40 45

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50 55 60

Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Ala Lys Asn Thr Val Tyr
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35 40 45

Al a Al a Ile Ser Gly Ser Gly Ser Ser Thr Asp Ser Al a Gl n Gly Arg
50 55 60

Phe Thr Ile Ser Arg Asp Asn Al a Lys Asn Thr Val Tyr Leu Gl n Met
65 70 75 80

Asn Ser Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys Al a Al a Gly
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Ser Cys Ile Ser Arg Ser Ala Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

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

Leu Gln Met Asn Ser Leu Lys Ala Asp Asp Thr Ala Val Tyr Tyr Cys
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 35 40 45

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 35 40 45

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

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

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

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Ser Ser
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 35 40 45

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 50 55 60

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85 90 95

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

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

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

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Ser Ser
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 35 40 45
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 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
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 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
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Thr Hi s Ile Thr Trp Asn Arg Gly Ser Thr Tyr Tyr Al a Asp Ser Val
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Leu Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Al a Val
35 40 45

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Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Al a Lys Asn Thr Val Tyr
65 70 75 80

Leu Gl n Met Asn Ser Leu Lys Ala Asp Asp Thr Ala Val Tyr Tyr Cys
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20 25 30

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35 40 45

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Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Ala Lys Asn Thr Val Tyr
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20 25 30

eol f-seql . txt

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Lys Gl u Arg Phe Thr Val Ser Arg Asp Asn Asp Lys Asn Thr Val Tyr
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50 55 60

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

Leu Gl n Met Asn Ser Leu Lys Ala Gl u Asp Thr Ala Val Tyr Tyr Cys
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35 40 45

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Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
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Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Ala Val Tyr Tyr Cys
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Ser Tyr
 20 25 30

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

Thr Ala Val Ser Trp Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

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

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

Ala Ala Gln Ser Thr Ile Val Glu Val Thr Thr Leu Glu Ala Tyr Asp
 100 105 110

Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
 115 120

<210> 19
 <211> 122
 <212> PRT
 <213> Lama gl ama

<400> 19

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Ser Val Gln Ala Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Glu Arg Thr Phe Ser Pro Tyr
 20 25 30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
 35 40 45

Ala His Ile Thr Trp Ser Ala Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

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

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

Ala Ala Lys Arg Arg Tyr Gly Ile Val Asp Arg Asp Tyr Asn Asp Trp
100 105 110

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

<210> 20
<211> 116
<212> PRT
<213> Lama gl ama

<400> 20

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

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

Ser Ala Thr Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Phe
35 40 45

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

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

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

Asn Val Leu Leu Trp Ser Gly Asn Leu Trp Gly Gln Gly Thr Gln Val
100 105 110

Thr Val Ser Ser
115

<210> 21
<211> 116
<212> PRT
<213> Lama gl ama

<400> 21

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ile Ala Ser Gly Arg Asp Ile Phe Ser Ile

Thr Ala Ile Gly Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Glu Phe
35 40 45

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

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

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

Asn Val Leu Leu Trp Ser Ala Asn Tyr Trp Gly Gln Gly Thr Gln Val
100 105 110

Thr Val Ser Ser
115

<210> 22
<211> 126
<212> PRT
<213> Lama gl ama

<400> 22

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ala Phe Asp Asp His
20 25 30

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

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

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

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

Ala Ala Gly Pro Ala Trp Gly Arg Pro Ala Ser Pro Leu Pro Tyr Glu
100 105 110

Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120 125

<210> 23
<211> 134

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<212> PRT
 <213> Lama gl ama
 <400> 23

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

<210> 24
 <211> 125
 <212> PRT
 <213> Lama gl ama
 <400> 24

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Al a Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Val Al a Ser Gly Phe Thr Phe Asp Asp Tyr
 20 25 30
 Al a Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
 35 40 45
 Ser Cys Ile Ser Ser Ser Asp Gly Ser Thr Tyr Tyr Al a Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Gly Asp Asn Al a Lys Asn Thr Val Tyr
 65 70 75 80

Leu Gl n Met Asn Ser 85 Leu Lys Pro Gl u Asp 90 Thr Al a Val Tyr Tyr Cys 95

Al a Al a Gly Ile 100 Thr Pro Cys Ser Asp 105 Tyr Thr Gl n Thr Tyr 110 Gl u Tyr

Asp Val Trp 115 Gly Gl n Gly Thr Gl n 120 Val Thr Val Ser Ser 125

<210> 25
<211> 134
<212> PRT
<213> Lama gl ama

<400> 25

Gl u Val Gl n Leu Val 5 Gl u Ser Gly Gly 10 Gl y Leu Val Gl n Al a Gly 15 Gl y

Ser Leu Arg Leu 20 Ser Cys Al a Al a Ser 25 Gl y Phe Thr Phe Asp 30 Asp Tyr

Al a Ile Gly 35 Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg 45 Gl u Gly Val

Ser Cys 50 Ile Ser Arg Ser Asp 55 Gly Ser Thr Ser Tyr 60 Al a Asp Ser Val

Lys Gly Arg Phe Thr 70 Ile Ser Ser Asp Asn 75 Al a Lys Asn Thr Val Tyr 80

Leu Val Met Asn Ser 85 Leu Lys Pro Gl u Asp 90 Thr Al a Val Tyr Tyr Cys 95

Thr Al a Val Pro 100 Al a Thr Arg Arg Thr 105 Pro Gl n Met Val Val 110 Al a Asn

Met Cys Trp 115 Leu Al a Gl u Tyr Gl u 120 Tyr Asp Tyr Trp Gly 125 Gl n Gly Thr

Gl n Val Thr Val Ser Ser 130

<210> 26
<211> 125
<212> PRT
<213> Lama gl ama

<400> 26

Gl u Val Gl n Leu Val 5 Gl u Ser Gly Gly 10 Gl y Leu Val Gl n Al a Gly 15 Gl y

Ser Leu Arg Leu 20 Ser Cys Al a Al a Ser 25 Gl y Phe Thr Phe Asp 30 Asp Tyr

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Al a Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

Ser Cys Ile Ser Ser Ser Asp Gly Ser Thr Tyr Tyr Al a Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Al a Lys Asn Thr Val Tyr
65 70 75 80

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Al a Gly Ile Thr Pro Cys Ser Asp Tyr Thr Gl n Thr Tyr Gl u Tyr
100 105 110

Asp Val Trp Gly Gl n Gly Thr Gl n Val Thr Val Ser Ser
115 120 125

<210> 27
<211> 134
<212> PRT
<213> Lama gl ama

<400> 27

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Al a Gly Gly
1 5 10 15

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

Al a Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

Ser Cys Ile Ser Ser Ser Asp Gly Ser Thr Al a Tyr Al a Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Al a Lys Asn Thr Val Tyr
65 70 75 80

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Thr Al a Val Pro Al a Thr Arg Arg Thr Pro Gl n Met Val Val Al a Asn
100 105 110

Val Cys Trp Leu Al a Gl u Tyr Gl u Tyr Asp Tyr Trp Gly Gl n Gly Thr
115 120 125

Gl n Val Thr Val Ser Ser
130

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<210> 28
<211> 132
<212> PRT
<213> Lama gl ama

<400> 28

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Al a Gly Gly
1 5 10 15

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

Al a Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

Ser Tyr Ile Ser Ser Ser Asp Gly Ser Thr Tyr Tyr Al a Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ser Ser Ser Asp Asn Al a Lys Asn Thr Val Tyr
65 70 75 80

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Al a Arg Pro Thr Leu Arg Val Arg Leu Asp Asn Asp Arg His His
100 105 110

Leu Leu Tyr Gl u Tyr Gl u Tyr Asp Tyr Trp Gly Gl n Gly Thr Gl n Val
115 120 125

Thr Val Ser Ser
130

<210> 29
<211> 134
<212> PRT
<213> Lama gl ama

<400> 29

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Al a Gly Gly
1 5 10 15

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

Thr Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

Ser Cys Ile Ser Ser Ser Asp Gly Ser Thr Ser Tyr Al a Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Al a Lys Asn Thr Val Tyr

eol f-seql . txt

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
35 40 45

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

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

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

Thr Ala Val Pro Ala Thr Arg Arg Thr Pro Gln Met Val Asp Ala Asn
100 105 110

Met Cys Trp Leu Ala Glu Tyr Glu Tyr Asp Tyr Trp Gly Gln Gly Thr
115 120 125

Gln Val Thr Val Ser Ser
130

<210> 32
<211> 127
<212> PRT
<213> Lama gl ama

<400> 32

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ala Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Arg Phe Gly Gly His
20 25 30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Glu Glu Arg Glu Phe Val
35 40 45

Ala Thr Ile Tyr Trp Thr Ser Gly Met Thr Arg Tyr Ala Gly Ser Val
50 55 60

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

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

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

Al a Tyr Asp Tyr Trp Gly Gl n Gly Thr Gl n Val Thr Val Ser Ser
 115 120 125

<210> 33
 <211> 127
 <212> PRT
 <213> Lama gl ama

<400> 33

Gly Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Al a Gl n Al a Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Al a Al a Ser Gly Arg Arg Phe Gly Gly Hi s
 20 25 30

Al a Met Gly Trp Phe Arg Gl n Al a Pro Gly Lys Asp Arg Gl u Phe Val
 35 40 45

Al a Thr Ile Tyr Trp Thr Thr Gly Met Thr Arg Tyr Al a Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Al a Gl u Asn Thr Val Phe
 65 70 75 80

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
 85 90 95

Al a Leu Ile Arg Asp Phe Asn Ile Arg Leu Asp Val Thr Ser Al a Ser
 100 105 110

Al a Tyr Gly Tyr Trp Gly Gl n Gly Thr Gl n Val Thr Val Ser Ser
 115 120 125

<210> 34
 <211> 123
 <212> PRT
 <213> Lama gl ama

<400> 34

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Val Gly Asp
 1 5 10 15

Ser Leu Arg Leu Ser Cys Al a Al a Ser Gly Arg Thr Phe Ser Thr Tyr
 20 25 30

Leu Met Val Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Phe
 35 40 45

Al a Al a Gly Ile Trp Ser Ser Gly Asp Thr Al a Tyr Al a Asp Ser Val
 50 55 60

Arg Gly Arg Phe Thr Ile Ser Arg Asp Asn Al a Lys Asn Thr Val Tyr
 65 70 75 80

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Leu Gl n Met Asn Ser Leu Lys Thr Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Gly Ser Tyr Asp Gly Asn Tyr Tyr Ile Pro Gly Phe Tyr Lys Asp
100 105 110

