Brain Natriuretic Peptide engrafted Antibodies

Field of the Invention

The present invention relates to an antibody or a fragment thereof comprising at least one heterologous amino acid sequence incorporated within at least one CDR region of said antibody or fragment thereof, wherein said at least one heterologous amino acid sequence comprises an N-terminal linker sequence (Ntls), a Brain Natriuretic Peptide (BNP) and a C-terminal linker sequence (Ctls). Optionally, at least a portion of said at least one CDR region is replaced by said at least one heterologous amino acid sequence incorporated therein. At least 12 amino acid residues are present between amino acid residue HC (heavy chain) res25 according to Kabat and the first amino acid residue of the BNP in case of an incorporation of said heterologous amino acid sequence within CDRH1; amino acid residue HC res51 according to Kabat and the first amino acid residue of the BNP in case of an incorporation of said heterologous amino acid sequence within CDRH2; amino acid residue HC res92 according to Kabat and the first amino acid residue of the BNP in case of an incorporation of said heterologous amino acid sequence within CDRH3; amino acid residue LC (light chain) res26 according to Kabat and the first amino acid residue of the BNP in case of an incorporation of said heterologous amino acid sequence within CDRL1; amino acid residue LC res49 according to Kabat and the first amino acid residue of the BNP in case of an incorporation of said heterologous amino acid sequence within CDRL2; and/or amino acid residue LC res88 according to Kabat and the first amino acid residue of the BNP in case of an incorporation of said heterologous amino acid sequence within CDRL3. Additionally, at least 9 amino acid residues are present between the last amino acid residue of the BNP and amino acid residue HC res35a according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRH1; amino acid residue HC res57 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRH2; amino acid residue HC res106 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRH3; amino acid residue LC res 32 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRL1; amino acid residue LC res57 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRL2; and/or amino acid residue LC res98 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRL3. The present invention further relates to such antibody or fragment thereof for use in a method for treatment, a composition comprising such antibody or fragment thereof, a nucleic acid or a mixture of nucleic acids encoding such antibody or fragment thereof, a host cell comprising such nucleic acid or such mixture of nucleic acids and to a process for producing such antibody or fragment thereof.

Background of the Invention

Natriuretic peptides are a family of three structurally related peptides with neurohumoral actions. Atrial Natriuretic Peptide (ANP) is a peptide of 28 amino acids comprising a central ring structure formed by a disulfide bridge between cysteine residues 7 and 23. Human ANP is expressed as a 153 amino acid long pre-pro-hormone in atrial myocyte cells. Signal peptide cleavage yields the prohormone form, which is subsequently further cleaved into the mature ANP and the N-terminal remnant, known as NT-proANP. Similar to ANP, also Brain Natriuretic Peptide (BNP) and C-Type Natriuretic Peptide (CNP) are produced from precursor proteins and comprise a central ring structure. ANP is mainly produced and released by cardiomyocytes of the left and right heart atria, whereas BNP is mainly produced by cardiomyocytes of the ventricles. CNP is synthesized by endothelial cells of blood vessels. Apart from these locations natriuretic peptides are also produced in smaller amounts in other parts of the body, e.g., in brain, kidney and adrenal gland. Natriuretic peptides are encoded by three separate genes, NPPA, NPPB, and NPPC. The amino acid sequences of the three peptides are highly conserved in mammals (Potter et al., Handb Exp Pharmacol. 2009; (191):341-66). Yet, significant sequence modifications of natriuretic peptides such as truncations, amino acid exchanges as well chimeric fusions (e.g. CD-NP (McKie et al., Curr Heart Fail Rep. 2010 Sep; 7 (3): 93-9)) have been described to result in potent natriuretic peptides that activate or bind to cellular receptors and can elicit relevant physiological effects.

Natriuretic peptides bind to three different, membrane-bound receptor types - NPR-A, NPR-B, and NPR-C - thereby mediating their biological effects. ANP and BNP bind with greatest affinity to NPR-A; in contrast, CNP has the highest affinity for the NPR-B receptor. NPR-A and NPR-B comprise a (particulate) guanylate cyclase domain (pGC) whose enzymatic activity causes an increase in (intracellular) cyclic guanosine monophosphate (cGMP). As a second messenger, cGMP regulates diverse cellular processes. The NPR-C receptor exhibits no guanylate cyclase activity and is also termed “clearance” receptor, as it can bind natriuretic peptides, which leads to their degradation by endocytosis. An additional signaling function of the NPR-C receptor via modulation of cAMP has been described (Anand-Srivastava, Peptides. 2005 Jun; 26 (6): 1044-59).

The cardiac hormones ANP and BNP are excreted upon stretching of the ventricles and atria, e.g. due to excessive plasma volume. They exert vasodilating effects via relaxation of vascular smooth muscle and lead to a reduction in blood pressure. In the kidney ANP causes i.a. an increase in urinary excretion (diuresis), as well as an increase in the concentration of sodium ions in the urine (natriuresis). ANP is considered to constitute a compensatory antagonist of the renin-angiotensin-aldosterone system (RAAS), which is over-activated in a number of cardiovascular diseases. In addition, ANP exerts other neuro-humoral effects, including an inhibitory effect on the sympathetic nervous system, as well as a

complex regulatory effect on the baroreflex (Woods et al., Clin Exp Pharmacol Physiol. 2004 Nov; 31 (11): 791-4). For ANP, as well as BNP and CNP, anti-inflammatory, anti-hypertrophic and anti-fibrotic effects have been demonstrated in animal models for different diseases (e.g. Knowles et al., 2001, J. Clin. Invest. 107: 975-984; Dahrouj et al., J Pharmacol Exp Ther. 2013 Jan; 344 (1): 96-102; Baliga et al., Br J Pharmacol. 2014 Jul; 171 (14): 3463-75; Mitaka et al. Intensive Care Med Exp. 2014 Dec; 2 (1): 28; Werner et al., Basic Res Cardiol. 2016 Mar; 111 (2): 22; Kimura et al., Respir Res. 2016 Feb 19; 17: 19). Activation of NPR-B by CNP is plays a significant role in bone growth (Yasoda et al., Clin. Calcium. 2009 Jul; 19 (7): 1003-8) and vascular endothelium integrity (Moyes et al., J Clin Invest. 2014 Sep; 124 (9): 4039-51).

The broad spectrum of physiological effects of natriuretic peptides and their receptors make them attractive targets in drug discovery (Lumsden et al., Curr Pharm Des. 2010; 16 (37): 4080-8; Buglioni et al., Annu Rev Med. 2016; 67: 229-43). For example, the natriuretic cGMP system may be suppressed under various pathophysiological conditions, which may result in hypertension, increased cell proliferation, fibrosis, inflammation, endothelial dysfunction, diabetes, metabolic syndrome, atherosclerosis, cardiac insufficiency, myocardial infarction, pulmonary hypertension, ocular and renal diseases, bone disorders, stroke and/or sexual dysfunction.

A major hurdle for the therapeutic use of natriuretic peptides is their very short plasma half-life of only a few minutes in the organism (Hunt et al., J Clin Endocrinol Metab. 1994 Jun; 78 (6): 1428-35; Kimura et al., Eur J Clin Pharmacol. 2007 Jul; 63 (7): 699-702). In addition to endocytosis by the NPR-C receptor, the natriuretic peptides are efficiently proteolytically degraded by the enzymes neprilysin (NEP) and insulin degrading enzyme (IDE). The associated short-term biological effects of administered natriuretic peptides have restricted their therapeutic use primarily to acute indications. For example, infusions of recombinant carperitide (ANP) and nesiritide (BNP) are approved for the treatment of acute decompensated heart failure in different countries.

The treatment of chronic diseases would be greatly facilitated by the provision of NPR-A and NPR-B agonists with increased plasma half-lives, higher proteolytic stability and prolonged duration of action.

In recent years, several natriuretic peptide derivatives and variants have been described, e.g., CD-NP (McKie et al., Curr Heart Fail Rep. 2010 Sep; 7 (3): 93-9), ZD100 / MANP (McKie et al., Hypertension. 2010 Dec; 56 (6): 1152-9), PL-3994 (Edelson et al., Pulm Pharmacol Ther. 2013 Apr; 26 (2): 229-38), Ularitide (Anker et al., Eur Heart J. 2015 Mar 21; 36 (12): 715-2), ANX-042 (Pan et al., Proc Natl Acad Sci USA. 2009 Jul. 7; 106 (27): 11282-7) and BMN-111 (Wendt et al., J. Pharmacol Exp Ther. 2015 Apr; 353 (1): 132-49). The half-life of CD-NP is about 18.5 min (Lee et al., BMC Pharmacology 2007,

7 (Suppl I): P38). Further ANP and CNP derivatives are disclosed in US 9,193,777 and EP 2 432 489 A, respectively.

In addition, natriuretic peptide fusions including Fc fusions, albumin fusion and PEGylated natriuretic peptides have been described. Natriuretic peptide-Fc fusions are for example disclosed in US 2010/0310561, WO 2008/154226, WO 2010/117760, WO 2006/107124, WO 2008/136611 and WO 2008/079995. Natriuretic peptide-albumin fusions are disclosed in US 7,521,424 and US 2014/0148390 and PEGylated natriuretic peptides are disclosed in US 2014/0148390.

WO 2005/060642 describes the generation of ANP and BNP peptide engrafted antibody libraries obtained by inserting ANP or BNP with two randomized flanging amino acids on both ends into the CDRH3 region of a human tetanus toxoid specific antibody. Similarly, WO 2005/082004 discloses the generation of an ANP mimetic engrafted antibody library obtained by replacing the entire original CDRH3 region of a 2G12 antibody with an ANP mimetic peptide flanked by two random amino acid residues on either side. Neither one of WO 2005/060642 and WO 2005/082004 discloses any specific natriuretic peptide engrafted antibodies, let alone functionally characterizes such antibodies.

Objects of the Invention

In view of the prior art it is an object of the present invention to provide novel natriuretic peptide receptor agonists with increased stability in serum as compared to naturally occurring wild type natriuretic peptides.

Summary of the Invention

The above stated object is achieved by the teaching of the subject independent claims. The present inventors have surprisingly found that biologically active natriuretic peptide variants with significantly increased stability in serum as compared to naturally occurring wild type natriuretic peptides can be obtained by incorporating a natriuretic peptide amino acid sequence into one of the CDR regions of an immunoglobulin molecule or a fragment thereof, despite the short length and high sequence conservation of immunoglobulin CDR regions, which impose considerable conformational restrains to the incorporation of biologically active peptides. However, the activity of natriuretic peptides incorporated within an immunoglobulin CDR region was shown to vary considerably. The present inventors have found that the decisive factor for a successful incorporation yielding a biologically active natriuretic peptide variant is the number of amino acid residues between the incorporated natriuretic

peptide and the nearest neighboring CDR-framework junctions N-terminal and C-terminal from the incorporated natriuretic peptide. Below a certain number of N-terminal and C-terminal flanking amino acid residues between natriuretic peptide and neighboring CDR-framework junctions only natriuretic peptide immunoglobulin fusion constructs with no or drastically reduced biological activity were obtained. Specific linker sequences flanking the incorporated natriuretic peptide were found to be especially advantageous for achieving high peptide activity, good expression levels and/or low protein fragmentation levels.

Thus, in a first aspect, the present invention relates to an antibody or a fragment thereof comprising at least one heterologous amino acid sequence incorporated within at least one CDR region of said antibody or fragment thereof, wherein said at least one heterologous amino acid sequence comprises an N-terminal linker sequence (Ntls), a natriuretic peptide and a C-terminal linker sequence (Ctls), wherein optionally at least a portion of said at least one CDR region is replaced by said at least one heterologous amino acid sequence incorporated therein, and wherein

a) at least 12 amino acid residues are present between
   i) amino acid residue HC res25 according to Kabat (in the heavy chain having the amino acid sequence of SEQ ID NO 65 this corresponds to res S25) and the first amino acid residue of the natriuretic peptide in case of an incorporation of said heterologous amino acid sequence within CDRH1;
   ii) amino acid residue HC res51 according to Kabat (in the heavy chain having the amino acid sequence of SEQ ID NO 65 this corresponds to res I51) and the first amino acid residue of the natriuretic peptide in case of an incorporation of said heterologous amino acid sequence within CDRH2;
   iii) amino acid residue HC res92 according to Kabat (in the heavy chain having the amino acid sequence of SEQ ID NO 65 this corresponds to res C96) and the first amino acid residue of the natriuretic peptide in case of an incorporation of said heterologous amino acid sequence within CDRH3;
   iv) amino acid residue LC res26 according to Kabat (in the light chain having the amino acid sequence of SEQ ID NO 66 this corresponds to res S25) and the first amino acid residue of the natriuretic peptide in case of an incorporation of said heterologous amino acid sequence within CDRL1;
   v) amino acid residue LC res49 according to Kabat (in the light chain having the amino acid sequence of SEQ ID NO 66 this corresponds to res Y51) and the first amino acid residue of the natriuretic peptide in case of an incorporation of said heterologous amino acid sequence within CDRL2; and/or

vi) amino acid residue LC res88 according to Kabat (in the light chain having the amino acid sequence of SEQ ID NO 66 this corresponds to res C90) and the first amino acid residue of the natriuretic peptide in case of an incorporation of said heterologous amino acid sequence within CDRL3; and wherein

b) at least 9 amino acid residues are present between the last amino acid residue of the natriuretic peptide and

i) amino acid residue HC res35a according to Kabat (in the heavy chain having the amino acid sequence of SEQ ID NO 65 this corresponds to res M34) in case of an incorporation of said heterologous amino acid sequence within CDRH1;

ii) amino acid residue HC res57 according to Kabat (in the heavy chain having the amino acid sequence of SEQ ID NO 65 this corresponds to res T58) in case of an incorporation of said heterologous amino acid sequence within CDRH2;

iii) amino acid residue HC res106 according to Kabat (in the heavy chain having the amino acid sequence of SEQ ID NO 65 this corresponds to res G111) in case of an incorporation of said heterologous amino acid sequence within CDRH3;

iv) amino acid residue LC res 32 according to Kabat (in the light chain having the amino acid sequence of SEQ ID NO 66 this corresponds to res D34) in case of an incorporation of said heterologous amino acid sequence within CDRL1;

v) amino acid residue LC res57 according to Kabat (in the light chain having the amino acid sequence of SEQ ID NO 66 this corresponds to res G59) in case of an incorporation of said heterologous amino acid sequence within CDRL2; and/or

vi) amino acid residue LC res98 according to Kabat (in the light chain having the amino acid sequence of SEQ ID NO 66 this corresponds to res F102) in case of an incorporation of said heterologous amino acid sequence within CDRL3.