Trp Gly Gl n Gly Thr Gl n Val Thr Val Ser Ser
115 120

<210> 35
<211> 123
<212> PRT
<213> Lama gl ama
<400> 35

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Val Gly Asp
1 5 10 15

Ser Leu Arg Leu Ser Cys Al a Al a Ser Gly Arg Thr Phe Ser Thr Tyr
20 25 30

Leu Val Val Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Phe
35 40 45

Al a Al a Al a Ile Trp Ser Ser Gly Asp Thr Al a Tyr Al a Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Al a Lys Asn Thr Val Tyr
65 70 75 80

Leu Gl n Met Asn Ser Leu Lys Al a Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Gly Ser Tyr Gly Gly Asn Tyr Tyr Ile Pro Gly Phe Tyr Gl u Asp
100 105 110

Trp Gly Gl n Gly Thr Gl n Val Thr Val Ser Ser
115 120

<210> 36
<211> 121
<212> PRT
<213> Lama gl ama
<400> 36

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Al a Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Al a Al a Ser Gly Arg Thr Phe Ser Arg Asn
20 25 30

Al a Met Ala Trp Phe Arg Gln Val Pro Gly Lys Val Arg Gl u Phe Val
 35 40 45

Al a Gly Ile Arg Trp Asn Val Gly Arg Leu Asp Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Gl u Asn Thr Val Tyr
 65 70 75 80

Leu Gln Met Asn Asp Leu Lys Thr Gl u Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Al a Ala Tyr Ala Gly Leu Val Phe Ser Gly Ile Pro Asp Tyr Trp Gly
 100 105 110

Gln Gly Thr Gln Val Thr Val Ser Ser
 115 120

<210> 37
 <211> 118
 <212> PRT
 <213> Lama gl ama

<400> 37

Gl u Val Gln Leu Val Gl u Ser Gly Arg Gly Leu Val Gln Ala Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ser Ile Phe Ser Ile Asn
 20 25 30

Al a Met Leu Trp Tyr Arg Gln Ala Pro Gly Lys Gln Arg Gl u Leu Val
 35 40 45

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

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

Gln Met Asn Ser Leu Lys Pro Gl u Asp Thr Ala Val Tyr Tyr Cys Ala
 85 90 95

Al a Asp Ser Asp Tyr Ser Ser Asp Tyr Tyr Tyr Trp Gly Gln Gly Thr
 100 105 110

Gln Val Thr Val Ser Ser
 115

<210> 38
 <211> 133
 <212> PRT
 <213> Lama gl ama

<400> 38

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

<210> 39

<211> 124

<212> PRT

<213> Lama gl ama

<400> 39

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Al a Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Al a Al a Ser Gly Gly Thr Phe Ser Ser Tyr
 20 25 30
 Ser Met Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Phe Ile
 35 40 45
 Al a Al a Ile Asn Trp Asn Gly Asp Ser Thr Tyr Tyr Gl u Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Val Ser Arg Asp Asn Al a Lys Asn Thr Val Tyr
 65 70 75 80
 Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
 85 90 95

eol f-seql . txt

Al a Al a Thr Gly Trp Gly Arg Al a Tyr Gl u Gl n Al a Tyr Gl u Tyr Asp
100 105 110

Val Trp Gly Gl n Gly Thr Gl n Val Thr Val Ser Ser
115 120

<210> 40
<211> 119
<212> PRT
<213> Lama gl ama

<400> 40

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gl y Leu Val Gl n Pro Gly Gly
1 5 10 15

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

Al a Met Ser Trp Val Arg Gl n Al a Pro Gly Lys Gly Leu Gl u Trp Val
35 40 45

Ser Thr Ile Ser Trp Asn Asp Gl u Tyr Thr Tyr Tyr Al a Gl u Ser Met
50 55 60

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

Leu Gl n Met Asn Ser Leu Lys Ser Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Lys Gly Gly Ser Arg Leu Tyr Asp Tyr Hi s Tyr Trp Gly Gl n Gly
100 105 110

Thr Gl n Val Thr Val Ser Ser
115

<210> 41
<211> 123
<212> PRT
<213> Lama gl ama

<400> 41

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gl y Leu Val Gl n Al a Gly Gly
1 5 10 15

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

Al a Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

Ser Cys Ile Ser Ser Ser Asp Gly Ser Thr Tyr Tyr Al a Asp Ser Val

50

55

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

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

Ala Ala Arg Pro Pro Phe His Ser Cys Ser Glu Tyr Glu Asn Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 42
<211> 120
<212> PRT
<213> Lama gl ama
<400> 42

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

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

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

Ala Ala Ile Ser Gly Ser Gly Ser Ser Thr Asp Ser Ala Lys Asp Arg
50 55 60

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

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

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

Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 43
<211> 116
<212> PRT
<213> Lama gl ama
<400> 43

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

eol f-seql . txt

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

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

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

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

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

Asn Val Leu Leu Trp Ser Gly Asn Tyr Trp Gly Gln Gly Thr Gln Val
100 105 110

Thr Val Ser Ser
115

<210> 44
<211> 132
<212> PRT
<213> Lama gl ama

<400> 44

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
35 40 45

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

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

Leu Gln Ile Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ala Arg Pro Thr Leu Arg Val Arg Leu Asp Asn Asp Arg His His
100 105 110

Leu Leu Tyr Glu Tyr Glu Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val
115 120 125

Thr Val Ser Ser
130

<210> 45
<211> 132
<212> PRT
<213> Lama gl ama

<400> 45

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
35 40 45

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

Lys Gly Arg Val Thr Ser Ser Ser Asp Asn Ala Lys Asn Thr Val Tyr
65 70 75 80

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

Ala Ala Arg Pro Thr Leu Arg Val Arg Leu Asp Asn Asp Arg His His
100 105 110

Leu Leu Tyr Glu Tyr Glu Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val
115 120 125

Thr Val Ser Ser
130

<210> 46
<211> 124
<212> PRT
<213> Lama gl ama

<400> 46

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

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

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

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

eol f-seql . txt

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

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

Ala Ala Ser Ile Ala Leu Val Gly Gly Val Thr Pro His Ser Tyr Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 47
<211> 123
<212> PRT
<213> Lama gl ama

<400> 47

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

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

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

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

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

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

Ala Gly Ser Tyr Gly Gly Asn Tyr Tyr Ile Pro Gly Phe Tyr Lys Asp
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 48
<211> 123
<212> PRT
<213> Lama gl ama

<400> 48

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

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

Leu Met Val Gly Trp Phe Arg Gl n Ala Pro Gly Lys Gl u Arg Gl u Phe
35 40 45

Al a Ala Gly Ile Trp Ser Ser Gly Gly Thr Ala Tyr Ala Asp Ser Val
50 55 60

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

Leu Gl n Met Asn Ser Leu Lys Ala Gl u Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Al a Gly Ser Tyr Asp Gly Asn Tyr Tyr Ile Pro Gly Phe Tyr Lys Asp
100 105 110

Trp Gly Gl n Gly Thr Gl n Val Thr Val Ser Ser
115 120

<210> 49
<211> 128
<212> PRT
<213> Lama gl ama

<400> 49

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Ala Gly Gly
1 5 10 15

Ser Leu Gly Leu Ser Cys Ala Ala Ser Gl u Arg Thr Leu Pro Ser Tyr
20 25 30

Val Met Gly Trp Phe Arg Gl n Ala Pro Gly Lys Gl u Leu Gl u Phe Val
35 40 45

Al a Gly Ile Ser Trp Ser Ser Gly Arg Thr Tyr Tyr Thr Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Ala Ala Gl u Asn Thr Trp Tyr
65 70 75 80

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Al a Ser Asn Ser Val Ser Gl u Pro Thr Leu Hi s Thr Trp Gl n Tyr Gl u
100 105 110

Al a Ser Tyr Asp Tyr Trp Gly Gl n Gly Thr Gl n Val Thr Val Ser Ser
115 120 125

<210> 50

eol f-seql . txt

<211> 124
<212> PRT
<213> Lama gl ama

<400> 50

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

<210> 51
<211> 121
<212> PRT
<213> Lama gl ama

<400> 51

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

eol f-seql . txt

Al a Al a Tyr Ala Gly Leu Val Tyr Ser Gly Ile Pro Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 52
<211> 124
<212> PRT
<213> Lama gl ama

<400> 52

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

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

Ala Met Gly Trp Phe Arg Arg Val Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

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

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

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

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

Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 53
<211> 124
<212> PRT
<213> Lama gl ama

<400> 53

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Asp
1 5 10 15

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

Ala Met Gly Trp Phe Arg Arg Val Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

Thr His Ile Thr Trp Asn Arg Gly Ser Thr Tyr Tyr Ala Asp Ser Val

50

55

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

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

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

Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 54
<211> 115
<212> PRT
<213> Lama gl ama
<400> 54

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Val Cys Ser Ala Ser Gly Ile Asp Phe Ser Ile Asn
20 25 30

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

Ala Phe Met Ile Asn Asp Ser Ser Thr Asp Tyr Thr Asp Ser Val Lys
50 55 60

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

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

Thr Ala Tyr Glu Gln His Thr Tyr Trp Gly Gln Gly Thr Gln Val Thr
100 105 110

Val Ser Ser
115

<210> 55
<211> 128
<212> PRT
<213> Lama gl ama
<400> 55

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

eol f-seql . txt

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

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

Ser Cys Ile Thr Pro Ser Asp Asp Arg Thr Tyr Tyr Ala Asp Ser Val
50 55 60

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

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

Ala Ala Val Pro Arg Leu Arg Gly Leu Gly Tyr Trp Pro Tyr Pro Glu
100 105 110

Tyr Glu Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120 125

<210> 56
<211> 124
<212> PRT
<213> Lama gl ama

<400> 56

Lys Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

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

Ala Leu Gly Trp Phe Arg Gln Ala Ala Gly Lys Glu Arg Glu Gly Val
35 40 45

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

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

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

Ala Ala Ser Ile Val Pro Arg Ser Lys Leu Glu Pro Tyr Glu Tyr Asp
100 105 110

Ala Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120

eol f-seql . txt

<210> 57
 <211> 119
 <212> PRT
 <213> Lama gl ama

<400> 57

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
 1 5 10 15

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

Ala Met Ser Trp Val Arg Gl n Ala Pro Gly Lys Gly Leu Gl u Trp Val
 35 40 45

Ser Thr Ile Ser Trp Asn Asp Gl u Tyr Thr Tyr Tyr Ala Gl u Ser Met
 50 55 60

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

Leu Gl n Met Asn Ser Leu Lys Ser Gl u Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Lys Gly Gly Ser Arg Leu Tyr Asp Tyr His Tyr Trp Gly Gl n Gly
 100 105 110

Thr Gl n Val Thr Val Ser Ser
 115

<210> 58
 <211> 131
 <212> PRT
 <213> Lama gl ama

<400> 58

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Ala Gly Gly
 1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gl n Ala Pro Gly Lys Gl u Arg Gl u Gly Val
 35 40 45

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

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

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

eol f-seql . txt

Al a Al a Gly Leu Arg Gly Arg Tyr Tyr Arg Gly Thr Tyr Ser Leu Val
100 105 110

Cys Al a Pro Tyr Gl u Tyr Asp Phe Trp Gly Gl n Gly Thr Gl n Val Thr
115 120 125

Val Ser Ser
130

<210> 59
<211> 131
<212> PRT
<213> Lama gl ama

<400> 59

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Al a Gly Gly
1 5 10 15

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

Al a Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

Ser Cys Ile Ser Ser Ser Asp Gly Ser Thr Tyr Tyr Al a Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Al a Asp Asn Al a Lys Asn Thr Val Tyr
65 70 75 80

Leu Gl n Met His Ser Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Al a Gly Leu Arg Gly Arg Tyr Tyr Ser Gly Ser Asn Tyr Leu Val
100 105 110

Cys Al a Pro Tyr Gl u Tyr Asp Tyr Trp Gly Gl n Gly Thr Gl n Val Thr
115 120 125

Val Ser Ser
130

<210> 60
<211> 125
<212> PRT
<213> Lama gl ama

<400> 60

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Al a Gly Gly
1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
 35 40 45

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

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

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

Ala Ala Asp Phe Ile Ile Ser Ser Lys Arg Leu Cys Leu Asp Leu Phe
 100 105 110

Gly Ser Arg Gly Gln Gly Thr Gln Val Thr Val Ser Ser
 115 120 125

<210> 61
 <211> 125
 <212> PRT
 <213> Lama glama

<400> 61

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Ser Val Gln Ala Gly Gly
 1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
 35 40 45

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

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

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

Ala Ala Gly Ile Thr Pro Cys Ser Asp Tyr Thr Gln Thr Tyr Glu Tyr
 100 105 110

Asp Val Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
 115 120 125

<210> 62

eol f-seql . txt

<211> 134
<212> PRT
<213> Lama gl ama

<400> 62

Gl u Val Gl n Leu Val Gl u Ser Gl y Gl y Gl y Leu Val Gl n Al a Gl y Gl y
1 5 10 15
Ser Leu Arg Leu Ser Cys Al a Al a Ser Gl y Phe Thr Phe Asp Asp Tyr
20 25 30
Al a Ile Gl y Trp Phe Arg Arg Al a Pro Gl y Lys Gl u Arg Gl u Gl y Val
35 40 45
Ser Cys Ile Thr Ser Ser Asp Gl y Ser Thr Ser Tyr Al a Asp Ser Val
50 55 60
Lys Gl y Arg Phe Thr Ile Ser Ser Asp Ser Al a Lys Asn Thr Val Tyr
65 70 75 80
Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95
Ser Val Val Pro Al a Thr Arg Arg Asn Pro Gl n Met Val Val Al a Lys
100 105 110
Lys Cys Trp Leu Al a Gl u Tyr Gl u Tyr Asp Tyr Trp Gl y Gl n Gl y Thr
115 120 125
Gl n Val Thr Val Ser Ser
130

<210> 63
<211> 130
<212> PRT
<213> Lama gl ama

<400> 63

Gl u Val Gl n Leu Val Gl u Ser Gl y Gl y Gl y Leu Val Gl n Al a Gl y Gl y
1 5 10 15
Ser Leu Arg Leu Ser Cys Al a Val Ser Gl y Phe Thr Phe Asp Asp Tyr
20 25 30
Al a Ile Gl y Trp Phe Arg Gl n Al a Pro Gl y Lys Gl u Arg Gl u Gl y Val
35 40 45
Ser Cys Ile Ser Arg Ser Asp Gl y Ser Pro Tyr Tyr Al a Asp Ser Val
50 55 60
Lys Gl y Arg Phe Thr Ile Ser Ser Asp Asn Al a Lys Gl y Thr Val Tyr
65 70 75 80

eol f-seql . txt

Leu Gl n Met Ser Ser Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Al a Ser Trp Ser Gly Al a Tyr Tyr Ser Gly Thr Tyr Tyr Cys Asp
100 105 110

Arg Leu Tyr Gl u Tyr Asp Al a Trp Gly Gl n Gly Thr Gl n Val Thr Val
115 120 125

Ser Ser
130

<210> 64
<211> 123
<212> PRT
<213> Lama gl ama

<400> 64

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Val Gly Asp
1 5 10 15

Ser Leu Arg Leu Ser Cys Al a Al a Ser Gl u Arg Thr Phe Ser Thr Tyr
20 25 30

Leu Met Val Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Phe
35 40 45

Al a Al a Thr Met Trp Ser Ser Gly Asp Thr Al a Tyr Al a Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Al a Lys Asn Thr Val Tyr
65 70 75 80

Leu Gl n Met Asn Ser Leu Lys Al a Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Gly Ser Tyr Gly Gly Asn Tyr Tyr Ile Pro Gly Phe Tyr Gl u Asp
100 105 110

Trp Gly Gl n Gly Thr Gl n Val Thr Val Ser Ser
115 120

<210> 65
<211> 127
<212> PRT
<213> Lama gl ama

<400> 65

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Al a Al a Ser Gly Phe Al a Leu Asp Tyr Tyr

Al a Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

Ser Cys Ile Ser Ser Ser Asp Gly Ser Thr Tyr Tyr Al a Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Al a Lys Asn Thr Val Tyr
65 70 75 80

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Thr Asp Ser Leu Gly Tyr Gly Ser Ser Cys Arg Met Al a Pro Tyr
100 105 110

Gl u Tyr Asp Tyr Trp Gly Gl n Gly Thr Gl n Val Thr Val Ser Ser
115 120 125

<210> 66
<211> 123
<212> PRT
<213> Lama gl ama

<400> 66

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Val Gly Asp
1 5 10 15

Ser Leu Arg Leu Ser Cys Al a Al a Ser Gly Arg Thr Phe Ser Thr Tyr
20 25 30

Leu Met Val Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Phe
35 40 45

Al a Al a Val Ile Trp Ser Ser Gly Gly Thr Al a Tyr Al a Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Al a Lys Asn Thr Val Tyr
65 70 75 80

Leu Gl n Met Asn Ser Leu Lys Al a Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Gly Ser Tyr Asp Gly Asn Tyr Tyr Ile Pro Gly Phe Tyr Lys Asp
100 105 110

Trp Gly Gl n Gly Thr Gl n Val Thr Val Ser Ser
115 120

<210> 67
<211> 130

eol f-seql . txt

<212> PRT
 <213> Lama gl ama
 <400> 67

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

<210> 68
 <211> 123
 <212> PRT
 <213> Lama gl ama
 <400> 68

Gl u Val Gl n Leu Val Gl u Ser Gly Arg Arg Leu Val Gl n Val Gly Asp
 1 5 10 15
 Ser Leu Arg Leu Ala Cys Ala Ala Ser Gly Arg Thr Phe Ser Thr Tyr
 20 25 30
 Leu Met Val Gly Trp Phe Arg Gl n Ala Pro Gly Lys Gl u Arg Gl u Phe
 35 40 45
 Ala Ala Gly Ile Trp Ser Ser Gly Asp Thr Ala Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
 65 70 75 80

eol f-seq1 . txt

Leu Gl n Met Asn Ser 85 Leu Lys Thr Gl u Asp Thr Ala Val Tyr Tyr Cys 95

Ala Gly Ser Tyr 100 Asp Gly Asn Tyr Tyr 105 Ile Pro Gly Phe Tyr 110 Lys Asp

Trp Gly Gl n Gly Thr Gl n Val Thr Val Ser Ser 115 120

<210> 69
<211> 123
<212> PRT
<213> Lama gl ama

<400> 69

Gl u Val Gl n Leu Val 5 Gl u Ser Gly Gly Gl y Leu Val Gl n Val Gly Asp 1 15

Ser Leu Arg Leu 20 Ser Cys Ala Ala Ser 25 Gl u Arg Thr Phe Ser 30 Thr Tyr

Leu Met Val 35 Gly Trp Phe Arg Gl n Ala Pro Gly Lys Gl u Arg Gl u Phe 40 45

Ala Ala Thr Met Trp Val Ser 55 Gly Asp Thr Ala Tyr 60 Ala Asp Ser Val

Lys Gly Arg Phe Thr Ile 70 Ser Arg Asp Asn Pro 75 Lys Asn Thr Val Tyr 80

Leu Gl n Met Asn Ser 85 Leu Lys Ala Gl u Asp Thr Ala Val Tyr Tyr Cys 90 95

Ala Gly Ser Tyr 100 Gly Gly Asn Tyr Tyr 105 Ile Pro Gly Phe Tyr 110 Lys Asp

Trp Gly Gl n Gly Thr Gl n Val Thr Val Ser Ser 115 120

<210> 70
<211> 123
<212> PRT
<213> Lama gl ama

<400> 70

Gl u Val Gl n Leu Val 5 Gl u Ser Gly Gly Gl y Leu Val Gl n Ile Gly Asp 1 15

Ser Leu Arg Leu 20 Ser Cys Ala Ala Ser 25 Gl y Arg Thr Phe Ser 30 Thr Tyr

Leu Met Val 35 Gly Trp Phe Arg Gl n Ala Pro Gly Lys Gl u Arg Gl u Phe 40 45

eol f-seql . txt

Al a Al a Al a Ile Trp Ser Ser Gly Asp Thr Al a Val Al a Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Al a Lys Asn Thr Val Tyr
65 70 75 80

Leu Gl n Met Asn Ser Leu Lys Al a Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Gly Ser Tyr Gly Gly Asn Tyr Tyr Ile Pro Gly Phe Tyr Gl u Asp
100 105 110

Trp Gly Gl n Gly Thr Gl n Val Thr Val Ser Ser
115 120

<210> 71
<211> 122
<212> PRT
<213> Lama gl ama

<400> 71

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
1 5 10 15

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

Al a Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Trp Gl u Gly Val
35 40 45

Ser Cys Ile Ser Ser Ser Asp Gly Ser Thr Tyr Tyr Al a Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Al a Lys Asn Thr Val Tyr
65 70 75 80

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Thr Asp Ser Ile Val Cys Gly Ser Tyr Tyr Gly Met Asp Tyr Trp
100 105 110