In further aspects, the present invention relates to such antibody or fragment thereof for use in a method for treatment, a composition comprising such antibody or fragment thereof, a nucleic acid or a mixture of nucleic acids encoding such antibody or fragment thereof, a host cell comprising such nucleic acid or such mixture of nucleic acids and to a process for producing such antibody or fragment thereof.

Detailed Description of the Invention

The present invention may be understood more readily by reference to the following detailed description of the invention and the examples included therein.

In a first aspect, the present invention relates to an antibody or a fragment thereof comprising at least one heterologous amino acid sequence incorporated within at least one CDR region of said antibody or fragment thereof, wherein said at least one heterologous amino acid sequence comprises an N-terminal linker sequence (Ntls), a natriuretic peptide and a C-terminal linker sequence (Ctls), wherein optionally at least a portion of said at least one CDR region is replaced by said at least one heterologous amino acid sequence incorporated therein.

The present inventors have found that biologically active natriuretic peptide variants with significantly increased stability in serum as compared to naturally occurring wild type natriuretic peptides can be obtained by incorporating a natriuretic peptide amino acid sequence into one of the CDR regions of an immunoglobulin molecule or a fragment thereof. This finding was entirely unexpected. As is well known in the art, the short length and high sequence conservation of immunoglobulin CDR regions, which are especially pronounced in CDRL1, CDRL2, CDRL3, CDRH1 and CDRH2, impose considerable conformational restrains to the incorporation of biologically active peptides, and the surrounding immunoglobulin sequences may negatively affect expression, folding and/or biological activity of the incorporated peptide. Indeed, the present inventors have found that the activity of natriuretic peptides incorporated within an immunoglobulin CDR region varied considerably depending on the exact way the natriuretic peptide engrafted antibody was constructed. The decisive factor for a successful incorporation yielding a functional, i.e. biologically active natriuretic peptide variant was shown to be the number of amino acid residues between the incorporated natriuretic peptide and the nearest neighboring CDR-framework junctions N-terminal and C-terminal from the incorporated natriuretic peptide. Below a certain number of N-terminal and C-terminal flanking amino acid residues between natriuretic peptide and the neighboring CDR-framework junctions no biologically active natriuretic peptide immunoglobulin fusion constructs were obtained.

The terms “incorporated”, “inserted”, “integrated”, “engrafted” and “embedded” as well as “incorporation”, “insertion”, “integration”, “engrafting” and “embedding” are used interchangeably herein. Within the context of the present invention, these terms refer to the generation of hybrid polynucleic acids or hybrid polypeptides by the introduction of a heterologous sequence into the original sequence of an antibody or an antibody fragment. Such an incorporation may be done by any means. Typically, the antibody or fragment thereof comprising a natriuretic peptide flanked by an N-terminal and a C-terminal linker sequence is generated by recombinant DNA technology and expression as described herein.

Incorporation of the natriuretic peptide flanked by an N-terminal and a C-terminal linker sequence into a CDR region of the original antibody or antibody fragment sequence may result in the deletion of at least

a portion of said CDR region. For instance, cloning of a nucleic acid sequence encoding said heterologous amino acid sequence comprising an N-terminal linker sequence, a natriuretic peptide and a C-terminal linker sequence may be performed such that part of the CDR encoding sequence is replaced by the incorporated heterologous nucleic acid sequence. In particular other embodiments, the incorporation of the heterologous amino acid sequence comprising the natriuretic peptide does not result in the deletion of amino acid residues of the CDR region into which the heterologous amino acid sequence is inserted.

Within the context of the present invention, the term "heterologous amino acid sequence" refers to an amino acid sequence that does not originate from the initial "empty" antibody or fragment thereof, into which it is incorporated. Engrafting of the heterologous amino acid sequence into an antibody or fragment thereof thus yields an engineered, recombinant antibody molecule composed of amino acid sequences of different origin.

The term "natriuretic peptide" refers to peptides that can induce natriuresis, the excretion of sodium by the kidneys. Natriuretic peptides include Atrial Natriuretic Peptide (ANP), Brain Natriuretic Peptide (BNP), C-Type Natriuretic Peptide (CNP), Dendroaspis natriuretic peptide (DNP) and Urodilatin. Natriuretic peptides within the meaning of the present invention may be of any origin. Natriuretic peptides include natural natriuretic peptides such as wild type natriuretic peptides and mutant versions thereof as well as homolog natriuretic peptides of a different species. The term however also encompasses engineered natriuretic peptides such as engineered chimeric variants of distinct natriuretic peptides. It is known that the usage of codons is different between species. Thus, when expressing a heterologous protein in a target cell, it may be necessary, or at least helpful, to adapt the nucleic acid sequence to the codon usage of the target cell. Methods for designing and constructing derivatives of a given protein are well known to anyone of ordinary skill in the art.

In particular embodiments, the natriuretic peptide is selected from a wild type natriuretic peptide of any species and a functional variant of any such wild type natriuretic peptide. Within the context of the present invention, the term "functional variant of a natriuretic peptide" or "functional natriuretic peptide variant" refers to a natriuretic peptide of any origin, including natural and engineered peptides, that differs in the amino acid sequence and/or the nucleic acid sequence encoding the amino acid sequence of a given natriuretic peptide, such as a wild type natriuretic peptide of a given species, but is still functionally active. Within the context of the present invention, the term "functionally active" refers to the ability of a natriuretic peptide variant to perform the biological functions of a naturally occurring natriuretic peptide, in particular a wild type natriuretic peptide. In particular, "functionally active" means that the natriuretic peptide variant is able to bind to its respective receptor. In case of NPR-A and NPR-

B ligands, “functionally active” particularly means the ability to mediate an increase in (intracellular) cyclic guanosine monophosphate (cGMP) by binding to one or both of these receptors.

In particular embodiments, the functional natriuretic peptide variant is able to perform one or more biological functions of a given natriuretic peptide, such as a wild type natriuretic peptide of any given species to at least about 50%, particularly to at least about 60%, to at least about 70%, to at least about 80%, and most particularly to at least about 90%, wherein the one or more biological functions include, but are not limited to, binding of the natriuretic peptide to its respective receptor and/or induction of an increase in intracellular cGMP.

The functional activity of natriuretic peptides can be measured by any methods including in vitro methods that make it possible either to measure the increase of (intracellular) cyclic guanosine monophosphate (cGMP), or to measure changes in cellular processes regulated by cGMP, including the methods described in Examples 3 and 5. In particular embodiments, a (non-engrafted) natriuretic peptide variant is considered functionally active, if its EC_{50}value as determined by the fluorescence assay described in Example 3 is below 500 nM, more particularly below 250 nM, more particularly below 150 nM, more particularly below 100 nM, more particularly below 50 nM, most particularly below 25 nM.

Incorporation of such a functional natriuretic peptide variant into one of the CDR regions of an immunoglobulin molecule or a fragment thereof as described herein yields a natriuretic peptide engrafted immunoglobulin with natriuretic peptide functional activity and significantly increased stability in serum as compared to the non-engrafted functional natriuretic peptide variant as shown in the Examples. An natriuretic peptide engrafted immunoglobulin is considered biologically active (i.e. functional), if it gives a significant positive signal in any method that measures the increase of (intracellular) cyclic guanosine monophosphate (cGMP) either directly or indirectly by assessing changes in cellular processes regulated by cGMP. In particular, the functional activity of a natriuretic peptide engrafted immunoglobulin may be assessed by the methods described in Examples 3 and 5. In case of natriuretic peptide engrafted immunoglobulins, significance is typically assessed based on i) comparison to a negative sample such as an empty immunoglobulin scaffold, e.g. construct #209, an antibody comprising SEQ ID NO 65 and SEQ ID NO 66, TPP-5657, ii) comparison to a positive sample, e.g. construct #117, an antibody comprising SEQ ID NO 67 and SEQ ID NO 66, TPP-5661, and iii) dose dependency.

Even though the functional natriuretic peptide variant according to the present invention may contain any number of mutations comprising additions, deletions and/or substitutions of one or more amino acids in comparison to the reference natriuretic peptide, a functional natriuretic peptide variant will

typically maintain key features of the corresponding natriuretic peptide, such as key residues within the central ring domain. Conserved residues of natriuretic peptides are for instance described in Lincoln R. Potter et al. (Handb Exp Pharmacol. 2009; (191): 341–366). Thus, in particular embodiments, the functional natriuretic peptide variant shares at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90% or at least 95% sequence identity with the sequence shown below:

$X_1CFGX_2X_3X_4DRIX_5X_6X_7SX_8LGC$

wherein X_1 and X_5 are G or S;
X_3 is R or K;
X_6 is A or S; and
X_2, X_4, X_7 and X_8 may be any amino acid.

In principle, natriuretic peptides of any type may be incorporated within a CDR region of an immunoglobulin or fragment thereof as described herein. In particular, the present inventors have found that the findings for one type of natriuretic peptide regarding both minimal requirements for satisfactory biological activity of the engrafted natriuretic peptide and especially suitable N-terminal and C-terminal amino acid sequences may be conferred to other types of natriuretic peptides. Without wishing to be bound by theory it is hypothesized that these similar requirements for successful embedding of a natriuretic peptide within an immunoglobulin molecule among different natriuretic peptide types may be due to structural similarities and/or mechanisms of action within the natriuretic peptide family.

In particular embodiments, the natriuretic peptide is selected from the group consisting of human ANP having the sequence of SEQ ID NO 23, human BNP having the sequence of SEQ ID NO 24, human CNP having the sequence of SEQ ID NO 25 and a peptide having at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or at least 98% sequence identity with any one of SEQ ID NOs 23 to 25. Again, the natriuretic peptide having a sequence deviating from wild type human natriuretic peptides ANP, BNP and CNP may be of any natural origin, e.g. a mutant version of a wild type human natriuretic peptide, or a homolog of a different species, or an engineered natriuretic peptide. Methods for designing and constructing peptide variants are well known to anyone of ordinary skill in the art.

In particular such embodiments, the natriuretic peptide having at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or at least 98% sequence identity with any one of SEQ ID NOs 23 to 25 is a functional natriuretic peptide variant.

"Percent (%) sequence identity" with respect to a reference polynucleotide or polypeptide sequence, respectively, is defined as the percentage of nucleic acid or amino acid residues, respectively, in a candidate sequence that are identical to the nucleic acid or amino acid residues, respectively, in the reference polynucleotide or polypeptide sequence, respectively, after aligning the sequences and optionally introducing gaps, if necessary, to achieve the maximum percent sequence identity. Conservative substitutions are not considered as part of the sequence identity. In particular embodiments, any gaps introduced in the candidate sequence and/or the reference sequence may in total not amount to more than 50%, more than 40%, more than 30%, more than 25%, more than 20%, more than 15% or more than 10% of the total amount of residues of the reference sequence. In particular embodiments, the percentage sequence identity is determined without introducing any gaps into the candidate or the reference sequence (i.e. using an ungapped alignment). Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are well within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared.

The natriuretic peptide that shares a given percentage of sequence identity with a given reference natriuretic peptide, e.g., human BNP having the amino acid sequence of SEQ ID NO 24, may contain one or more mutations comprising an addition, a deletion and/or a substitution of one or more amino acids in comparison to the reference natriuretic peptide. According to the teaching of the present invention, said deleted, added and/or substituted amino acids may be consecutive amino acids or may be interspersed over the length of the amino acid sequence of the natriuretic peptide that shares a given percentage of sequence identity with a reference natriuretic peptide, e.g., human BNP having the amino acid sequence of SEQ ID NO 24. On the DNA level, the nucleic acid sequences encoding the natriuretic peptide that shares a given percentage of sequence identity with a given reference natriuretic peptide may differ to a larger extent due to the degeneracy of the genetic code.