Gly Lys Gly Thr Gl n Val Thr Val Ser Ser
115 120

<210> 72
<211> 123
<212> PRT
<213> Lama gl ama

<400> 72

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

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

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

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

Lys Glu Arg Phe Thr Val Ser Arg Asp Asn Asp Lys Asn Thr Val Tyr
65 70 75 80

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

Ala Gly Ser Tyr Asp Gly Asn Tyr Tyr Ile Pro Gly Phe Tyr Lys Asp
100 105 110

Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
115 120

<210> 73
<211> 128
<212> PRT
<213> Lama gl ama

<400> 73

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
35 40 45

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

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

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

Ala Ala Ala Trp Gly Ala Ser Arg Leu Pro Ile Gly Thr Met Pro Pro
100 105 110

Tyr Glu Tyr Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser
Page 43

115

120

125

<210> 74
 <211> 118
 <212> PRT
 <213> Lama gl ama

<400> 74

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Al a Gly Gly
 1 5 10 15

Ser Leu Arg Leu Val Cys Ser Al a Ser Gly Ile Asp Phe Ser Ile Asn
 20 25 30

Val Met Gly Trp Tyr Arg Gl n Al a Pro Gly Lys Gl n Arg Gl u Trp Val
 35 40 45

Al a Phe Ile Gly Ser Gly Gly Ser Thr Asp Tyr Ile Asp Tyr Thr Asp
 50 55 60

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

Leu Tyr Leu Arg Met Asn Asn Leu Asn Val Gl u Asp Thr Al a Val Tyr
 85 90 95

Tyr Cys Asn Thr Al a Tyr Gl u Gl n Hi s Thr Tyr Trp Gly Gl n Gly Thr
 100 105 110

Gl n Val Thr Val Ser Ser
 115

<210> 75
 <211> 125
 <212> PRT
 <213> Lama gl ama

<400> 75

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Al a Gly Gly
 1 5 10 15

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

Al a Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Asp Leu Gl u Gly Val
 35 40 45

Ser Cys Ile Ser Ser Ser Asp Gly Ser Thr Tyr Tyr Al a Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Al a Lys Asn Thr Val Tyr
 65 70 75 80

eol f-seql . txt

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Al a Val Asn Gly Leu Gly Pro Phe Ser Val Pro Val Pro Val Tyr
100 105 110

Asp Phe Trp Gly Gl n Gly Thr Gl n Val Thr Val Ser Ser
115 120 125

<210> 76
<211> 130
<212> PRT
<213> Lama gl ama
<400> 76

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Al a Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Al a Val Ser Gly Leu Pro Phe Asp Asp Tyr
20 25 30

Val Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

Ser Cys Ile Ser Ser Ser Asp Gly Ser Thr Tyr Tyr Al a Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Al a Lys Asn Thr Val Tyr
65 70 75 80

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Al a Al a Tyr Tyr Cys
85 90 95

Al a Al a Gly Gly Pro Arg Ile Asn Ile Al a Thr Met Thr Cys Ser Hi s
100 105 110

Asp Gl u Tyr Gl u Tyr Asp Tyr Trp Gly Gl n Gly Thr Gl n Val Thr Val
115 120 125

Ser Ser
130

<210> 77
<211> 133
<212> PRT
<213> Lama gl ama
<400> 77

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Al a Al a Ser Gly Phe Al a Leu Asp Tyr Tyr

Al a Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

Ser Cys Ile Gl u Ser Ser Asp Gly Ser Thr Tyr Tyr Al a Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Al a Lys Asn Thr Val Tyr
65 70 75 80

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Thr Asp Ser Al a Gly Val Pro Al a Gly Pro Al a Al a Val Tyr Gly
100 105 110

Ser Ser Cys Ser Arg Leu Gl u Tyr Asp Tyr Trp Gly Gl n Gly Thr Gl n
115 120 125

Val Thr Val Ser Ser
130

<210> 78
<211> 124
<212> PRT
<213> Lama gl ama

<400> 78

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Al a Al a Ser Gly Phe Thr Phe Gly Ser Tyr
20 25 30

Asp Met Ser Trp Val Arg Gl n Al a Pro Gly Lys Gly Pro Gl u Trp Val
35 40 45

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

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

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Thr Asp Pro Tyr Ser Leu Ser Tyr Tyr Gly Tyr Pro Leu Tyr Asp
100 105 110

Tyr Trp Gly Gl n Gly Thr Gl n Val Thr Val Ser Ser
115 120

eol f-seql . txt

<210> 79
<211> 115
<212> PRT
<213> Lama gl ama

<400> 79

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

<210> 80
<211> 129
<212> PRT
<213> Lama gl ama

<400> 80

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Ala Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Asp Asp Tyr
20 25 30
Al a Ile Gly Trp Phe Arg Gl n Ala Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45
Ser Cys Ile Arg Asp Ser Asp Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Ser Asp Asn Asp Lys Asn Thr Val Tyr
65 70 75 80

Leu Gl n Met Asn Ser 85 Leu Lys Pro Gl u Asp 90 Thr Al a Val Tyr Tyr Cys 95

Al a Al a Val Pro 100 Al a Gly Arg Leu Arg 105 Phe Gly Gl u Gl n Trp Tyr Pro 110

Leu Tyr Gl u 115 Tyr Asp Al a Trp Gly 120 Gl n Gly Thr Gl n Val 125 Thr Val Ser

Ser

<210> 81
<211> 124
<212> PRT
<213> Lama gl ama

<400> 81

Gl u Val Gl n Leu Val 5 Gl u Ser Gly Gly 10 Gly Val Val Gl n Al a Gly Asp 15

Ser Val Arg Leu Ser Cys Al a Al a Ser 25 Gly Pro Thr Phe Arg Ser Tyr 30

Thr Met Al a Trp Phe Arg Gl n Thr 40 Pro Gly Lys Gl u Arg Asp Ile Val 45

Al a Al a Ile Ser Ser Ser 55 Leu Gly Arg Thr Tyr Tyr 60 Al a Asp Ser Val

Lys Gly Arg Phe Gl n Ile 70 Leu Arg Asp Asn 75 Al a Lys Gl u Thr Val Trp 80

Leu Gl n Met Asn Ser 85 Leu Lys Pro Gl u Asp 90 Thr Al a Val Tyr Ile Cys 95

Al a Al a Ser Arg Ser Leu Asn Leu 105 Tyr Thr Thr Lys Pro Tyr Asp 110

Tyr Trp Gly Gl n Gly Thr Gl n Val 120 Thr Val Ser Ser

<210> 82
<211> 133
<212> PRT
<213> Lama gl ama

<400> 82

Gl u Val Gl n Leu Val 5 Gl u Ser Gly Gly 10 Gly Leu Val Gl n Al a Gly Gly 15

Ser Leu Arg Leu Ser Cys Al a Al a Ser 25 Gly Phe Asp Phe Gl u Asp Tyr 30

eol f-seql . txt

Asp Met Gly Trp Phe Arg Gl n Ala Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

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

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

Leu Gl n Met Asn Ser Leu Ile Pro Gl u Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ala Arg Pro Trp Thr Arg Arg Val Tyr Gly Ser Ser Trp Leu Ala
100 105 110

Arg Ser Leu Asp Gl u Tyr Gl u Tyr Asp Tyr Trp Gly Gl n Gly Thr Gl n
115 120 125

Val Thr Val Ser Ser
130

<210> 83
<211> 123
<212> PRT
<213> Lama gl ama

<400> 83

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Val Gly Asp
1 5 10 15

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

Leu Met Val Gly Trp Phe Arg Gl n Thr Pro Gly Lys Gl u Arg Gl u Phe
35 40 45

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

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

Leu Gl n Met Asn Ser Leu Lys Ala Gl u Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Gly Ser Tyr Gly Gly Asn Tyr Tyr Ile Pro Gly Phe Tyr Gl u Asp
100 105 110

Trp Gly Gl n Gly Thr Gl n Val Thr Val Ser Ser
115 120

eol f-seql . txt

<210> 84
<211> 126
<212> PRT
<213> Lama gl ama

<400> 84

Gl u Val Gl n Leu Met Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Al a Al a Ser Gly Phe Al a Leu Asp Tyr Tyr
20 25 30

Al a Ile Gly Trp Phe Arg Gl n Val Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

Ser Cys Ile Ser Ser Ser Asp Gly Ile Thr Tyr Tyr Val Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Al a Lys Asn Thr Val Tyr
65 70 75 80

Leu Gl n Met Asn Ser Leu Lys Pro Gly Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Thr Asp Ser Gly Gly Tyr Ile Asp Tyr Asp Cys Met Gly Leu Gly
100 105 110

Tyr Asp Tyr Trp Gly Gl n Gly Thr Gl n Val Thr Val Ser Ser
115 120 125

<210> 85
<211> 126
<212> PRT
<213> Lama gl ama

<400> 85

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Al a Al a Ser Gly Phe Al a Leu Asp Tyr Tyr
20 25 30

Al a Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

Ser Cys Ile Ser Ser Ser Asp Gly Ile Thr Tyr Tyr Val Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Al a Lys Asn Thr Val Tyr
65 70 75 80

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys

Al a Thr Asp Ser Gly Gly Tyr Ile Asp Tyr Asp Cys Met Gly Leu Gly
100 105 110

Tyr Asp Tyr Trp Gly Gl n Gly Thr Gl n Val Thr Val Ser Ser
115 120 125

<210> 86
<211> 123
<212> PRT
<213> Lama gl ama

<400> 86

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Val Gly Asp
1 5 10 15

Ser Leu Arg Leu Ser Cys Al a Al a Ser Gly Arg Thr Phe Ser Thr Tyr
20 25 30

Leu Met Val Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Phe
35 40 45

Al a Al a Val Ile Trp Ser Ser Gly Asp Thr Al a Tyr Al a Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Al a Lys Asn Thr Val Tyr
65 70 75 80

Leu Gl n Met Asn Ser Leu Lys Al a Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Gly Ser Tyr Asp Gly Asn Tyr Tyr Ile Pro Gly Phe Tyr Lys Asp
100 105 110

Trp Gly Gl n Gly Thr Gl n Val Thr Val Ser Ser
115 120

<210> 87
<211> 129
<212> PRT
<213> Arti ficial

<220>
<223> Mutated Lama sequence

<400> 87

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Al a Gly Gly
1 5 10 15

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

Al a I l e G l y T r p P h e A r g G l n A l a P r o G l y L y s G l u A r g G l u G l y V a l
35 40 45

S e r S e r I l e A r g A s p A s n A s p G l y S e r T h r T y r T y r A l a A s p S e r V a l
50 55 60

L y s G l y A r g S e r T h r I l e S e r S e r A s p A s n A s p L y s A s n T h r V a l T y r
65 70 75 80

L e u G l n M e t A s p S e r L e u L y s P r o G l u A s p T h r A l a V a l T y r T y r C y s
85 90 95

A l a A l a V a l P r o A l a G l y A r g L e u A r g T y r G l y G l u G l n T r p T y r P r o
100 105 110

I l e T y r G l u T y r A s p A l a T r p G l y G l n G l y T h r L e u V a l T h r V a l S e r
115 120 125

S e r

- <210> 88
- <211> 129
- <212> PRT
- <213> A r t i f i c i a l

- <220>
- <223> M u t a t e d L a m a s e q u e n c e

<400> 88

G l u V a l G l n L e u V a l G l u S e r G l y G l y G l y L e u V a l G l n A l a G l y G l y
1 5 10 15

S e r L e u A r g L e u S e r C y s A l a V a l S e r G l y I l e T h r L e u A s p A s p T y r
20 25 30

A l a V a l G l y T r p P h e A r g G l n A l a P r o G l y L y s G l u A r g G l u G l y V a l
35 40 45

S e r T h r I l e A r g A s p A s n A s p G l y S e r T h r T y r T y r A l a A s p S e r V a l
50 55 60

L y s G l y A r g P h e T h r I l e S e r S e r A s p A s n A s p L y s A s n T h r V a l T y r
65 70 75 80

L e u G l n M e t A s n S e r L e u L y s P r o L y s A s p T h r A l a V a l T y r T y r C y s
85 90 95

A l a A l a V a l P r o A l a G l y A r g L e u A r g P h e G l y G l u G l n T r p T y r P r o
100 105 110

I l e T y r G l u T y r A s p A l a T r p G l y G l n G l y T h r L e u V a l T h r V a l S e r
115 120 125

Ser

<210> 89
<211> 129
<212> PRT
<213> Arti fi ci al

<220>
<223> Mutated Lama sequence

<400> 89

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

Ser

<210> 90
<211> 129
<212> PRT
<213> Arti fi ci al

<220>
<223> Mutated Lama sequence

<400> 90

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Al a Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Al a Al a Ser Gly Ile Thr Leu Asp Asp Tyr
20 25 30

eol f-seql . txt

Al a Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Val Gly Val
35 40 45

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

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

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Al a Val Pro Al a Gly Arg Leu Arg Phe Gly Gl u Gl n Trp Tyr Pro
100 105 110

Ile Tyr Gl u Tyr Asp Al a Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 91
<211> 129
<212> PRT
<213> Arti ficial

<220>
<223> Mutated Lama sequence

<400> 91

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Al a Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Al a Al a Ser Gly Leu Thr Leu Asp Asp Tyr
20 25 30

Al a Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

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

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

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Al a Val Pro Al a Gly Arg Leu Arg Phe Gly Gl u Gl n Trp Tyr Pro
100 105 110

I l e T y r G l u T y r A s p A l a T r p G l y G l n G l y T h r L e u V a l T h r V a l S e r
 115 120 125

Ser

<210> 92
 <211> 129
 <212> PRT
 <213> A r t i f i c i a l

<220>
 <223> M u t a t e d L a m a s e q u e n c e

<400> 92

G l n V a l G l n L e u V a l G l u S e r G l y G l y G l y L e u V a l G l n A l a G l y G l y
 1 5 10 15

S e r L e u A r g L e u S e r C y s A l a V a l S e r G l y P h e T h r L e u A s p A s p T y r
 20 25 30

A l a I l e G l y T r p P h e A r g G l n A l a P r o G l y L y s G l u A r g G l u G l y V a l
 35 40 45

S e r S e r I l e A r g A s p A s n A s p G l y S e r T h r T y r T y r A l a A s p S e r V a l
 50 55 60

L y s G l y A r g P h e T h r I l e S e r S e r A s p A s n A s p G l n A s n T h r V a l T y r
 65 70 75 80

L e u G l n M e t A s n S e r L e u L y s S e r G l u A s p T h r A l a V a l T y r T y r C y s
 85 90 95

A l a A l a V a l P r o A l a G l y A r g L e u A r g P h e G l y G l u G l n T r p T y r P r o
 100 105 110

I l e T y r G l u T y r A s p A l a T r p G l y G l n G l y T h r L e u V a l T h r V a l S e r
 115 120 125

Ser

<210> 93
 <211> 129
 <212> PRT
 <213> A r t i f i c i a l

<220>
 <223> M u t a t e d L a m a s e q u e n c e

<400> 93

G l u V a l G l n L e u V a l G l u S e r G l y G l y G l y L e u V a l G l n A l a G l y G l y
 1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
35 40 45

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

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

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

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

Ile Tyr Glu Tyr Asp Ala Trp Gly Gln Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

- <210> 94
- <211> 129
- <212> PRT
- <213> Arti fici al

- <220>
- <223> Mutated Lama sequence

<400> 94

Glu Val Gln Leu Met Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
35 40 45

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

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

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

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

I l e T y r G l u T y r A s p A l a T r p G l y G l n G l y T h r L e u V a l T h r V a l S e r
115 120 125

Ser

<210> 95
<211> 129
<212> PRT
<213> Arti f i c i a l

<220>
<223> Mutated Lama sequence

<400> 95

G l u V a l G l n L e u V a l G l u S e r G l y G l y G l y L e u V a l G l n A l a G l y G l y
1 5 10 15

S e r L e u A r g L e u S e r C y s A l a A l a S e r G l y P h e T h r L e u A s p A s p T y r
20 25 30

A l a I l e G l y T r p P h e A r g G l n A l a P r o G l y L y s G l u A r g G l u G l y V a l
35 40 45

S e r S e r I l e A r g A s p A s n A s p G l y S e r T h r T y r T y r A l a A s p S e r V a l
50 55 60

L y s G l y A r g P h e T h r I l e S e r S e r A s p A s n A s p L y s A s n T h r V a l T y r
65 70 75 80

L e u G l n M e t A s n S e r L e u L y s P r o G l u A s p T h r A l a V a l T y r T y r C y s
85 90 95

A l a A l a V a l P r o A l a G l y A r g L e u A r g T y r G l y G l u G l n T r p T y r P r o
100 105 110

I l e T y r G l u T y r A s p A l a T r p G l y G l n G l y T h r L e u V a l T h r V a l S e r
115 120 125

Ser

<210> 96
<211> 129
<212> PRT
<213> Arti f i c i a l

<220>
<223> Mutated Lama sequence

<400> 96

G l u V a l G l n L e u V a l G l u S e r G l y G l y G l y L e u V a l G l n A l a G l y G l y
1 5 10 15

eol f-seql . txt

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
35 40 45

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

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

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

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

Ile Tyr Glu Tyr Asp Ala Trp Gly Gln Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 97
<211> 129
<212> PRT
<213> Arti fici al

<220>
<223> Mutated Lama sequence

<400> 97

Glu Val Gln Met Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
35 40 45

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

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

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

eol f-seq1 . txt

Al a Al a Val Pro Al a Gly Arg Leu Arg Phe Gly Gl u Gl n Trp Tyr Pro
100 105 110

I l e Tyr Gl u Tyr Asp Al a Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 98
<211> 129
<212> PRT
<213> Arti f i c i a l

<220>
<223> Mutated Lama sequence

<400> 98

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gl y Leu Val Gl n Ser Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Al a Al a Ser Gly Leu Thr Leu Asp Asp Tyr
20 25 30

Al a I l e Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

Ser Ser I l e Arg Asp Asn Asp Gly Ser Thr Tyr Tyr Al a Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr I l e Ser Ser Asp Asn Asp Lys Asn Thr Val Tyr
65 70 75 80

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Al a Val Pro Al a Gly Arg Leu Arg Phe Gly Gl u Gl n Trp Tyr Pro
100 105 110

I l e Tyr Gl u Tyr Asp Al a Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 99
<211> 129
<212> PRT
<213> Arti f i c i a l

<220>
<223> Mutated Lama sequence

<400> 99

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
 1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
 35 40 45

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

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

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

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

Ile Tyr Glu Tyr Asp Ala Trp Gly Gln Gly Thr Leu Val Thr Val Ser
 115 120 125

Ser

<210> 100
 <211> 129
 <212> PRT
 <213> Artificial

<220>
 <223> Mutated Lama sequence

<400> 100

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
 1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
 35 40 45

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

Lys Trp Arg Phe Thr Ile Ser Ser Asp Asn Asp Lys Asn Thr Val Tyr
 65 70 75 80

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

eol f-seql . txt

Al a Al a Val Pro Al a Gly Arg Leu Arg Phe Gly Gl u Gl n Trp Tyr Pro
100 105 110

I l e Tyr Gl u Tyr Asp Al a Trp Gly Gl n Gly I l e Leu Val Thr Val Ser
115 120 125

Ser

<210> 101
<211> 129
<212> PRT
<213> Arti fi ci al

<220>
<223> Mutated Lama sequence

<400> 101

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gl y Leu Val Gl n Al a Gly Gl y
1 5 10 15

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

Al a I l e Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

Ser Ser I l e Arg Asp Asn Asp Gly Ser Thr Tyr Tyr Al a Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr I l e Ser Ser Asp Asn Val Lys Asn Thr Val Tyr
65 70 75 80

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Al a Val Pro Al a Gly Arg Leu Arg Phe Gly Gl u Gl n Trp Tyr Pro
100 105 110

I l e Tyr Gl u Tyr Asp Al a Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 102
<211> 129
<212> PRT
<213> Arti fi ci al

<220>
<223> Mutated Lama sequence

<400> 102

Gl u Val Gl n Leu Leu Gl u Ser Gly Gly Gly Leu Val Gl n Al a Gly Gly
 1 5 10 15

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

Al a Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
 35 40 45

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

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

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
 85 90 95

Al a Al a Val Pro Al a Gly Arg Leu Arg Ile Gly Gl u Gl n Trp Tyr Pro
 100 105 110

Ile Tyr Gl u Tyr Asp Al a Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
 115 120 125

Ser

<210> 103

<211> 129

<212> PRT

<213> Arti fici al

<220>

<223> Mutated Lama sequence

<400> 103

Gl u Val His Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Al a Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Al a Al a Ser Gly Leu Thr Leu Asp Asp Tyr
 20 25 30

Al a Ile Gly Trp Phe Arg Gl n Al a Pro Gly Val Gl u Arg Gl u Gly Val
 35 40 45

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

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

eol f-seq1 . txt

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Al a Val Pro Al a Gly Arg Leu Arg Phe Gly Gl u Gl n Trp Tyr Pro
100 105 110

I l e Tyr Gl u Tyr Asp Al a Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 104
<211> 129
<212> PRT
<213> Arti ficial