According to the teaching of the present invention, any number of amino acids may be added, deleted, and/or substituted, as long as the stipulated amino acid sequence identity with the reference natriuretic peptide is adhered to. In particular embodiments, the stipulated amino acid sequence identity is adhered to and the natriuretic peptide variant is biologically active, i.e. is a functional natriuretic peptide variant. Preferably, the biologic activity of the natriuretic peptide that shares a given percentage of sequence identity with a given reference natriuretic peptide, e.g., human BNP having the amino acid sequence as found in SEQ ID NO 24, is reduced by less than 90%, less than 80%, less than 70%, less than 60%, less

than 50%, less than 25% or less than 10% compared to said reference natriuretic peptide as measured in the above described assay.

The term "antibody", as used herein, is intended to refer to immunoglobulin molecules, particularly dimeric immunoglobulin molecules comprised of four polypeptide chains - two heavy (H) chains and two light (L) chains which are typically inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. The heavy chain constant region can comprise e.g. three domains CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as VL) and a light chain constant region. The light chain constant region is comprised of one domain (CL). The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is typically composed of three CDRs and four FRs arranged from amino-terminus to carboxy-terminus e.g. in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4.

As used herein, the term "Complementarity Determining Regions" (CDRs; e.g., CDR1, CDR2, and CDR3) refers to the amino acid residues of an antibody variable domain the presence of which are necessary for antigen binding. Each variable domain typically has three CDR regions identified as CDR1, CDR2 and CDR3. Each complementarity determining region may comprise amino acid residues from a "complementarity determining region" as defined by Kabat (e.g. about residues 24-34 (CDRL1), 50-56 (CDRL2) and 89-97 (CDRL3) in the light chain variable domain and 31-35 (CDRH1), 50-65 (CDRH2) and 95-102 (CDRH3) in the heavy chain variable domain; (Kabat et al., Sequences of Proteins of Immulological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991)) and/or those residues from a "hypervariable loop" (e.g. about residues 26-32 (CDRL1), 50-52 (CDRL2) and 91-96 (CDRL3) in the light chain variable domain and 26- 32 (CDRH1), 53-55 (CDRH2) and 96-101 (CDRH3) in the heavy chain variable domain (Chothia and Lesk; J Mol Biol 196: 901-917 (1987)). In some instances, a complementarity determining region can include amino acids from both a CDR region defined according to Kabat and a hypervariable loop.

Depending on the amino acid sequence of the constant domain of their heavy chains, intact antibodies can be assigned to different "classes". There are five major classes of intact antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these maybe further divided into "subclasses" (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2. Within the context of the present invention, the term "antibody" includes immunoglobulin molecules of any primary class - including IgG, IgE, IgM, IgD, IgA and IgY - and any subclass - including, IgG1, lgG2, lgG3, lgG4, IgA1 and Ig A2 - isolated from nature or prepared by recombinant means and includes all conventionally known antibodies. A preferred class of

immunoglobulins for use in the present invention is IgG. The term "antibody" also extends to other protein scaffolds that are able to orient antibody CDR inserts into the same active binding conformation as that found in natural antibodies such that binding of the target antigen observed with these chimeric proteins is maintained relative to the binding activity of the natural antibody from which the CDRs were derived.

Within the context of the present invention, the term "fragment" of an antibody/immunoglobulin refers to any part of an antibody/immunoglobulin that comprises at least one CDR region. Particularly, the antibody fragment according to the present invention retains the ability to increase the serum half-life of a biologically active peptide, preferably a natriuretic peptide, incorporated therein. Antibody fragments according to the present invention include Fab, Fab', Fab'-SH, F(ab')2, and Fv fragments; diabodies; single domain antibodies (Dabs); linear antibodies; single-chain antibody molecules (scFv); and disulfide-stabilized Fv antibody fragments (dsFv); as well as multispecific antibodies formed from antibody fragments and fragments comprising a VL or VH domain, which are prepared from intact immunoglobulins or prepared by recombinant means.

The $F(ab')_2$ or Fab may be engineered to minimize or completely remove the intermolecular disulfide interactions that occur between the CH1 and CL domains. Antibody fragments according to the present invention may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, CH3 and CL domains. Also included are antibody fragments comprising any combination of variable region(s) with a hinge region, CH1, CH2, CH3 and CL domain.

The antibody or fragment thereof constitutes a scaffold that confers stability to the natriuretic peptide incorporated therein. For example, the serum half-life of a natriuretic peptide incorporated within the CDR region of an antibody as described herein may be increased as compared to that of a naturally occurring natriuretic peptide.

Principally, the heterologous amino acid sequence comprising the natriuretic peptide may be incorporated within any immunoglobulin molecule or fragment thereof. In particular, immunoglobulins of any species (including but not limited to human, bovine, murine, rat, pig, dog, shark, lama and camel) and any primary class and subclass may be used according to the present invention. For therapeutic use a human or humanized antibody may however be preferable. Within the context of the present invention, the term "human antibody" refers to antibodies having the amino acid sequence of a human immunoglobulin and includes antibodies isolated from human immunoglobulin libraries, from human B cells, or from animals transgenic for one or more human immunoglobulin as well as synthetic human antibodies. In particular embodiments the amino acid light chain and heavy chain sequences of the

variable domain derive from human germline sequences LV 1-40 and HV 3-23, respectively (for more information see Example 1).

Within the context of the present invention, the term "humanized antibody" or "humanized antibody fragment" refers to an antibody or fragment thereof that is (i) derived from a non-human source (e.g., a transgenic mouse which bears a heterologous immune system), which antibody is based on a human germline sequence; or (ii) chimeric, wherein the variable domain is derived from a non-human origin and the constant domain is derived from a human origin or (iii) CDR-grafted, wherein the CDRs of the variable domain are from a non-human origin, while one or more frameworks of the variable domain are of human origin and the constant domain (if any) is of human origin.

The antibody or fragment thereof according to the present invention may be monospecific, bispecific, trispecific or of greater multispecificity.

In the context of the present invention, the term "comprises" or "comprising" means "including, but not limited to". The term is intended to be open-ended, to specify the presence of any stated features, elements, integers, steps or components, but not to preclude the presence or addition of one or more other features, elements, integers, steps, components or groups thereof. The term "comprising" thus includes the more restrictive terms "consisting of" and "essentially consisting of". In one embodiment, the term "comprising" as used throughout the application and in particular within the claims may be replaced by the term "consisting of".

In the context of the present invention, the term "about" or "approximately" means within 80% to 120%, alternatively within 90% to 110%, including within 95% to 105% of a given value.

In the antibody or fragment thereof according to the invention, a) at least 12 amino acid residues are present between

i) amino acid residue HC res25 according to Kabat (in the heavy chain having the amino acid sequence of SEQ ID NO 65 this corresponds to res S25) and the first amino acid residue of the natriuretic peptide in case of an incorporation of the heterologous amino acid sequence within CDRH1;

ii) amino acid residue HC res51 according to Kabat (in the heavy chain having the amino acid sequence of SEQ ID NO 65 this corresponds to res I51) and the first amino acid residue of the natriuretic peptide in case of an incorporation of the heterologous amino acid sequence within CDRH2;

iii) amino acid residue HC res92 according to Kabat (in the heavy chain having the amino acid sequence of SEQ ID NO 65 this corresponds to res C96) and the first amino acid residue of the natriuretic peptide in case of an incorporation of the heterologous amino acid sequence within CDRH3;

iv) amino acid residue LC res26 according to Kabat (in the light chain having the amino acid sequence of SEQ ID NO 66 this corresponds to res S25) and the first amino acid residue of the natriuretic peptide in case of an incorporation of the heterologous amino acid sequence within CDRL1;

v) amino acid residue LC res49 according to Kabat (in the light chain having the amino acid sequence of SEQ ID NO 66 this corresponds to res Y51) and the first amino acid residue of the natriuretic peptide in case of an incorporation of the heterologous amino acid sequence within CDRL2; and/or

vi) amino acid residue LC res88 according to Kabat (in the light chain having the amino acid sequence of SEQ ID NO 66 this corresponds to res C90) and the first amino acid residue of the natriuretic peptide in case of an incorporation of the heterologous amino acid sequence within CDRL3;

and b) at least 9 amino acid residues are present between the last amino acid residue of the natriuretic peptide and

i) amino acid residue HC res35a according to Kabat (in the heavy chain having the amino acid sequence of SEQ ID NO 65 this corresponds to res M34) in case of an incorporation of the heterologous amino acid sequence within CDRH1;

ii) amino acid residue HC res57 according to Kabat (in the heavy chain having the amino acid sequence of SEQ ID NO 65 this corresponds to res T58) in case of an incorporation of the heterologous amino acid sequence within CDRH2;

iii) amino acid residue HC res106 according to Kabat (in the heavy chain having the amino acid sequence of SEQ ID NO 65 this corresponds to res G111) in case of an incorporation of the heterologous amino acid sequence within CDRH3;

iv) amino acid residue LC res 32 according to Kabat (in the light chain having the amino acid sequence of SEQ ID NO 66 this corresponds to res D34) in case of an incorporation of the heterologous amino acid sequence within CDRL1;

v) amino acid residue LC res57 according to Kabat (in the light chain having the amino acid sequence of SEQ ID NO 66 this corresponds to res G59) in case of an incorporation of the heterologous amino acid sequence within CDRL2; and/or

vi) amino acid residue LC res98 according to Kabat (in the light chain having the amino acid sequence of SEQ ID NO 66 this corresponds to res F102) in case of an incorporation of the heterologous amino acid sequence within CDRL3.

The denomination of the above listed amino acid residues refers to the amino acid position in the original immunoglobulin molecule before incorporation of the heterologous amino acid sequence. Within the context of the present invention, the above listed amino acid residues are referred to as "reference amino acids" or "reference aa". These reference amino acid residues lie at or near CDR framework junctions but do not necessarily correspond to standard CDR border definitions (standard CDR border definitions are amino acid residues S25 and W36 for CDRH1; S49 and R67 for CDRH2; K98 and W108 for CDRH3; C22 and W37 for CDRL1; Y51 and G59 for CDRL2; C90 and F102 for CDRL3. Jarasch and Skerra, Proteins 2017 Jan; 85 (1): 65-71).

The nearest neighboring reference aa N-terminal from the inserted natriuretic peptide plus the amino acid stretch present between said reference aa and the first amino acid residue of the inserted natriuretic peptide are herein referred to as "N-terminal sequence". The N-terminal sequence comprises the Ntls. In particular embodiments, the N-terminal sequence consists of the Ntls plus the neighboring N-terminal reference aa.

The amino acid stretch present between the last amino acid residue of the inserted natriuretic peptide and the nearest neighboring reference aa C-terminal from the inserted natriuretic peptide plus and said reference aa are herein referred to as "C-terminal sequence". The C-terminal sequence comprises the Ctls. In particular embodiments, the C-terminal sequence consists of the Ctls plus the neighboring C-terminal reference aa.

In particular embodiments, the Ntls comprises a GS linker sequence; a PN linker sequence; an amino acid sequence which is part of a human IgG antibody scaffold or a sequence that shares at least 80% sequence identity therewith, particularly an amino acid sequence which is part of the fab domain scaffold of a human IgG antibody or a sequence that shares at least 80% sequence identity therewith, more particularly the sequence of any one of SEQ ID NOs 1, 2 or 4, or a sequence that shares at least 80% sequence identity with any one of SEQ ID NOs 1, 2 or 4; the sequence of any one of SEQ ID NOs 6, 7, 9, 11, 13, 15, 16, 17, 19 or 21; or a sequence that shares at least 60%, at least 70%, at least 80%, at least 90% or at least 95% sequence identity with any one of SEQ ID NO 6, 7, 9, 11, 13, 15, 16, 17, 19 or 21. The Ntls may also comprise any combination of the above listed amino acid sequences.

In particular such embodiments, the Ntls comprises a GS linker sequence; a PN linker sequence; an amino acid sequence which is part of a human IgG antibody scaffold or a sequence that shares at least 80% sequence identity therewith, particularly an amino acid sequence which is part of the fab domain scaffold of a human IgG antibody or a sequence that shares at least 80% sequence identity therewith,

more particularly the sequence of any one of SEQ ID NOs 1, 2 or 4, or a sequence that shares at least 80% sequence identity with any one of SEQ ID NOs 1, 2 or 4; the sequence of any one of SEQ ID NOs 6, 7, 9, 11, 13, 15 or 21; a sequence that shares at least 60%, at least 70%, at least 80%, at least 90%, or at least 95% sequence identity with any one of SEQ ID NO 6, 7, 9, 11, 13, 15, or 21; or any combination thereof.