<220>
<223> Mutated Lama sequence

<400> 104

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Al a Gly Gly
1 5 10 15

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

Al a I l e Gly Trp Phe Arg Gl n Al a Pro Gly Lys Asp Arg Gl u Gly Val
35 40 45

Ser Ser I l e Arg Asp Asn Asp Gly Ser Thr Tyr Tyr Al a Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr I l e Ser Ser Asp Asn Asp Lys Asn Thr Val Tyr
65 70 75 80

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Al a Val Pro Al a Gly Arg Leu Arg Tyr Gly Gl u Gl n Trp Tyr Pro
100 105 110

I l e Tyr Gl u Tyr Asp Al a Trp Gly Gl n Gly Thr Val Val Thr Val Ser
115 120 125

Ser

<210> 105
<211> 129
<212> PRT
<213> Arti ficial

<220>

<223> Mutated Lama sequence

<400> 105

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
 1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
 35 40 45

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

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

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

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

Ile Tyr Glu Tyr Asp Ala Trp Gly Gln Gly Ile Leu Val Thr Val Ser
 115 120 125

Ser

<210> 106

<211> 129

<212> PRT

<213> Artificial

<220>

<223> Mutated Lama sequence

<400> 106

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
 1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
 35 40 45

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

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

eol f-seql . txt

Leu Gl n Met Asn Asn Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Al a Val Pro Al a Gly Arg Leu Arg Tyr Gly Gl u Gl n Trp Tyr Pro
100 105 110

Ile Tyr Gl u Tyr Asp Al a Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 107
<211> 129
<212> PRT
<213> Arti ficial

<220>
<223> Mutated Lama sequence

<400> 107

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gl y Leu Val Gl n Al a Gly Gly
1 5 10 15

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

Al a Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

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

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

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Al a Val Pro Al a Gly Arg Leu Arg Phe Gly Gl u Gl n Trp Tyr Pro
100 105 110

Ile Tyr Gl u Tyr Asp Al a Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 108
<211> 129
<212> PRT
<213> Arti ficial

eol f-seql . txt

<220>

<223> Mutated Lama sequence

<400> 108

Gl u Gl u Leu Leu Val Gl u Ser Gly Gly Gly Ser Val Gl n Al a Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Al a Al a Ser Gly Leu Thr Leu Asp Asp Tyr
20 25 30

Al a Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

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

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

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Al a Val Pro Al a Gly Arg Leu Arg Phe Gly Gl u Gl n Trp Tyr Pro
100 105 110

Ile Tyr Gl u Tyr Asp Al a Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 109

<211> 129

<212> PRT

<213> Arti ficial

<220>

<223> Mutated Lama sequence

<400> 109

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Al a Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Al a Al a Ser Gly Leu Thr Leu Asp Asp Tyr
20 25 30

Al a Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

Ser Ser Ile Arg Asp Asn Asp Gly Ser Arg Tyr Tyr Al a Asp Ser Val
50 55 60

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

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

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

Ile Tyr Glu Tyr Asp Ala Trp Gly Gln Gly Thr Leu Val Thr Val Ser
 115 120 125

Ser

<210> 110
 <211> 129
 <212> PRT
 <213> Artificial

<220>
 <223> Mutated Lama sequence

<400> 110

Glu Val Gln Leu Val Glu Ser Gly Gly Ser Leu Val Gln Ala Gly Gly
 1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
 35 40 45

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

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

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

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

Ile Tyr Glu Tyr Asp Ala Trp Gly Gln Gly Thr Leu Val Thr Val Ser
 115 120 125

Ser

<210> 111
 <211> 129

<212> PRT
 <213> Arti ficial

<220>
 <223> Mutated Lama sequence

<400> 111

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Ser Leu Val Gl n Al a Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Al a Al a Ser Gly Leu Thr Leu Asp Asp Tyr
 20 25 30

Al a Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
 35 40 45

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

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

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
 85 90 95

Al a Al a Val Pro Al a Gly Arg Leu Arg Phe Gly Gl u Gl n Trp Tyr Pro
 100 105 110

Ile Tyr Gl u Tyr Asp Al a Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
 115 120 125

Ser

<210> 112
 <211> 129
 <212> PRT
 <213> Arti ficial

<220>
 <223> Mutated Lama sequence

<400> 112

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
 1 5 10 15

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

Al a Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
 35 40 45

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

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

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

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

Ile Tyr Glu Tyr Asp Ala Trp Gly Gln Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 113
<211> 129
<212> PRT
<213> Artificial

<220>
<223> Mutated Lama sequence

<400> 113

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

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
35 40 45

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

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

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

Ala Ala Val Pro Ala Gly Arg Leu Arg Tyr Gly Glu Gln Trp Tyr Pro
100 105 110

Ile Tyr Glu Tyr Asp Ala Trp Gly Gln Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

eol f-seql . txt

<210> 114
<211> 129
<212> PRT
<213> Arti f i c i a l

<220>
<223> Mutated Lama sequence

<400> 114

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gl n Ala Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

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

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

Leu Gl n Met Asn Ser Leu Arg Pro Gl u Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ala Val Pro Ala Gly Arg Leu Arg Phe Gly Gl u Gl n Trp Tyr Pro
100 105 110

Ile Tyr Gl u Tyr Asp Ala Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 115
<211> 129
<212> PRT
<213> Arti f i c i a l

<220>
<223> Mutated Lama sequence

<400> 115

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gl n Ala Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

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

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

Leu Gl n Met Asn Ser Leu Arg Pro Gl u Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Al a Al a Val Pro Al a Gly Arg Leu Arg Tyr Gly Gl u Gl n Trp Tyr Pro
 100 105 110

Ile Tyr Gl u Tyr Asp Al a Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
 115 120 125

Ser

<210> 116
 <211> 129
 <212> PRT
 <213> Arti ficial

<220>
 <223> Mutated Lama sequence

<400> 116

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Al a Al a Ser Gly Ile Thr Leu Asp Asp Tyr
 20 25 30

Al a Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
 35 40 45

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

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

Leu Gl n Met Asn Ser Leu Arg Pro Gl u Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Al a Al a Val Pro Al a Gly Arg Leu Arg Phe Gly Gl u Gl n Trp Tyr Pro
 100 105 110

Ile Tyr Gl u Tyr Asp Al a Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
 115 120 125

Ser

eol f-seql . txt

<210> 117
<211> 129
<212> PRT
<213> Arti ficial

<220>
<223> Mutated Lama sequence

<400> 117

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gl n Ala Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

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

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

Leu Gl n Met Asn Ser Leu Arg Pro Gl u Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ala Val Pro Ala Gly Arg Leu Arg Tyr Gly Gl u Gl n Trp Tyr Pro
100 105 110

Ile Tyr Gl u Tyr Asp Ala Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 118
<211> 129
<212> PRT
<213> Arti ficial

<220>
<223> Mutated Lama sequence

<400> 118

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gl n Ala Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

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

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

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

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

Ile Tyr Glu Tyr Asp Ala Trp Gly Gln Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 119
<211> 129
<212> PRT
<213> Arti ficial

<220>
<223> Mutated Lama sequence

<400> 119

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

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
35 40 45

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

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

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

Ala Ala Val Pro Ala Gly Arg Leu Arg Tyr Gly Glu Gln Trp Tyr Pro
100 105 110

Ile Tyr Glu Tyr Asp Ala Trp Gly Gln Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 120
 <211> 129
 <212> PRT
 <213> Arti fici al

<220>
 <223> Mutated Lama sequence

<400> 120

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
 1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gl n Ala Pro Gly Lys Gl u Arg Gl u Gly Val
 35 40 45

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

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

Leu Gl n Met Asn Ser Leu Arg Pro Gl u Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Ala Val Pro Ala Gly Arg Leu Arg Phe Gly Gl u Gl n Trp Tyr Pro
 100 105 110

Ile Tyr Gl u Tyr Asp Ala Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
 115 120 125

Ser

<210> 121
 <211> 129
 <212> PRT
 <213> Arti fici al

<220>
 <223> Mutated Lama sequence

<400> 121

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
 1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
35 40 45

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

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

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

Ala Ala Val Pro Ala Gly Arg Leu Arg Tyr Gly Glu Gln Trp Tyr Pro
100 105 110

Ile Tyr Glu Tyr Asp Ala Trp Gly Gln Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

- <210> 122
- <211> 129
- <212> PRT
- <213> Arti f i c i a l

- <220>
- <223> Mutated Lama sequence

<400> 122

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

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
35 40 45

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

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

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

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

Ile Tyr Glu Tyr Asp Ala Trp Gly Gln Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 123
<211> 129
<212> PRT
<213> Arti fi ci al

<220>
<223> Mutated Lama sequence

<400> 123

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gl n Ala Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

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

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

Leu Gl n Met Asn Ser Leu Arg Pro Gl u Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ala Val Pro Ala Gly Arg Leu Arg Tyr Gly Gl u Gl n Trp Tyr Pro
100 105 110

Ile Tyr Gl u Tyr Asp Ala Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 124
<211> 124
<212> PRT
<213> Arti fi ci al

<220>
<223> Mutated Lama sequence

<400> 124

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
1 5 10 15

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

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Al a Leu Gly Trp Phe Arg Gl n Al a Al a Gly Lys Gl u Arg Gl u Gly Val
35 40 45

Ser Cys Ile Arg Cys Ser Asp Gly Ser Thr Tyr Tyr Al a Asp Ser Val
50 55 60

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

Leu Gl n Met Asn Ser Leu Arg Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Al a Ser Ile Val Pro Arg Ser Lys Leu Gl u Pro Tyr Gl u Tyr Asp
100 105 110

Al a Trp Gly Gl n Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 125
<211> 124
<212> PRT
<213> Arti fi cial

<220>
<223> Mutated Lama sequence

<400> 125

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
1 5 10 15

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

Al a Leu Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

Ser Cys Ile Arg Cys Ser Asp Gly Ser Thr Tyr Tyr Al a Asp Ser Val
50 55 60

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

Leu Gl n Met Asn Ser Leu Arg Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Al a Ser Ile Val Pro Arg Ser Lys Leu Gl u Pro Tyr Gl u Tyr Asp
100 105 110

Al a Trp Gly Gl n Gly Thr Leu Val Thr Val Ser Ser
115 120

eol f-seql . txt

<210> 126
<211> 124
<212> PRT
<213> Arti ficial

<220>
<223> Mutated Lama sequence

<400> 126

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
1 5 10 15

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

Ala Leu Gly Trp Phe Arg Gl n Ala Ala Gly Lys Gl u Arg Gl u Gly Val
35 40 45

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

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

Leu Gl n Met Asn Ser Leu Arg Pro Gl u Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ala Ser Ile Val Pro Arg Ser Lys Leu Gl u Pro Tyr Gl u Tyr Asp
100 105 110

Ala Trp Gly Gl n Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 127
<211> 124
<212> PRT
<213> Arti ficial

<220>
<223> Mutated Lama sequence

<400> 127

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
1 5 10 15

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

Ala Leu Gly Trp Phe Arg Gl n Ala Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

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

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

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

Ala Ala Ser Ile Val Pro Arg Ser Lys Leu Glu Pro Tyr Glu Tyr Asp
100 105 110

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

<210> 128
<211> 124
<212> PRT
<213> Artificial

<220>
<223> Mutated Lama sequence

<400> 128

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

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

Ala Leu Gly Trp Phe Arg Gln Ala Ala Gly Lys Glu Arg Glu Gly Val
35 40 45

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

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

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

Ala Ala Ser Ile Val Pro Arg Ser Lys Leu Glu Pro Tyr Glu Tyr Asp
100 105 110

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

<210> 129
<211> 124
<212> PRT
<213> Artificial

<220>
<223> Mutated Lama sequence

<400> 129

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

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

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

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

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

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

Ala Ala Ser Ile Val Pro Arg Ser Lys Leu Glu Pro Tyr Glu Tyr Asp
 100 105 110

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

<210> 130
 <211> 124
 <212> PRT
 <213> Artificial

<220>
 <223> Mutated Lama sequence

<400> 130

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

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

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

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

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

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

Ala Ala Ser Ile Val Pro Arg Ser Lys Leu Glu Pro Tyr Glu Tyr Asp
 100 105 110

Al a Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 131
<211> 126
<212> PRT
<213> Arti ficial

<220>
<223> Mutated Lama sequence

<400> 131

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

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
35 40 45

Ser Cys Ile Ser Ser Ser Asp Gly Ile Thr Tyr Tyr Val Asp Ser Val
50 55 60

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

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

Ala Thr Asp Ser Gly Gly Tyr Ile Asp Tyr Asp Cys Met Gly Leu Gly
100 105 110

Tyr Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 132
<211> 126
<212> PRT
<213> Arti ficial

<220>
<223> Mutated Lama sequence

<400> 132

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

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
35 40 45

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

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

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

Ala Thr Asp Ser Gly Gly Tyr Ile Asp Tyr Asp Cys Met Gly Leu Gly
100 105 110

Tyr Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 133
<211> 126
<212> PRT
<213> Arti ficial

<220>
<223> Mutated Lama sequence

<400> 133

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

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
35 40 45

Ser Cys Ile Ser Ser Ser Gly Gly Ile Thr Tyr Tyr Val Asp Ser Val
50 55 60

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

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

Ala Thr Asp Ser Gly Gly Tyr Ile Asp Tyr Asp Cys Met Gly Leu Gly
100 105 110

Tyr Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 134
<211> 126
<212> PRT
<213> Arti ficial

eol f-seql . txt

<220>

<223> Mutated Lama sequence

<400> 134

Gl u Val Gl n Leu Val Gl u Ser Gl y Gl y Gl y Leu Val Gl n Pro Gl y Gl y
1 5 10 15

Ser Leu Arg Leu Ser Cys Al a Al a Ser Gl y Phe Al a Leu Asp Tyr Tyr
20 25 30

Al a Ile Gl y Trp Phe Arg Gl n Al a Pro Gl y Lys Gl u Arg Gl u Gl y Val
35 40 45

Ser Cys Ile Ser Ser Ser Gl y Gl y Ile Thr Tyr Tyr Al a Asp Ser Val
50 55 60

Lys Gl y Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr
65 70 75 80

Leu Gl n Met Asn Ser Leu Arg Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Thr Asp Ser Gl y Gl y Tyr Ile Asp Tyr Asp Cys Met Gl y Leu Gl y
100 105 110

Tyr Asp Tyr Trp Gl y Gl n Gl y Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 135

<211> 126

<212> PRT

<213> Arti ficial

<220>

<223> Mutated Lama sequence

<400> 135

Asp Val Gl n Leu Val Gl u Ser Gl y Gl y Gl y Leu Val Gl n Pro Gl y Gl y
1 5 10 15

Ser Leu Arg Leu Ser Cys Al a Al a Ser Gl y Phe Al a Leu Asp Tyr Tyr
20 25 30

Al a Ile Gl y Trp Phe Arg Gl n Al a Pro Gl y Lys Gl u Arg Gl u Gl y Val
35 40 45

Ser Cys Ile Ser Ser Ser Gl y Gl y Ile Thr Tyr Tyr Al a Asp Ser Val
50 55 60

Lys Gl y Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val Tyr
65 70 75 80

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Leu Gl n Met Asn Ser Leu Arg Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Thr Asp Ser Gly Gly Tyr Ile Asp Tyr Asp Cys Met Gly Leu Gly
100 105 110

Tyr Asp Tyr Trp Gly Gl n Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 136
<211> 126
<212> PRT
<213> Arti ficial

<220>
<223> Mutated Lama sequence

<400> 136

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Al a Al a Ser Gly Phe Al a Leu Asp Tyr Tyr
20 25 30

Al a Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

Ser Cys Ile Ser Ser Ser Gly Gly Ile Thr Tyr Tyr Al a Asp Ser Val
50 55 60

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

Leu Gl n Met Asn Ser Leu Arg Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Thr Asp Ser Gly Gly Tyr Ile Asp Tyr Asp Cys Gl n Gly Leu Gly
100 105 110

Tyr Asp Tyr Trp Gly Gl n Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 137
<211> 126
<212> PRT
<213> Arti ficial

<220>
<223> Mutated Lama sequence

<400> 137

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
 35 40 45

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

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

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

Ala Thr Asp Ser Gly Gly Tyr Ile Asp Tyr Asp Cys Arg Gly Leu Gly
 100 105 110

Tyr Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

<210> 138
 <211> 126
 <212> PRT
 <213> Arti fici al

<220>
 <223> Mutated Lama sequence

<400> 138

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
 1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
 35 40 45

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

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

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

Ala Thr Asp Ser Gly Gly Tyr Ile Asp Tyr Asp Cys Ser Gly Leu Gly
 100 105 110

Tyr Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120 125

eol f-seql . txt

<210> 139
<211> 126
<212> PRT
<213> Arti fici al

<220>
<223> Mutated Lama sequence

<400> 139

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gl n Ala Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

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

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

Leu Gl n Met Asn Ser Leu Arg Pro Gl u Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Gl u Ser Gly Gly Tyr Ile Asp Tyr Asp Cys Gl n Gly Leu Gly
100 105 110

Tyr Asp Tyr Trp Gly Gl n Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 140
<211> 126
<212> PRT
<213> Arti fici al

<220>
<223> Mutated Lama sequence

<400> 140

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gl n Ala Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

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

eol f-seql . txt

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

Leu Gl n Met Asn Ser Leu Arg Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Thr Gl u Ser Gly Gly Tyr Ile Asp Tyr Asp Cys Arg Gly Leu Gly
100 105 110

Tyr Asp Tyr Trp Gly Gl n Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 141
<211> 126
<212> PRT
<213> Arti fici al

<220>
<223> Mutated Lama sequence

<400> 141

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Al a Al a Ser Gly Phe Al a Leu Asp Tyr Tyr
20 25 30

Al a Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

Ser Cys Ile Ser Ser Ser Gly Gly Ile Thr Tyr Tyr Al a Asp Ser Val
50 55 60

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

Leu Gl n Met Asn Ser Leu Arg Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Thr Gl u Ser Gly Gly Tyr Ile Asp Tyr Asp Cys Ser Gly Leu Gly
100 105 110

Tyr Asp Tyr Trp Gly Gl n Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 142
<211> 129
<212> PRT
<213> Arti fici al

<220>
<223> Mutated Lama sequence

<400> 142

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Al a Gly Gly
 1 5 10 15

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

Al a Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
 35 40 45

Ser Thr Ile Arg Asp Ser Asp Gly Ser Thr Tyr Tyr Al a Asp Ser Val
 50 55 60

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

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
 85 90 95

Al a Al a Val Pro Al a Gly Arg Leu Arg Phe Gly Gl u Gl n Trp Tyr Pro
 100 105 110

Leu Tyr Gl u Tyr Asp Al a Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
 115 120 125

Ser

<210> 143

<211> 129

<212> PRT

<213> Arti fici al

<220>

<223> Mutated Lama sequence

<400> 143

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Al a Gly Gly
 1 5 10 15

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

Al a Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
 35 40 45

Ser Al a Ile Arg Asp Ser Asp Gly Ser Thr Tyr Tyr Al a Asp Ser Val
 50 55 60

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

eol f-seq1 . txt

Leu Gl n Met Asn Ser 85 Leu Lys Pro Gl u Asp 90 Thr Al a Val Tyr Tyr Cys 95

Al a Al a Val Pro 100 Al a Gly Arg Leu Arg 105 Phe Gly Gl u Gl n Trp Tyr Pro 110

Leu Tyr Gl u Tyr Asp Al a Trp Gly 120 Gl n Gly Thr Leu Val 125 Thr Val Ser

Ser

<210> 144
<211> 129
<212> PRT
<213> Arti ficial

<220>
<223> Mutated Lama sequence

<400> 144

Gl u Val Gl n Leu Val 5 Gl u Ser Gly Gly 10 Gl y Leu Val Gl n Al a Gly Gly 15

Ser Leu Arg 20 Leu Ser Cys Al a Al a Ser 25 Gl y Phe Thr Leu Asp 30 Asp Tyr

Al a Ile Gly 35 Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg 45 Gl u Gly Val

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

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

Leu Gl n Met Asn Ser 85 Leu Lys Pro Gl u Asp 90 Thr Al a Val Tyr Tyr Cys 95

Al a Al a Val Pro 100 Al a Gly Arg Leu Arg 105 Phe Gly Gl u Gl n Trp Tyr Pro 110

Leu Tyr Gl u Tyr Asp Al a Trp Gly 120 Gl n Gly Thr Leu Val 125 Thr Val Ser

Ser

<210> 145
<211> 129
<212> PRT
<213> Arti ficial

<220>

<223> Mutated Lama sequence

<400> 145

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
 1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gl n Ala Pro Gly Lys Gl u Arg Gl u Gly Val
 35 40 45

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

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

Leu Gl n Met Asn Ser Leu Arg Pro Gl u Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Ala Val Pro Ala Gly Arg Leu Arg Phe Gly Gl u Gl n Trp Tyr Pro
 100 105 110

Leu Tyr Gl u Tyr Asp Ala Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
 115 120 125