In particular embodiments, the Ctls comprises a GS linker sequence; a PN linker sequence; an amino acid sequence which is part of a human IgG antibody scaffold or a sequence that shares at least 80% sequence identity therewith, particularly an amino acid sequence which is part of the fab domain scaffold of a human IgG antibody or a sequence that shares at least 80% sequence identity therewith, more particularly the sequence of any one of SEQ ID NOs 1, 3 or 5, or a sequence that shares at least 80% sequence identity with any one of SEQ ID NOs 1, 3 or 5; the sequence of any one of SEQ ID NOs 6, 8, 10, 12, 14, 15, 17, 18, 19, 20 or 22; or a sequence that shares at least 60%, at least 70%, at least 80%, at least 90% or at least 95% sequence identity with any one of SEQ ID NOs 6, 8, 10, 12, 14, 15, 17, 18, 19, 20 or 22. The Ctls may also comprise any combination of the above listed amino acid sequences.

In particular embodiments, the Ctls comprises a GS linker sequence; a PN linker sequence; an amino acid sequence which is part of a human IgG antibody scaffold or a sequence that shares at least 80% sequence identity therewith, particularly an amino acid sequence which is part of the fab domain scaffold of a human IgG antibody or a sequence that shares at least 80% sequence identity therewith, more particularly the sequence of any one of SEQ ID NOs 1, 3 or 5, or a sequence that shares at least 80% sequence identity with any one of SEQ ID NOs 1, 3 or 5; the sequence of any one of SEQ ID NOs 6, 8, 10, 12, 14, 15, 20 or 22; a sequence that shares at least 60%, at least 70%, at least 80%, at least 90% or at least 95% sequence identity with any one of SEQ ID NOs 6, 8, 10, 12, 14, 15, 20 or 22; or any combination thereof.

In particular embodiments the sequence identity between the sequence comprised in the Ntls and/or the Ctls and any one of SEQ ID NOs 1 to 22 is at least 60%, particularly at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or 100%.

Within the context of the present invention the term “GS linker sequence” refers to a peptide linker comprising mainly glycine and serine residues. Particularly, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or 100% of the amino acid residues of the GS linker sequence according to the present invention are selected from glycine and serine residues. The GS linker sequence according to the present invention may for example comprise from 1 to 30

amino acid residues in total. Particularly, the GS linker sequence according to the present invention does not comprise more than 3, 2 or 1 amino acid residue(s) other than glycine or serine.

Within the context of the present invention the term "PN linker sequence" refers to a peptide linker comprising mainly proline and asparagine residues. Particularly, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or 100% of the amino acid residues of the PN linker sequence according to the present invention are selected from proline and asparagine residues. The PN linker sequence according to the present invention may for example comprise from 1 to 30 amino acid residues in total. Particularly, the PN linker sequence according to the present invention does not comprise more than 3, 2 or 1 amino acid residue(s) other than proline or asparagine. Other amino acid residues that may be present in a PN linker sequence according to the present invention are for instance lysine or glutamic acid residues.

In particular embodiments, the linker sequence comprised in the Ntls and/or the Ctls and selected from a GS linker sequence; a PN linker sequence; a human IgG antibody scaffold linker sequence; a human IgG fab domain scaffold sequence; a sequence that shares at least 80% sequence identity with the human IgG antibody scaffold linker sequence, the human IgG fab domain scaffold sequence or the sequence of any one of SEQ ID NOs 1 to 5; and a sequence that shares at least 60% sequence identity with any one of SEQ ID NOs 6 to 22, comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid residues. The linker sequence comprised in the Ntls and/or the Ctls may for instance comprise up to 30, 28, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11 or 10 amino acid residues.

In the case of linkers comprising a sequence of a human IgG antibody scaffold or a sequence that shares at least 80% sequence identity therewith, it may be particularly advantageous to use a sequence of a scaffold region which is adjacent to the CDR into which the heterologous amino acid sequence is incorporated. For example, the Ntls and/or the Ctls may comprise a linker comprising an amino acid sequence that is part of framework region FRH2 or FRH3 in case the heterologous amino acid sequence is incorporated within the CDRH2 domain. Similarly, the Ntls and/or the Ctls may comprise a linker comprising an amino acid sequence that is part of framework region FRL2 or FRL3 in case the heterologous amino acid sequence is incorporated within the CDRL2 region.

In particular embodiments, the Ntls consists of a GS linker sequence; a PN linker sequence; an amino acid sequence which is part of a human IgG antibody scaffold or a sequence that shares at least 80% sequence identity therewith, particularly an amino acid sequence which is part of the fab domain scaffold of a human IgG antibody or a sequence that shares at least 80% sequence identity therewith, more particularly the sequence of any one of SEQ ID NOs 1, 2 or 4 or a sequence that shares at least

80% sequence identity with any one of SEQ ID NOs 1, 2 or 4; the sequence of any one of SEQ ID NOs 6, 7, 9, 11, 13, 15, 16, 17, 19 or 21; a sequence that shares at least 60%, at least 70%, at least 80%, at least 90% or at least 95% sequence identity with any one of SEQ ID NOs 6, 7, 9, 11, 13, 15, 16, 17, 19 or 21; or any combination thereof.

In particular embodiments, the Ctls consists of a GS linker sequence; a PN linker sequence; an amino acid sequence which is part of a human IgG antibody scaffold or a sequence that shares at least 80% sequence identity therewith, particularly an amino acid sequence which is part of the fab domain scaffold of a human IgG antibody or a sequence that shares at least 80% sequence identity therewith, more particularly the sequence of any one of SEQ ID NOs 1, 3 or 5 a sequence that shares at least 80% sequence identity with any one of SEQ ID NOs 1, 3 or 5; the sequence of any one of SEQ ID NOs 6, 8, 10, 12, 14, 15, 17, 18, 19, 20 or 22; a sequence that shares at least 60%, at least 70%, at least 80%, at least 90% or at least 95% sequence identity with any one of SEQ ID NOs 6, 8, 10, 12, 14, 15, 17, 18, 19, 20 or 22; or any combination thereof.

In particular embodiments, both the Ntls and the Ctls comprise at least one of the above listed linker sequences or any combination thereof. In principle, any of the above listed Ntls linker sequences may be combined with any of the above listed Ctls linker sequences. In particular, any linker sequence may be combined with a GS linker. As a non-limiting example, a GS Ctls linker may be combined with an Ntls linker comprising the sequence of any one of SEQ ID NOs 6, 9 or 15 or a sequence that shares at least 60% sequence identity with any one of SEQ ID NOs 6, 9 or 15. A further non-limiting example is a GS Ntls linker combined with a Ctls linker comprising the sequence of SEQ ID NO 15 or a sequence that shares at least 60% sequence identity therewith.

The above listed linker sequences have proven particularly advantageous for achieving good natriuretic peptide activities, given a sufficient total length of the N-terminal and C-terminal flanking sequences. Without wishing to be bound by theory, it is believed that the above listed linker peptide stretches result in a conformation/folding that contributes to a favorable state of the system in presentation of a biologically active natriuretic peptide to its respective receptor with minimal sterical hindrance.

In particular embodiments, i) the Ntls comprises a GS linker sequence; a PN linker sequence; the sequence of SEQ ID NOs 2, 4, 9, 11, 13 or 15; a sequence that shares at least 60% sequence identity with SEQ ID NOs 2, 4, 9, 11, 13 or 15; or any combination thereof and ii) the Ctls comprises a GS linker sequence; a PN linker sequence; the sequence of SEQ ID NOs 3, 5, 12, 14, 15 or 20; a sequence that shares at least 60% sequence identity with SEQ ID NOs 3, 5, 12, 14, 15 or 20; or any combination thereof. These linker sequences have proven particularly useful as they not only achieve high natriuretic

peptide activities but also good expression levels in recombinant expression and are not prone to protein fragmentation upon expression (see Table 9).

In particular embodiments, the Ntls and the Ctls each comprise a GS linker sequence; the Ntls and the Ctls each comprise a PN linker sequence; the Ntls and the Ctls each comprise an amino acid sequence which is part of a human IgG antibody scaffold or a sequence that shares at least 80% sequence identity therewith, particularly an amino acid sequence which is part of the fab domain scaffold of a human IgG antibody or a sequence that shares at least 80% sequence identity therewith, more particularly the Ntls comprises the sequence of any one of SEQ ID NOs 1, 2 or 4 or a sequence that shares at least 80% sequence identity with any one of SEQ ID NOs 1, 2 or 4 and the Ctls comprises the sequence of any one of SEQ ID NOs 1, 3 or 5 or a sequence that shares at least 80% sequence identity therewith; the Ntls and the Ctls each comprise the sequence of SEQ ID NO 6 or a sequence that shares at least 60% sequence identity therewith; the Ntls comprises the sequence of SEQ ID NO 7 or a sequence that shares at least 60% sequence identity therewith and the Ctls comprises the sequence of SEQ ID NO 8 or a sequence that shares at least 60% sequence identity therewith; the Ntls comprises the sequence of SEQ ID NO 9 or a sequence that shares at least 60% sequence identity therewith and the Ctls comprises the sequence of SEQ ID NO 10 or a sequence that shares at least 60% sequence identity therewith; the Ntls comprises the sequence of SEQ ID NO 11 or a sequence that shares at least 60% sequence identity therewith and the Ctls comprises the sequence of SEQ ID NO 12 or a sequence that shares at least 60% sequence identity therewith; the Ntls comprises the sequence of SEQ ID NO 13 or a sequence that shares at least 60% sequence identity therewith and the Ctls comprises the sequence of SEQ ID NO 14 or a sequence that shares at least 60% sequence identity therewith; the Ntls and the Ctls each comprise the sequence of SEQ ID NO 15 or a sequence that shares at least 60% sequence identity therewith; the Ntls comprises the sequence of SEQ ID NO 16 or a sequence that shares at least 60% sequence identity therewith and the Ctls comprises the sequence of SEQ ID NO 17 or a sequence that shares at least 60% sequence identity therewith; the Ntls comprises the sequence of SEQ ID NO 17 or a sequence that shares at least 60% sequence identity therewith and the Ctls comprises the sequence of SEQ ID NO 18 or a sequence that shares at least 60% sequence identity therewith; the Ntls and the Ctls each comprise the sequence of SEQ ID NO 19 or a sequence that shares at least 60% sequence identity therewith; the Ntls comprises the sequence of SEQ ID NO 9 or a sequence that shares at least 60% sequence identity therewith and the Ctls comprises the sequence of SEQ ID NO 20 or a sequence that shares at least 60% sequence identity therewith; or the Ntls comprises the sequence of SEQ ID NO 21 or a sequence that shares at least 60% sequence identity therewith and the Ctls comprises the sequence of SEQ ID NO 22 or a sequence that shares at least 60% sequence identity therewith.

In particular such embodiments, the Ntls and the Ctls each comprise a GS linker sequence; the Ntls and the Ctls each comprise a PN linker sequence; the Ntls and the Ctls each comprise an amino acid sequence which is part of a human IgG antibody scaffold or a sequence that shares at least 80% sequence identity therewith, particularly an amino acid sequence which is part of the fab domain scaffold of a human IgG antibody or a sequence that shares at least 80% sequence identity therewith, more particularly the Ntls comprises the sequence of any one of SEQ ID NOs 1, 2 or 4 or a sequence that shares at least 80% sequence identity with any one of SEQ ID NOs 1, 2 or 4 and the Ctls comprises the sequence of any one of SEQ ID NOs 1, 3 or 5 or a sequence that shares at least 80% sequence identity therewith; the Ntls and the Ctls each comprise the sequence of SEQ ID NO 6 or a sequence that shares at least 60% sequence identity therewith; the Ntls comprises the sequence of SEQ ID NO 7 or a sequence that shares at least 60% sequence identity therewith and the Ctls comprises the sequence of SEQ ID NO 8 or a sequence that shares at least 60% sequence identity therewith; the Ntls comprises the sequence of SEQ ID NO 9 or a sequence that shares at least 60% sequence identity therewith and the Ctls comprises the sequence of SEQ ID NO 10 or a sequence that shares at least 60% sequence identity therewith; the Ntls comprises the sequence of SEQ ID NO 11 or a sequence that shares at least 60% sequence identity therewith and the Ctls comprises the sequence of SEQ ID NO 12 or a sequence that shares at least 60% sequence identity therewith; the Ntls comprises the sequence of SEQ ID NO 13 or a sequence that shares at least 60% sequence identity therewith and the Ctls comprises the sequence of SEQ ID NO 14 or a sequence that shares at least 60% sequence identity therewith; the Ntls and the Ctls each comprise the sequence of SEQ ID NO 15 or a sequence that shares at least 60% sequence identity therewith; the Ntls comprises the sequence of SEQ ID NO 9 or a sequence that shares at least 60% sequence identity therewith and the Ctls comprises the sequence of SEQ ID NO 20 or a sequence that shares at least 60% sequence identity therewith; or the Ntls comprises the sequence of SEQ ID NO 21 or a sequence that shares at least 60% sequence identity therewith and the Ctls comprises the sequence of SEQ ID NO 22 or a sequence that shares at least 60% sequence identity therewith .

In particular such embodiments, the Ntls and the Ctls each comprise a GS linker sequence; the Ntls and the Ctls each comprise a PN linker sequence; the Ntls comprises the sequence of SEQ ID NO 2 or a sequence that shares at least 80% sequence identity therewith and the Ctls comprises the sequence of SEQ ID NO 3 or a sequence that shares at least 80% sequence identity therewith; the Ntls comprises the sequence of SEQ ID NO 4 or a sequence that shares at least 80% sequence identity therewith and the Ctls comprises the sequence of SEQ ID NO 5 or a sequence that shares at least 80% sequence identity therewith; the Ntls comprises the sequence of SEQ ID NO 11 or a sequence that shares at least 60% sequence identity therewith and the Ctls comprises the sequence of SEQ ID NO 12 or a sequence that shares at least 60% sequence identity therewith; the Ntls comprises the sequence of SEQ ID NO 13 or a sequence that shares at least 60% sequence identity therewith and the Ctls comprises the sequence of

SEQ ID NO 14 or a sequence that shares at least 60% sequence identity therewith; the Ntls and the Ctls each comprise the sequence of SEQ ID NO 15 or a sequence that shares at least 60% sequence identity therewith; or the Ntls comprises the sequence of SEQ ID NO 9 or a sequence that shares at least 60% sequence identity therewith and the Ctls comprises the sequence of SEQ ID NO 20 or a sequence that shares at least 60% sequence identity therewith. These linker combinations have proven particularly useful for achieving high natriuretic peptide activities, good expression levels in recombinant expression and minimal or no protein fragmentation, as shown in Table 9.

In particular embodiments, the Ntls further comprises an anchoring element A1 at its C terminal end and/or the Ctls further comprises an anchoring element A2 at its N terminal end, wherein A1 and A2 predominantly comprise glycine and serine residues. In particular embodiments, A1 and/or A2 comprise at least 1, 2, 3, 4, or 5 amino acid residues. A1 and/or A2 may comprise up to 10, 9, 8, 7, 6 or 5 amino acid residues in total. In particular embodiments, at least 60%, at least 70%, at least 80%, at least 90%, or 100% of the amino acid residues of A1 and/or A2 are selected from glycine and serine residues. Particularly A1 and/or A2 do/does not comprise more than 3, 2 or 1 amino acid residue other than glycine or serine.

In particular embodiments the Ntls consists of i) an anchoring element A1 at its C terminal end and ii) a GS linker sequence; a PN linker sequence; an amino acid sequence which is part of a human IgG antibody scaffold or a sequence that shares at least 80% sequence identity therewith, particularly an amino acid sequence which is part of the fab domain scaffold of a human IgG antibody or a sequence that shares at least 80% sequence identity therewith, more particularly the sequence of any one of SEQ ID NOs 1, 2 or 4 or a sequence that shares at least 80% sequence identity with any one of SEQ ID NOs 1, 2 or 4; the sequence of any one of SEQ ID NOs 6, 7, 9, 11, 13, 15, 16, 17, 19 or 21; a sequence that shares at least 60% sequence identity with any one of SEQ ID NO 6, 7, 9, 11, 13, 15, 16, 17, 19 or 21; or any combination thereof.

In particular embodiments, the Ctls consists of i) an anchoring element A2 at its N terminal end and ii) a GS linker sequence; a PN linker sequence; an amino acid sequence which is part of a human IgG antibody scaffold or a sequence that shares at least 80% sequence identity therewith, particularly an amino acid sequence which is part of the fab domain scaffold of a human IgG antibody or a sequence that shares at least 80% sequence identity therewith, more particularly the sequence of any one of SEQ ID NOs 1, 3 or 5 a sequence that shares at least 80% sequence identity with any one of SEQ ID NOs 1, 3 or 5; the sequence of any one of SEQ ID NOs 6, 8, 10, 12, 14, 15, 17, 18, 19, 20 or 22; a sequence that

shares at least 60% sequence identity with any one of SEQ ID NOs 6, 8, 10, 12, 14, 15, 17, 18, 19, 20 or 22; or any combination thereof.

In particular embodiments, the Ntls and/or the Ctls comprise(s) at least 3, 4, 5, 6, 7, 8, 9 or 10 amino acid residues in total. The Ntls and/or the Ctls may for instance comprise up to 30, 28, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11 or 10 amino acid residues in total.

In particular embodiments, the amino acid stretch present between

i) amino acid residue HC res25 according to Kabat and the first amino acid residue of the natriuretic peptide in case of an incorporation of said heterologous amino acid sequence within CDRH1;
ii) amino acid residue HC res51 according to Kabat and the first amino acid residue of the natriuretic peptide in case of an incorporation of said heterologous amino acid sequence within CDRH2;
iii) amino acid residue HC res92 according to Kabat and the first amino acid residue of the natriuretic peptide in case of an incorporation of said heterologous amino acid sequence within CDRH3;
iv) amino acid residue LC res26 according to Kabat and the first amino acid residue of the natriuretic peptide in case of an incorporation of said heterologous amino acid sequence within CDRL1;
v) amino acid residue LC res49 according to Kabat and the first amino acid residue of the natriuretic peptide in case of an incorporation of said heterologous amino acid sequence within CDRL2; and/or
vi) amino acid residue LC res88 according to Kabat and the first amino acid residue of the natriuretic peptide in case of an incorporation of said heterologous amino acid sequence within CDRL3

comprises the sequence of any one of SEQ ID NOs 26 to 38 or a sequence having at least 80%, 85%, 90%, 95% or at least 98% sequence identity with any one of SEQ ID NOs 26 to 38.

In particular embodiments, the amino acid stretch present between the last amino acid residue of the natriuretic peptide and

i) amino acid residue HC res35a according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRH1;
ii) amino acid residue HC res57 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRH2;
iii) amino acid residue HC res106 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRH3;
iv) amino acid residue LC res 32 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRL1;
v) amino acid residue LC res57 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRL2; and/or

vi) amino acid residue LC res98 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRL3

comprises the sequence of any one of SEQ ID NOs 39 to 51 or a sequence having at least 80%, 85%, 90%, 95% or at least 98% sequence identity with any one of SEQ ID NOs 39 to 51.

In particular embodiments, the heterologous amino acid sequence consists of the Ntls, the natriuretic peptide and the Ctls.

In particular embodiments, the amino acid stretch present between

i) amino acid residue HC res25 according to Kabat and amino acid residue HC res35a according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRH1;

ii) amino acid residue HC res51 according to Kabat and amino acid residue HC res57 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRH2;

iii) amino acid residue HC res92 according to Kabat and amino acid residue HC res106 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRH3;

iv) amino acid residue LC res26 according to Kabat and amino acid residue LC res 32 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRL1;

v) amino acid residue LC res49 according to Kabat and amino acid residue LC res57 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRL2; and/or

vi) amino acid residue LC res88 according to Kabat and amino acid residue LC res98 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRL3

comprises the sequence of any one of SEQ ID NOs 52 to 64 or a sequence having at least 80%, 85%, 90%, 95% or at least 98% sequence identity with any one of SEQ ID NOs 52 to 64.

In particular embodiments, the antibody or fragment thereof comprises at least two natriuretic peptides. In particular embodiments, both natriuretic peptides are comprised in a heterologous amino acid sequence further comprising an Ntls and a Ctls and incorporated within a CDR region of said antibody or fragment thereof, as described herein. The at least two natriuretic peptides may be incorporated within the two corresponding CDR regions of two light chains or two heavy chains or the at least two natriuretic peptides may be incorporated within two separate CDR regions. The at least two natriuretic peptides may be the same or different. In particular such embodiments, the antibody or fragment thereof comprises at least two different natriuretic peptides that are incorporated within at least two CDR regions.

Due to the dimeric structure of antibody molecules, the insertion of one nucleic acid sequence encoding the heterologous amino acid sequence (Ntls-natriuretic peptide-Ctls) into the nucleic acid encoding either the light or the heavy chain of an immunoglobulin molecule typically yields an antibody protein carrying two natriuretic peptides located in the corresponding CDR regions of the two identical light or the two identical heavy chains. However, it is also envisaged to insert two natriuretic peptide encoding nucleic acids into two different CDR encoding regions of the nucleic acid sequences encoding the light and/or the heavy chain, thereby yielding an antibody molecule with four natriuretic peptides located in two corresponding CDR pairs of the dimeric antibody. Also encompassed are dimeric immunoglobulin molecules whose light chains and/or heavy chains are not identical, for instance including dimeric antibodies carrying a single natriuretic peptide as well as dimeric antibodies carrying two different natriuretic peptides in two corresponding CDR regions of the two light or the two heavy chains.

In particular embodiments, natriuretic peptides are inserted in the CDRH1 and CDRH2, CDRH1 and CDRH3, CDRH2 and CDRH3, CDRH1 and CDRL1, CDRH1 and CDRL2, CDRH1 and CDRL3, CDRH2 and CDRL1, or CDRH2 and CDRL2. In particular embodiments, the antibody or fragment thereof comprises one ANP and one BNP molecule; one ANP and one CNP molecule; or one BNP and one CNP molecule.

In particular embodiments, the natriuretic peptide comprised in the at least one heterologous amino acid sequence incorporated within at least one CDR region of said antibody or fragment thereof is an BNP and the antibody or fragment thereof comprises at least one further natriuretic peptide. In particular embodiments, the at least one further natriuretic peptide is also comprised in a heterologous amino acid sequence further comprising an Ntls and a Ctls and incorporated within a CDR region of said antibody or fragment thereof. In particular embodiments, the BNP and the at least one further natriuretic peptide are incorporated within two corresponding CDR regions of either the two light or the two heavy chains of the antibody or fragment thereof. In particular other embodiments, the BNP and the at least one further natriuretic peptide are incorporated within at least two separate CDR regions. Particularly, said at least one further natriuretic peptide is selected from ANP, BNP and CNP, more particularly from ANP and CNP.

The “empty” antibody molecule not harboring a heterologous amino acid sequence comprising a natriuretic peptide which is composed of two heavy chains having the sequence of SEQ ID NO 65 and two light chains having the sequence of SEQ ID NO 66 is termed TPP-5657. In particular embodiments, an antibody molecule composed of two heavy chains having the sequence of SEQ ID NO 65 or a sequence having at least 80%, at least 85%, at least 90% or at least 95% sequence identity therewith and two light chains having the sequence of SEQ ID NO 66 or a sequence having at least 80%, at least 85%,

at least 90% or at least 95% sequence identity therewith serves as the initial or parental antibody, into which the heterologous amino acid sequence comprising the natriuretic peptide is incorporated. In particular such embodiments, the heterologous amino acid sequence comprising the natriuretic peptide is incorporated within a CDR region of one or both heavy chains of such antibody molecule.

In particular such embodiments, the heavy chain(s) comprising the at least one heterologous amino acid sequence incorporated within at least one of its CDR regions has the sequence of any one of SEQ ID NOs 67 to 79 or a sequence having at least 80%, at least 85%, at least 90% or at least 95% sequence identity with any one of SEQ ID NOs 67 to 79. In particular embodiments, the antibody according to the present invention is composed of two identical heavy chains having the sequence of any one of SEQ ID NOs 67 to 79 or a sequence having at least 80%, at least 85%, at least 90% or at least 95% sequence identity with any one of SEQ ID NOs 67 to 79 and two identical light chains having the sequence of SEQ ID NO 66 or a sequence having at least 80%, at least 85%, at least 90% or at least 95% sequence identity therewith.

In particular other embodiments, the heterologous amino acid sequence comprising the natriuretic peptide is incorporated within a CDR region of one or both light chains of such antibody molecule. In particular such embodiments, the light chain(s) comprising the at least one heterologous amino acid sequence incorporated within at least one of its CDR regions has(have) the sequence of any one of SEQ ID NOs 80 or 81 a sequence having at least 80%, at least 85%, at least 90% or at least 95% sequence identity with any one of SEQ ID NOs 80 or 81. In particular embodiments, the antibody according to the present invention is composed of two identical light chains having the sequence of any one of SEQ ID NOs 80 or 81 or a sequence having at least 80%, at least 85%, at least 90% or at least 95% sequence identity with any one of SEQ ID NOs 80 or 81 and two identical heavy chains having the sequence of SEQ ID NO 65 or a sequence having at least 80%, at least 85%, at least 90% or at least 95% sequence identity therewith.

The table below depicts the heavy and light chain composition of exemplary antibodies according to the present invention.

Table 1: Exemplary natriuretic peptide engrafted antibody constructs

TPP-Number	Heavy Chain	Light Chain
TPP-5661	SEQ ID NO 67	SEQ ID NO 66
TPP-10274	SEQ ID NO 68	SEQ ID NO 66
TPP-10282	SEQ ID NO 69	SEQ ID NO 66
TPP-10283	SEQ ID NO 70	SEQ ID NO 66
TPP-10290	SEQ ID NO 71	SEQ ID NO 66
TPP-10294	SEQ ID NO 72	SEQ ID NO 66

TPP-10765	SEQ ID NO 73	SEQ ID NO 66
TPP-10845	SEQ ID NO 74	SEQ ID NO 66
TPP-10847	SEQ ID NO 75	SEQ ID NO 66
TPP-10992	SEQ ID NO 76	SEQ ID NO 66
TPP-13054	SEQ ID NO 77	SEQ ID NO 66
TPP-13061	SEQ ID NO 78	SEQ ID NO 66
TPP-13230	SEQ ID NO 79	SEQ ID NO 66
TPP-10355	SEQ ID NO 65	SEQ ID NO 80
TPP-10361	SEQ ID NO 65	SEQ ID NO 81
TPP-9902	SEQ ID NO 442	SEQ ID NO 66
TPP-11156	SEQ ID NO 443	SEQ ID NO 66
TPP-18034	SEQ ID NO 444	SEQ ID NO 66
TPP-12897	SEQ ID NO 445	SEQ ID NO 447
TPP-12377	SEQ ID NO 445	SEQ ID NO 66
TPP-9465	SEQ ID NO 446	SEQ ID NO 66

Antibodies of the present invention or fragments thereof include naturally occurring purified products, products of chemical synthetic procedures, and products produced by recombinant techniques. Depending on its origin, the antibody or fragment thereof according to the present invention may be glycosylated or non-glycosylated.