Ser

<210> 146

<211> 129

<212> PRT

<213> Arti fici al

<220>

<223> Mutated Lama sequence

<400> 146

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
 1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gl n Ala Pro Gly Lys Gl u Arg Gl u Gly Val
 35 40 45

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

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

eol f-seql . txt

Leu Gl n Met Asn Ser Leu Arg Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Al a Val Pro Al a Gly Arg Leu Arg Phe Gly Gl u Gl n Trp Tyr Pro
100 105 110

Leu Tyr Gl u Tyr Asp Al a Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 147
<211> 129
<212> PRT
<213> Arti fici al

<220>
<223> Mutated Lama sequence

<400> 147

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gl y Leu Val Gl n Pro Gly Gly
1 5 10 15

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

Al a Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Al a Lys Asn Thr Val Tyr
65 70 75 80

Leu Gl n Met Asn Ser Leu Arg Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Al a Val Pro Al a Gly Arg Leu Arg Phe Gly Gl u Gl n Trp Tyr Pro
100 105 110

Leu Tyr Gl u Tyr Asp Al a Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 148
<211> 129
<212> PRT
<213> Arti fici al

eol f-seql . txt

<220>

<223> Mutated Lama sequence

<400> 148

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

Ser

<210> 149

<211> 129

<212> PRT

<213> Arti ficial

<220>

<223> Mutated Lama sequence

<400> 149

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

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

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

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

Leu Tyr Glu Tyr Asp Ala Trp Gly Gln Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 150
<211> 129
<212> PRT
<213> Arti fici al

<220>
<223> Mutated Lama sequence

<400> 150

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

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
35 40 45

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

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

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

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

Leu Tyr Glu Tyr Asp Ala Trp Gly Gln Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 151
<211> 129

<212> PRT
<213> Arti ficial

<220>
<223> Mutated Lama sequence

<400> 151

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gl n Ala Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

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

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

Leu Gl n Met Asn Ser Leu Arg Pro Gl u Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ala Val Pro Ala Gly Arg Leu Arg Phe Gly Gl u Gl n Trp Tyr Pro
100 105 110

Leu Tyr Gl u Tyr Asp Ala Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 152
<211> 129
<212> PRT
<213> Arti ficial

<220>
<223> Mutated Lama sequence

<400> 152

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Ala Gly Gly
1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gl n Ala Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

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

eol f-seql . txt

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

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

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

Leu Tyr Glu Tyr Asp Ala Trp Gly Gln Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 153
<211> 129
<212> PRT
<213> Artificial

<220>
<223> Mutated Lama sequence

<400> 153

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
35 40 45

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

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

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

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

Leu Tyr Glu Tyr Asp Ala Trp Gly Gln Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

eol f-seql . txt

<210> 154
<211> 129
<212> PRT
<213> Arti f i c i a l

<220>
<223> Mutated Lama sequence

<400> 154

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Al a Gly Gly
1 5 10 15

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

Al a Il e Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

Ser Ser Il e Arg Asp Il e Asp Gly Ser Thr Tyr Tyr Al a Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Il e Ser Ser Asp Asn Asp Lys Asn Thr Val Tyr
65 70 75 80

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Al a Val Tyr Tyr Cys
85 90 95

Al a Al a Val Pro Al a Gly Arg Leu Arg Phe Gly Gl u Gl n Trp Tyr Pro
100 105 110

Leu Tyr Gl u Tyr Asp Al a Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 155
<211> 129
<212> PRT
<213> Arti f i c i a l

<220>
<223> Mutated Lama sequence

<400> 155

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Al a Gly Gly
1 5 10 15

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

Al a Il e Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

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

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

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Al a Al a Val Pro Al a Gly Arg Leu Arg Phe Gly Gl u Gl n Trp Tyr Pro
100 105 110

Leu Tyr Gl u Tyr Asp Al a Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 156
<211> 129
<212> PRT
<213> Arti fici al

<220>
<223> Mutated Lama sequence

<400> 156

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Al a Gly Gly
1 5 10 15

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

Al a Ile Gly Trp Phe Arg Gl n Al a Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

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

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

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Al a Al a Val Pro Al a Gly Arg Leu Arg Phe Gly Gl u Gl n Trp Tyr Pro
100 105 110

Leu Tyr Gl u Tyr Asp Al a Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

eol f-seql . txt

<210> 157
<211> 129
<212> PRT
<213> Arti fici al

<220>
<223> Mutated Lama sequence

<400> 157

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Ala Gly Gly
1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gl n Ala Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

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

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

Leu Gl n Met Asn Ser Leu Lys Pro Gl u Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ala Val Pro Ala Gly Arg Leu Arg Phe Gly Gl u Gl n Trp Tyr Pro
100 105 110

Leu Tyr Gl u Tyr Asp Ala Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 158
<211> 129
<212> PRT
<213> Arti fici al

<220>
<223> Mutated Lama sequence

<400> 158

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gl n Ala Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

eol f-seql . txt

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

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

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

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

Leu Tyr Glu Tyr Asp Ala Trp Gly Gln Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 159
<211> 129
<212> PRT
<213> Arti ficial

<220>
<223> Mutated Lama sequence

<400> 159

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

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
35 40 45

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

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

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

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

Leu Tyr Glu Tyr Asp Ala Trp Gly Gln Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 160
 <211> 129
 <212> PRT
 <213> Arti fici al

<220>
 <223> Mutated Lama sequence

<400> 160

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
 1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gl n Ala Pro Gly Lys Gl u Arg Gl u Gly Val
 35 40 45

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

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

Leu Gl n Met Asn Ser Leu Arg Pro Gl u Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Ala Val Pro Ala Gly Arg Leu Arg Tyr Gly Gl u Gl n Trp Tyr Pro
 100 105 110

Ile Tyr Gl u Tyr Asp Ala Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
 115 120 125

Ser

<210> 161
 <211> 129
 <212> PRT
 <213> Arti fici al

<220>
 <223> Mutated Lama sequence

<400> 161

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
 1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
35 40 45

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

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

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

Ala Ala Val Pro Ala Gly Arg Leu Arg Tyr Gly Glu Gln Trp Tyr Pro
100 105 110

Ile Tyr Glu Tyr Asp Ala Trp Gly Gln Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

- <210> 162
- <211> 129
- <212> PRT
- <213> Arti fici al

- <220>
- <223> Mutated Lama sequence

<400> 162

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

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
35 40 45

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

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

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

Ala Ala Val Pro Ala Gly Arg Leu Arg Tyr Gly Glu Gln Trp Tyr Pro
100 105 110

Ile Tyr Glu Tyr Asp Ala Trp Gly Gln Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 163
<211> 129
<212> PRT
<213> Arti fi ci al

<220>
<223> Mutated Lama sequence

<400> 163

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gl n Ala Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

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

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

Leu Gl n Met Asn Ser Leu Arg Pro Gl u Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ala Val Pro Ala Gly Arg Leu Arg Tyr Gly Gl u Gl n Trp Tyr Pro
100 105 110

Ile Tyr Gl u Tyr Asp Ala Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 164
<211> 129
<212> PRT
<213> Arti fi ci al

<220>
<223> Mutated Lama sequence

<400> 164

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
1 5 10 15

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

eol f-seql . txt

Al a Ile Gly Trp Phe Arg Gl n Ala Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

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

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

Leu Gl n Met Asn Ser Leu Arg Pro Gl u Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Al a Ala Val Pro Ala Gly Arg Leu Arg Tyr Gly Gl u Gl n Trp Tyr Pro
100 105 110

Ile Tyr Gl u Tyr Asp Ala Trp Gly Gl n Gly Thr Leu Val Thr Val Ser
115 120 125

Ser

<210> 165
<211> 129
<212> PRT
<213> Arti ficial

<220>
<223> Mutated Lama sequence

<400> 165

Gl u Val Gl n Leu Val Gl u Ser Gly Gly Gly Leu Val Gl n Pro Gly Gly
1 5 10 15

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

Al a Ile Gly Trp Phe Arg Gl n Ala Pro Gly Lys Gl u Arg Gl u Gly Val
35 40 45

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

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

Leu Gl n Met Asn Ser Leu Arg Pro Gl u Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Al a Ala Val Pro Ala Gly Arg Leu Arg Tyr Gly Gl u Gl n Trp Tyr Pro
100 105 110

I l e T y r G l u T y r A s p A l a T r p G l y G l n G l y T h r L e u V a l T h r V a l S e r
 115 120 125

Ser

<210> 166
 <211> 129
 <212> PRT
 <213> Arti f i c i a l

<220>
 <223> Mutated Lama sequence

<400> 166

G l u V a l G l n L e u V a l G l u S e r G l y G l y G l y L e u V a l G l n P r o G l y G l y
 1 5 10 15

S e r L e u A r g L e u S e r C y s A l a V a l S e r G l y I l e T h r L e u A s p A s p T y r
 20 25 30

A l a I l e G l y T r p P h e A r g G l n A l a P r o G l y L y s G l u A r g G l u G l y V a l
 35 40 45

S e r A l a I l e A r g S e r S e r G l y G l y S e r T h r T y r T y r A l a A s p S e r V a l
 50 55 60

L y s G l y A r g P h e T h r I l e S e r S e r A s p A s n S e r L y s A s n T h r V a l T y r
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L e u G l n M e t A s n S e r L e u A r g P r o G l u A s p T h r A l a V a l T y r T y r C y s
 85 90 95

A l a A l a V a l P r o A l a G l y A r g L e u A r g T y r G l y G l u G l n T r p T y r P r o
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 <213> Arti f i c i a l

<220>
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<400> 167

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 1 5 10 15

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

Ala Ile Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Gly Val
35 40 45

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

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

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

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

Leu Tyr Glu Tyr Asp Ala Trp Gly Gln Gly Thr Leu Val Thr Val Ser
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Ser

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<220>
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<400> 168

Asp Tyr Ala Ile Gly
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Asp Tyr Ala Leu Gly
1 5

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<400> 170

Tyr Tyr Ala Ile Gly
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Ala Ile Arg Ser Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
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Gly

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Cys Ile Arg Cys Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
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Gly

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Gly

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Glu Tyr Asp Ala
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Val Pro Ala Gly Arg Leu Arg Tyr Gly Glu Gln Trp Tyr Pro Ile Tyr
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Glu Tyr Asp Ala
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<212> DNA

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 Ser Val Ile Asp Glu Leu Glu Lys Lys Leu Val Thr Ala Thr Val Asn
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 Asn Ser Leu Leu Gln Lys Gln Gln His Asp Leu Met Glu Thr Val Asn
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Val Ile Gln His Arg Glu Asp Gly Ser Val Asp Phe Gln Arg Thr Trp
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