For example, standard recombinant DNA methodologies may be used to prepare and/or obtain nucleic acids encoding the heavy and light chains, incorporate these nucleic acids into expression vectors and introduce the vectors into host cells for recombinant expression (see, for example, Sambrook, Fritsch and Maniatis (eds.), Molecular Cloning; A Laboratory Manual, Second Edition, Cold Spring Harbor, N.Y., (1989); Ausubel, F. M. et al. (eds.) Current Protocols in Molecular Biology, Greene Publishing Associates, (1989); Goeddel, Gene Expression Technology, Methods in Enzymology 185, Academic Press, San Diego, Calif. (1990); and US 4,816,397 by Boss et al.).

Thus, in a second aspect, the present invention relates to a nucleic acid or a mixture of nucleic acids encoding the antibody or fragment thereof according to the present invention. These nucleic acid sequences may be optimized in certain cases for mammalian expression. DNA molecules of the invention are not limited to the sequences disclosed herein, but also include variants thereof.

The present invention further provides recombinant nucleic acid constructs comprising one or more of the nucleic acid sequences according to the present invention. The recombinant nucleic acid construct according to the present invention may for instance comprise a nucleic acid vector, such as a plasmid, into which a nucleic acid molecule encoding an antibody or fragment thereof according to the present invention has been inserted. It is understood that the design of the expression vector, including the selection of regulatory sequences is affected by factors such as the choice of the host cell, the desired protein expression level and whether constitutive or inducible expression is desired.

Useful expression vectors for bacterial use may be constructed by inserting one or more nucleic acid sequences according to the present invention together with suitable translation initiation and termination signals in operable reading phase with a functional promoter. Bacterial expression vectors typically comprise one or more phenotypic selectable markers and an origin of replication to ensure maintenance of the vector and, if desirable, to provide amplification within the bacterial host. Bacterial expression vectors may comprise elements derived from commercially available plasmids such as the well-known cloning vector pBR322 (ATCC 37017). A number of bacterial expression vectors may be advantageously selected depending upon the use intended of the expressed antibody or fragment thereof. For example, if a large quantity of such antibody is desired, vectors mediating high level expression of antibody fusion proteins that are readily purified may be desirable.

Recombinant nucleic acid constructs intended for antibody expression in a eukaryotic host cell may comprise regulatory sequences that are able to control the expression of an open reading frame in a eukaryotic cell, preferably a promoter and a polyadenylation signal. Promoters and polyadenylation signals are preferably selected to be functional within the specific cell type intended for antibody expression. Examples of suitable promoters include but are not limited to promoters from Cytomegalovirus (CMV), such as the strong CMV immediate early promoter, Simian Virus 40 (SV40), Mouse Mammary Tumor Virus (MMTV), Human Immunodeficiency Virus (HIV), such as the HIV Long Terminal Repeat (LTR) promoter, Moloney virus, Epstein Barr Virus (EBV), adenovirus (e.g., the adenovirus major late promoter (AdMLP)), polyoma and from Rous Sarcoma Virus (RSV), the synthetic CAG promoter composed of the CMV early enhancer element, the promoter, the first exon and the first intron of chicken beta-actin gene and the splice acceptor of the rabbit beta globin gene, as well as promoters from mammalian genes such as actin, myosin, hemoglobin, muscle creatine, and metallothionein. In a particular embodiment, the eukaryotic expression cassette contains the CMV promoter. In the context of the present invention, the term “CMV promoter” refers to the strong immediate-early cytomegalovirus promoter.

Examples of suitable polyadenylation signals include but are not limited to the bovine growth hormone (BGH) polyadenylation site, SV40 polyadenylation signals and LTR polyadenylation signals.

In addition, the recombinant nucleic acid sequence may comprise one or more enhancer sequences. The enhancer can be, for example, an enhancer of mammalian actin, myosin, hemoglobin, muscle creatine or a viral enhancer, e.g. an enhancer from CMV, RSV, SV40 or EBV. For further description of viral regulatory elements, and sequences thereof, see e.g., US 5,168,062 by Stinski, US 4,510,245 by Bell et al. and US 4,968,615 by Schaffner et al..

Regulatory sequences and codons are generally species dependent, so in order to maximize protein production, the regulatory sequences and codons are preferably selected to be effective in the species/cell type intended for antibody expression. The person skilled in the art can produce recombinant DNA molecules that are functional in a given subject species.

The mammalian recombinant expression vectors can also include origins of replication and selectable markers (see e.g., US 4,399,216, US 4,634,665 and US 5,179,017). Suitable selectable markers include genes that confer resistance to drugs such as G418, puromycin, hygromycin, blasticidin, zeocin/bleomycin or methotrexate or selectable marker that exploit auxotrophies such as Glutamine Synthetase on a host cell into which the vector has been introduced. For example, the dihydrofolate reductase (DHFR) gene confers resistance to methotrexate, the neo gene confers resistance to G418, the bsd gene from Aspergillus terreus confers resistance to blasticidin, puromycin N-acetyl-transferase confers resistance to puromycin, the Sh ble gene product confers resitance to zeocin, and resistance to hygromycin is conferred by the E. coli hygromycin resistance gene (hyg or hph). Selectable markers like DHFR or Glutamine Synthetase are also useful for amplification techniques in conjunction with MTX and MSX.

In some embodiments, the nucleic acid sequences encoding the heavy and light chains are inserted into separate vectors. In other embodiments, the nucleic acid sequences encoding the heavy and light chains are inserted into the same vector. In addition, the nucleic acid sequences encoding variable regions of the heavy and/or light chains can be converted, for example, to nucleic acid sequences encoding full-length antibody chains, Fab fragments, or to scFv. The VL- or VH-encoding DNA fragment can be operatively linked, (such that the amino acid sequences encoded by the two DNA fragments are in-frame) to another DNA fragment encoding, for example, an antibody constant region or a flexible linker. As an example, to create a polynucleotide sequence that encodes a scFv, the VH- and VL-encoding nucleic acids can be operatively linked to another fragment encoding a flexible linker such that the VH and VL sequences can be expressed as a contiguous single-chain protein, with the VL and VH regions joined by the flexible linker (see e.g., Bird et al. (1988) Science 242:423-426; Huston et al. (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883; McCafferty et al., Nature (1990) 348:552-554). The sequences of human heavy chain and light chain constant regions are known in the art (see e.g., Kabat, E. A., el al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242) and DNA fragments encompassing these regions can be obtained by standard PCR amplification.

In particular embodiments, the nucleic acid sequences encoding the heavy chain into which the heterologous amino acid sequence comprising the natriuretic peptide is incorporated comprises the sequence of any one of SEQ ID NOs 82 or 83 or a sequence having at least 80%, at least 85%, at least 90% or at least 95% sequence identity with any one of SEQ ID NOs 82 or 83. In particular such embodiments, the nucleic acid sequence encoding the light chain comprises the sequence of SEQ ID NO 84 or a sequence having at least 80%, at least 85%, at least 90% or at least 95% sequence identity therewith.

In a third aspect, the present invention relates to a host cell comprising the nucleic acid or the mixture of nucleic acids according to the present invention. Within the context of the present invention, the terms "host cell", "host cell line", and "host cell culture" are used interchangeably and refer to cells into which an exogenous nucleic acid has been introduced, including the progeny of such cells. Host cells include "transformants", "transformed cells", "transfectants", "transfected cells", and "transduced cells", which include the primary transformed/transfected/transduced cell and progeny derived therefrom without regard to the number of passages. Progeny may not be completely identical in nucleic acid content to a parent cell, and the comprised exogenous nucleic acid may contain mutations. Mutant progeny that have the same function or biological activity as screened or selected for in the originally transformed cell are included herein.

Transfection of the expression vector into a host cell can be carried out using standard techniques such as electroporation, nucleofection, calcium-phosphate precipitation, lipofection, polycation-based transfection such as polyethlylenimine (PEI)-based transfection and DEAE-dextran transfection.

Suitable host cells include prokaryotic and eukaryotic cells. Examples for prokaryotic host cells are e.g. bacteria and include but are not limited to Escherichia coli, Bacillus subtilis, Salmonella typhimurium and various species within the genera Pseudomonas, Streptomyces, and Staphylococcus.

Non limiting examples of eukaryotic hosts cells include yeasts, insects and insect cells, plants and plant cells, transgenic animals and mammalian cells. Suitable mammalian host cells for antibody expression include Chinese Hamster Ovary (CHO cells) such as CHO-K1, CHO-S, CHO-K1SV (including dhfr-CHO cells, described in Urlaub and Chasin, (1980) Proc. Natl. Acad. Sci. USA 77:4216-4220 and Urlaub et al., Cell. 1983 Jun;33(2):405-12, used with a DHFR selectable marker, e.g., as described in R. J. Kaufman and P. A. Sharp (1982) Mol. Biol. 159:601-621; and other knockout cells exemplified in Fan et al., Biotechnol Bioeng. 2012 Apr;109(4):1007-15), NS0 myeloma cells, COS cells, HEK293 cells, HKB11 cells, BHK21 cells, CAP cells, EB66 cells, and SP2 cells.

Expression may also be transient or semi-stable in expression systems such as HEK293, HEK293T, HEK293-EBNA, HEK293E, HEK293-6E, HEK293-Freestyle, HKB11, Expi293F, 293EBNALT75, CHO Freestyle, CHO-S, CHO-K1, CHO-K1SV, CHOEBNALT85, CHOS-XE, CHO-3E7 or CAP-T cells (for instance Durocher et al., Nucleic Acids Res. 2002 Jan 15;30(2):E9).

In a fourth aspect, the present invention relates to a process for producing an antibody or fragment thereof, comprising culturing the host cell according to the present invention. Particularly, the host cell according to the present invention is cultured under conditions suitable for expression of the antibody or fragment thereof.

Antibody expression may be constitutive or regulated (e.g., inducible). For inducible antibody expression the host cell according to the present invention is typically grown to an appropriate cell density followed by de-repression/induction of the selected promoter by appropriate means (e.g., temperature shift or chemical induction such as addition or removal of small molecule inductors such as tetracycline in conjunction with Tet system) and culturing of the host cell for an additional period.

In particular embodiments, the process for producing an antibody or fragment thereof according to the present invention further comprises the step of recovering the antibody or fragment thereof from the host cell culture. Cells may for instance be harvested by centrifugation, disrupted by physical or chemical means, and the antibody or fragment thereof may be further purified from the resulting crude extract. In some embodiments, the expression vector is designed such that the expressed antibody or fragment thereof is secreted into the culture medium in which the host cells are grown. In that case, the antibody or fragment thereof can be directly recovered from the culture medium using standard protein purification methods.

In particular embodiments, the process according to the present invention further comprises the step of purifying the recovered antibody or fragment thereof. Particularly, the antibody is purified (1) to greater than 90% as determined e.g. by analytical chromatography or by SDS-Capillary Gel electrophoresis (for example on a Caliper LabChip GXII, GX 90 or Biorad Bioanalyzer device), and, more particularly, purification yields an antibody homogeneity of at least about 92.5%, 95%, 98% or 99%; alternatively, the antibody is purified (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence, or (3) to homogeneity by SDS-PAGE under reducing or non-reducing conditions using Coomassie blue or, preferably, silver stain.

Antibodies or fragments thereof according to the present invention can be recovered and purified from recombinant cell cultures by well-known methods including, but not limited to ammonium sulfate or

ethanol precipitation, acid extraction, Protein A chromatography, Protein G chromatography, size exclusion chromatography, anion or cation exchange chromatography, phospho-cellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. High performance liquid chromatography ("HPLC") can also be employed for purification (see, e.g., Colligan, Current Protocols in Immunology, or Current Protocols in Protein Science, John Wiley & Sons, NY, N.Y., (1997-2001), e.g., Chapters 1, 4, 6, 8, 9, 10).

In a fifth aspect, the present invention relates to a composition comprising the antibody or fragment thereof according the present invention. Particularly, the composition according to the present invention is a pharmaceutical composition suitable for use in a method for treatment, wherein the antibody or fragment thereof according to the present invention is contained in an amount effective to achieve the intended purpose, i.e. prevention or treatment of a particular disease state.

The composition optionally further comprises at least one pharmaceutically acceptable excipient. In the context of the present invention, the term "excipient" refers to a natural or synthetic substance formulated alongside the active ingredient of a medication. Suitable excipients include antiadherents, binders, coatings, disintegrants, flavors, colors, lubricants, glidants, sorbents, preservatives and sweeteners. Specific examples of pharmaceutically acceptable excipients include but are not limited to saline, buffered saline, dextrose, and water. In the context of the present invention, the term "pharmaceutically acceptable" refers to molecular entities and other ingredients of pharmaceutical compositions that are physiologically tolerable and do not typically produce untoward reactions when administered to a mammal (e.g., human). The term "pharmaceutically acceptable" may also mean approved by a regulatory agency of a Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in mammals, and, more particularly, in humans.

The composition according to the present invention may further comprise one or more further therapeutically active agents.

The pharmaceutical composition may be in the form of a solution, a suspension, an enteric coated capsule, a lyophilized powder or any other form suitable for the intended use.

Pharmaceutical compositions for oral administration can be formulated using pharmaceutically acceptable excipients well known in the art in dosages suitable for oral administration. Such excipients enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for ingestion by the patient.

Pharmaceutical preparations for oral use can be obtained through combination of active compounds with solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are carbohydrate or protein fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose such as methyl-cellulose, hydroxypropylmethylcellulose, or sodium carboxymethyl cellulose; and gums including arabic and tragacanth; and proteins such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, alginic acid, or a salt thereof, such as sodium alginate.

Dragee cores can be provided with suitable coatings such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound, i.e. dosage.

Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating such as glycerol or sorbitol. Push-fit capsules can contain active ingredients mixed with a filler or binders such as lactose or starches, lubricants such as talc or magnesium stearate, and optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycol with or without stabilizers.

Pharmaceutical formulations for parenteral administration include aqueous solutions of a therapeutically active agent. For injection, the pharmaceutical compositions of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiologically buffered saline. Aqueous injection suspensions may contain substances that increase viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Additionally, suspensions of the active agent may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the therapeutically active agent to allow for the preparation of highly concentrated solutions.

For topical or nasal administration, penetrants appropriate to the particular barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

The pharmaceutical compositions of the present invention may be manufactured in a manner that is known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

The pharmaceutical composition may be provided as a salt and can be formed with acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. Salts tend to be more soluble in aqueous or other protonic solvents that are the corresponding free base forms. In other cases, the preferred preparation may be a lyophilized powder in 1 mM - 50 mM histidine, 0.1%-2% sucrose, 2%-7% mannitol at a pH range of 4.5 to 7.5 that is combined with buffer prior to use.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Ed. Maack Publishing Co, Easton, Pa.).

After preparation of a pharmaceutical composition comprising the antibody or fragment thereof according to the present invention, it may be placed in an appropriate container and labeled for treatment of an indicated condition. For administration of the antibody or fragment according to the present invention, such labeling would include amount, frequency and method of administration.

The present invention further provides pharmaceutical packs and kits comprising one or more containers filled with one or more of the ingredients of the aforementioned compositions according to the present invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, reflecting approval by the agency of the manufacture, use or sale of the product for human administration.

In a sixth aspect, the present invention relates to the antibody or fragment thereof according to the present invention or the composition according to the present invention for use in a method for treatment.

Particularly, such method for treatment involves administering to a subject in need thereof a therapeutically effective amount of the antibody or fragment thereof according to the present invention. The subject may be a human or non-human animal (e.g., rabbit, rat, mouse, dog, monkey or other lower-order primate).

Within the context of the present invention, the term "therapeutically effective amount" is defined as the amount of an antibody or fragment thereof according to the present invention that is sufficient to prevent or alleviate disease symptoms of any of the disorders and diseases mentioned herein - either as a single dose or according to a multiple dose regimen, alone or in combination with other agents. In particular embodiments, said "therapeutically effective amount" is toxicologically tolerable. The determination of an effective dose is well within the capability of those skilled in the art. The therapeutically effective amount of a therapeutic agent usually largely depends on particular patient characteristics such as age, weight, gender and disease state, time, frequency and route of administration, drug combination(s), and the nature of the disorder being treated. Common dosage amounts for antibodies vary from 0.1 to 100,000 micrograms, up to a total dose of about 10 g, depending upon the route of administration.

General guidance for its determination can be found, for example, in the publications of the International Conference on Harmonization and in REMINGTON'S PHARMACEUTICAL SCIENCES, chapters 27 and 28, pp. 484-528 (18th ed., Alfonso R. Gennaro, Ed., Easton, Pa.: Mack Pub. Co., 1990). More specifically, determining a therapeutically effective amount will depend on such factors as toxicity and efficacy of the medicament that may be determined using methods well known in the art and found in the foregoing references. In brief, therapeutic efficacy and toxicity of therapeutic agents may be determined in cell culture assays or in animal models, e.g., as ED50 (the dose therapeutically effective in 50% of the population) and LD50 (the dose lethal to 50% of the population), respectively. The dose ratio between ED50 and LD50 is the therapeutic index.

The antibody or fragment thereof according to the present invention is suitable for treatment and/or prophylaxis of cardiovascular, renal, pulmonary, skeletal, ocular, thromboembolic and fibrotic diseases and disorders, dwarfism, achondroplasia as well as other cGMP-related and/or natriuretic peptide responsive disorders. Thus, in particular embodiments, the antibody or fragment thereof is for use in the treatment and/or prophylaxis of any one of these disorders and diseases or any combination thereof.

The antibody or fragment thereof according to the present invention can therefore be used in medicaments for treatment and/or prophylaxis of cardiovascular disorders, for example arterial and pulmonary hypertension, resistant and refractory hypertension, acute and chronic heart failure, coronary heart disease, Bronchiolitis obliterans Syndrome (BOS), tumor related and oncological diseases, graft versus host disease, sickle cell disease, stable and unstable angina pectoris, peripheral and cardiac vascular disorders, arrhythmias, atrial and ventricular arrhythmias and impaired conduction, for example atrioventricular blocks degrees I-III (AB block I-III), supraventricular tachyarrhythmia, atrial fibrillation, atrial flutter, ventricular fibrillation, ventricular flutter, ventricular tachyarrhythmia, Torsade de pointes tachycardia, atrial and ventricular extrasystoles, AV-junctional extrasystoles, sick sinus

syndrome, syncopes, AV-nodal re-entry tachycardia, Wolff-Parkinson-White syndrome, of acute coronary syndrome (ACS), autoimmune cardiac disorders (pericarditis, endocarditis, valvolitis, aortitis, cardiomyopathies), shock such as cardiogenic shock, septic shock and anaphylactic shock, aneurysms, boxer cardiomyopathy (premature ventricular contraction (PVC)), for treatment and/or prophylaxis of thromboembolic disorders and ischaemias such as myocardial ischaemia, myocardial infarction, stroke, cardiac hypertrophy, transient and ischaemic attacks, preeclampsia, inflammatory cardiovascular disorders, spasms of the coronary arteries and peripheral arteries, oedema formation, for example pulmonary oedema, cerebral oedema, renal oedema or oedema caused by heart failure, peripheral circulatory disturbances, reperfusion damage, arterial and venous thromboses, microalbuminuria, myocardial insufficiency, endothelial dysfunction, to prevent restenosis, for example after thrombolysis therapies, percutaneous transluminal angioplasties (PTA), transluminal coronary angioplasties (PTCA), heart transplants and bypass operations, and also micro- and macrovascular damage (vasculitis), increased levels of fibrinogen and of low-density lipoprotein (LDL) and increased concentrations of plasminogen activator inhibitor 1 (PAI-1), and also for treatment and/or prophylaxis of erectile dysfunction and female sexual dysfunction.

In the context of the present invention, the term “heart failure” encompasses both acute and chronic forms of heart failure, and also more specific or related types of disease, such as acute decompensated heart failure, right heart failure, left heart failure, global failure, ischaemic cardiomyopathy, dilated cardiomyopathy, hypertrophic cardiomyopathy, idiopathic cardiomyopathy, congenital heart defects, heart failure associated with heart valve defects, mitral valve stenosis, mitral valve insufficiency, aortic valve stenosis, aortic valve insufficiency, tricuspid valve stenosis, tricuspid valve insufficiency, pulmonary valve stenosis, pulmonary valve insufficiency, combined heart valve defects, myocardial inflammation (myocarditis), chronic myocarditis, acute myocarditis, viral myocarditis, diabetic heart failure, alcoholic cardiomyopathy, cardiac storage disorders, diastolic heart failure and systolic heart failure, heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF) and acute phases of worsening of existing chronic heart failure (worsening heart failure).

In addition, the antibody or fragment thereof according to the present invention can also be used for treatment and/or prophylaxis of arteriosclerosis, peripheral artery disease (PAD), impaired lipid metabolism, hypolipoproteinaemias, dyslipidaemias, hypertriglyceridaemias, hyperlipidaemias, hypercholesterolaemias, abetalipoproteinaemia, sitosterolaemia, xanthomatosis, Tangier disease, adiposity, obesity and of combined hyperlipidaemias and metabolic syndrome.

The antibody or fragment thereof according to the present invention can additionally be used for treatment and/or prophylaxis of primary and secondary Raynaud's phenomenon, of microcirculation impairments, claudication, peripheral and autonomic neuropathies, diabetic microangiopathies, diabetic retinopathy, diabetic ulcers on the extremities, gangrene, CREST syndrome, erythematosis, onychomycosis, rheumatic disorders and for promoting wound healing.

The antibody or fragment thereof according to the present invention is also suitable for treating urological disorders, for example benign prostate syndrome (BPS), benign prostate hyperplasia (BPH), benign prostate enlargement (BPE), bladder outlet obstruction (BOO), lower urinary tract syndromes (LUTS, including Feline Urological Syndrome (FUS)), disorders of the urogenital system including neurogenic overactive bladder (OAB) and (IC), incontinence (UI), for example mixed urinary incontinence, urge urinary incontinence, stress urinary incontinence or overflow urinary incontinence (MUI, UUI, SUI, OUI), pelvic pain, benign and malignant disorders of the organs of the male and female urogenital system.

The antibody or fragment thereof according to the present invention is also suitable for treatment and/or prophylaxis of kidney disorders, in particular of acute and chronic renal insufficiency and acute and chronic renal failure. In the context of the present invention, the term "renal insufficiency" encompasses both acute and chronic manifestations of renal insufficiency, and also underlying or related renal disorders such as renal hypoperfusion, intradialytic hypotension, obstructive uropathy, glomerulopathies, glomerulonephritis, acute glomerulonephritis, glomerulosclerosis, tubulointerstitial diseases, nephropathic disorders such as primary and congenital kidney disease, nephritis, immunological kidney disorders such as kidney transplant rejection and immunocomplex-induced kidney disorders, nephropathy induced by toxic substances, nephropathy induced by contrast agents, diabetic and non-diabetic nephropathy, pyelonephritis, renal cysts, nephrosclerosis, hypertensive nephrosclerosis and nephrotic syndrome which can be characterized diagnostically, for example by abnormally reduced creatinine and/or water excretion, abnormally elevated blood concentrations of urea, nitrogen, potassium and/or creatinine, altered activity of renal enzymes, for example glutamyl synthetase, altered urine osmolarity or urine volume, elevated microalbuminuria, macroalbuminuria, lesions on glomerulae and arterioles, tubular dilatation, hyperphosphatemia and/or need for dialysis. The present invention also encompasses the use of the antibody or fragment thereof according to the present invention for treatment and/or prophylaxis of sequelae of renal insufficiency, for example pulmonary oedema, heart failure, uraemia, anaemia, electrolyte disturbances (for example hyperkalaemia, hyponatraemia) and disturbances in bone and carbohydrate metabolism.

In addition, the antibody or fragment thereof according to the present invention are also suitable for treatment and/or prophylaxis of asthmatic disorders, pulmonary arterial hypertension (PAH) and other forms of pulmonary hypertension (PH) including left-heart disease, HIV, sickle cell anaemia, thromboembolisms (CTEPH), sarcoidosis, COPD or pulmonary fibrosis-associated pulmonary hypertension, chronic-obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), acute lung injury (ALI), alpha-1-antitrypsin deficiency (AATD), pulmonary fibrosis, pulmonary emphysema (for example pulmonary emphysema induced by cigarette smoke). Bronchiolitis obliterans Syndrom (BOS), and cystic fibrosis (CF).

The antibody or fragment thereof according to the present invention is also suitable for control of central nervous system disorders characterized by disturbances of the NO/cGMP system. It is suitable in particular for improving perception, concentration, learning or memory after cognitive impairments like those occurring in particular in association with situations/diseases/syndromes such as mild cognitive impairment, age-associated learning and memory impairments, age-associated memory losses, vascular dementia, craniocerebral trauma, stroke, dementia occurring after strokes (post stroke dementia), post-traumatic craniocerebral trauma, general concentration impairments, concentration impairments in children with learning and memory problems, Alzheimer's disease, Lewy body dementia, dementia with degeneration of the frontal lobes including Pick´s syndrome, Parkinson's disease, progressive nuclear palsy, dementia with corticobasal degeneration, amyolateral sclerosis (ALS), Huntington's disease, demyelination, multiple sclerosis, thalamic degeneration, Creutzfeld-Jacob dementia, HIV dementia, schizophrenia with dementia or Korsakoff's psychosis. It is also suitable for treatment and/or prophylaxis of central nervous system disorders such as states of anxiety, tension and depression, CNS-related sexual dysfunctions and sleep disturbances, and for controlling pathological disturbances of the intake of food, stimulants and addictive substances.

The antibody or fragment thereof according to the present invention is additionally also suitable for controlling cerebral blood flow and thus represent effective agents for controlling migraine. It is also suitable for the prophylaxis and control of sequelae of cerebral infarct (Apoplexia cerebri) such as stroke, cerebral ischaemias and skull-brain trauma. It can likewise be used for controlling states of pain and tinnitus.

In addition, the antibody or fragment according to the present invention has anti-inflammatory action and can therefore be used as anti-inflammatory agents for treatment and/or prophylaxis of sepsis (SIRS), multiple organ failure (MODS, MOF), inflammatory disorders of the kidney, chronic intestinal inflammations (IBD, Crohn's disease, UC), pancreatitis, peritonitis, rheumatoid disorders, inflammatory skin diseases and inflammatory eye diseases.

Furthermore, the antibody or fragment thereof according to the present invention can also be used for treatment and/or prophylaxis of autoimmune diseases.

The antibody or fragment thereof is also suitable for treatment and/or prophylaxis of fibrotic disorders of the internal organs, for example the lung, the heart, the kidney, the reproductive system, the bone marrow and in particular the liver, and also dermatological fibroses and fibrotic eye disorders. In the context of the present invention, the term fibrotic disorders includes in particular the following terms: hepatic fibrosis, cirrhosis of the liver, pulmonary fibrosis, endomyocardial fibrosis, nephropathy, glomerulonephritis, interstitial renal fibrosis, fibrotic damage resulting from diabetes, uterine fibroids, endometriosis, bone marrow fibrosis and similar fibrotic disorders, scleroderma, morphea, keloids, hypertrophic scarring (also following surgical procedures), naevi, diabetic retinopathy, proliferative vitroretinopathy and disorders of the connective tissue (for example sarcoidosis).

The antibody or fragment thereof according to the present invention is also suitable for controlling postoperative scarring, for example as a result of glaucoma operations.

The antibody or fragment thereof according to the present invention can likewise be used cosmetically for ageing and keratinized skin.

Moreover, the antibody or fragment thereof according to the present invention is suitable for treatment and/or prophylaxis of hepatitis, neoplasms, osteoporosis, glaucoma and gastroparesis.

The antibody or fragment thereof according to the present invention is moreover suitable for treatment and/or prophylaxis of eye disorders such as ophthalmic diseases responsive to natriuretic peptides, retina disorders, glaucoma including primary open angle glaucoma (POAG), angle closure glaucoma, and congenital/developmental glaucoma, retinopathies, ocular trauma, optic neuropathies, ocular hypertension, elevated intraocular pressure, diabetic retinopathy, macular degeneration (AMD), age-related eye diseases, macular oedema, scleritis, uveitis, dry eye, corneal epithelial abrasion, corneal ulcer.

Moreover, the antibody or fragment thereof according to the present invention is suitable for the treatment of bone and cartilage disorders such as bone and cartilage diseases responsive to natriuretic peptides, arthritis, degenerative diseases of cartilage tissue, osteoarthritis, cartilage degeneration, bone fractures, skeletal dysplasias, achondroplasia, osteoporosis, osteogenesis imperfecta, Paget disease of bone (PDB), metabolic bone disease, age-related bone diseases, osteomyelitis, osteonecrosis, rickets,

osteomalacia, growth plate injuries and diseases, joint and bone replacement associated defects, Marfan syndrome, sports injuries, muscular dystrophies, Duchenne muscular dystrophy.

Thus, in another aspect, the present invention relates to the use of the antibody or fragment thereof according to the present invention for treatment and/or prophylaxis of disorders, in particular the disorders mentioned above.

In particular embodiments, the antibody or fragment thereof according to the present invention is for use in a method for treatment and/or prophylaxis of heart failure, angina pectoris, hypertension, pulmonary hypertension, ischaemias, vascular disorders, renal insufficiency, thromboembolic disorders, fibrotic disorders, skeletal and bone disorders, ocular disorders and arteriosclerosis.

In another aspect, the present invention relates to the use of antibody or fragment thereof according to the present invention for production of a medicament for treatment and/or prophylaxis of disorders, especially of the aforementioned disorders.

In particular embodiments, the present invention relates to the use of the antibody or fragment thereof according to the present invention for production of a medicament for treatment and/or prophylaxis of heart failure, angina pectoris, hypertension, pulmonary hypertension, ischaemias, vascular disorders, renal insufficiency, thromboembolic disorders, fibrotic disorders, dementia illness, arteriosclerosis, skeletal and bone disorders, ocular disorders, dwarfism, achondroplasia and erectile dysfunction.

In another aspect, the present invention relates to a method for treatment and/or prophylaxis of disorders, in particular the disorders mentioned above, using an effective amount of at least one antibody or fragment thereof according to the present invention.

In particular embodiments, the present invention relates to a method for treatment and/or prophylaxis of heart failure, angina pectoris, hypertension, pulmonary hypertension, ischaemias, vascular disorders, renal insufficiency, thromboembolic disorders, fibrotic disorders, tumor and oncological diseases, skeletal and bone disorders, ocular disorders, dwarfism, achondroplasia and arteriosclerosis using an effective amount of at least one antibody or fragment thereof according to the present invention.

An antibody of the invention or fragment thereof according to the present invention may be administered as the sole pharmaceutical agent or in combination with one or more additional therapeutic agents, and in some instances the antibody might itself be modified. For example, an antibody or fragment thereof could be conjugated to a chemical entity e.g., to further increase efficacy, stability

and/or half-life. Particularly, the antibody or fragment thereof according to the present invention may be PEGylated and/or HESylated.

Thus, in particular embodiments, the antibody or fragment thereof according to the present invention is used in combination with at least one additional therapeutic agent in a method of treatment, in particular for the above cited purposes.

The present invention further provides pharmaceutical combinations comprising at least one antibody or fragment thereof according to the present invention and at least one additional therapeutic agent.

Within the context of the present invention, the term "pharmaceutical combination" is used as known to persons skilled in the art, it being possible for such combination to be a fixed combination, a non-fixed combination or a kit-of-parts.

Within the context of the present invention, the term "fixed combination" is used as known to persons skilled in the art and is defined as a combination wherein, for example, a first active ingredient, such as one or more antibody or fragment thereof according to the present invention, and a further active ingredient are present together in one unit dosage or in one single entity, e.g., a single dosage formulation. One example of a "fixed combination" is a pharmaceutical composition wherein a first active ingredient and a further active ingredient are present in admixture for simultaneous administration, such as in a formulation. Another example of a "fixed combination" is a pharmaceutical combination wherein a first active ingredient and a further active ingredient are present in one unit without being in admixture. The present invention thus provides such pharmaceutical compositions comprising at least one antibody or fragment thereof and at least one additional therapeutic agent, in particular for use in treatment and/or prophylaxis of the aforementioned disorders.

Within the context of the present invention, the terms "non-fixed combination" and "kit-of-parts" are used as known to persons skilled in the art and are defined as a combination wherein a first active ingredient and a further active ingredient are present in more than one unit, e.g., in separate dosage formulations. One example of a non-fixed combination or kit-of-parts is a combination wherein the first active ingredient and the further active ingredient are present separately.

It is possible for the components of the non-fixed combination or kit-of-parts to be administered separately, sequentially, simultaneously, concurrently or chronologically staggered.

The antibody or fragment thereof according to the present invention may be administered simultaneously with, prior to or after said further therapeutically active agent. In the context of the present invention, the term "simultaneously with" means administration of the antibody or fragment thereof according to the present invention and the at least one further therapeutically active agent on the same day, more particularly within 12 hours, more particularly within 2 hours.

In particular embodiments, administration of the antibody or fragment thereof according to the present invention and the at least one further therapeutically active agent occurs within eight consecutive weeks, more particularly within one to six consecutive weeks. The antibody or fragment thereof according to the present invention and the at least one further therapeutically active agent may be administered via the same route or via different routes.

The antibody or fragment thereof according to the present invention may for instance be combined with known agents of the same indication treatment group, such as agents used for the treatment and/or prophylaxis of diseases and/or conditions associated with hypertension, heart failure, pulmonary hypertension, COPD, asthma, cystic fibrosis, achondroplasia, hyperphosphatemia, chronic kidney disease (CKD), soft tissue calcification, chronic kidney disease associated calcification, non- chronic kidney disease associated calcification, media calcifications including Moenckeberg's medial sclerosis, atherosclerosis, intima calcification, CKD associated heart hypertrophy, CKD associated renal dystrophy, osteoporosis, post-menopausal osteoporosis, diabetes mellitus II, chronic renal disease, aging, hypophosphaturia ,hyperparathyroidism, Vitamin D disorders, Vitamin K deficiency, Vitamin K-antagonist coagulants, Kawasaki disease, ACDC (arterial calcification due to deficiency of CD73), GACI (generalized arterial calcification of infancy), IBGC (idiopathic basal ganglia calcification), PXE (pseudoxanthoma elasticum), rheumatoid arthritis, Singleton-Merten syndrome, P-thalassemia,calciphylaxis, heterotrophic ossification, preterm placental calcification, calcification of the uterus, calcified uterine fibroids, morbus fahr, mircocalcification and calcification of the aortic valve.

Preferred examples of suitable further therapeutic agents to be combined with the antibody or fragment thereof according to the present invention:

- organic nitrates and NO donors, for example sodium nitroprusside, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, molsidomine or SIN-1, and inhaled NO;
- compounds which inhibit the breakdown of cyclic guanosine monophosphate (cGMP), for example inhibitors of phosphodiesterases (PDE) 1, 2 and/or 5, especially PDE 5 inhibitors such as sildenafil, vardenafil, tadalafil, udenafil, desantafil, avanafil, mirodenafil, lodenafil or PF-00489791;

- antithrombotic agents, by way of example and with preference from the group of the platelet aggregation inhibitors, the anticoagulants or the profibrinolytic substances;
- hypotensive active ingredients, by way of example and with preference from the group of the calcium antagonists, angiotensin AII antagonists, ACE inhibitors, NEP-inhibitors, vasopeptidase-inhibitors, endothelin antagonists, renin inhibitors, alpha-receptor blockers, beta-receptor blockers, mineralocorticoid receptor antagonists, rho-kinase-inhibitors and the diuretics;
- antiarrhythmic agents, by way of example and with preference from the group of sodium channel blocker, beta-receptor blocker, potassium channel blocker, calcium antagonists, If-channel blocker, digitalis, parasympatholytics (vagoliytics), sympathomimetics and other antiarrhythmics as adenosin, adenosine receptor agonists as well as vernakalant;
- positive-inotropic agents, by way of example cardiac glycoside (Dogoxin), beta-adrenergic and dopaminergic agonists, such as isoprenalin, adrenalin, noradrenalin, dopamin or dobutamin;
- vasopressin-rezeptor-antagonists, by way of example and with preference from the group of conivaptan, tolvaptan, lixivaptan, mozavaptan, satavaptan, SR-121463, RWJ 676070 or BAY 86-8050, as well as the compounds described in WO 2010/105770, WO2011/104322 and WO 2016/071212;
- active ingredients which alter lipid metabolism, for example and with preference from the group of the thyroid receptor agonists, PCSK9 inhibitors, cholesterol synthesis inhibitors such as, by way of example and preferably, HMG-CoA reductase inhibitors or squalene synthesis inhibitors, of ACAT inhibitors, CETP inhibitors, MTP inhibitors, PPAR-alpha, PPAR-gamma and/or PPAR-delta agonists, cholesterol absorption inhibitors, lipase inhibitors, polymeric bile acid adsorbents, bile acid reabsorption inhibitors and lipoprotein(a) antagonists.
- anti-inflammatory agents, for example and with preference from the group of the gluco-corticoids, such as, by way of example and preferably, prednison, prednisolon, methylprednisolon, triamcinolon, dexamethason, beclomethason, betamethason, flunisolid, budesonid or fluticason as well as the non-steroidal anti-inflammatory agents (NSAIDs), by way of example and preferably, acetyl salicylic acid (aspirin), ibuprofen and naproxen, 5-amino salicylic acid-derivates, leukotriene-antagonists, TNF-alpha-inhibitors and chemokine-receptor antagonists, such as CCR1, 2 and/or 5 inhibitors;
- agents that inhibit the signal transductions cascade, for example and with preference from the group of the kinase inhibitors, by way of example and preferably, from the group of the tyrosine kinase and/or serine/threonine kinase inhibitors;
- agents, that inhibit the degradation and modification of the extracellular matrix, for example and with preference from the group of the inhibitors of the matrix-metalloproteases (MMPs), by way of example and preferably, inhibitors of chymasee, stromelysine, collagenases, gelatinases and aggrecanases (with preference from the group of MMP-1, MMP-3, MMP-8, MMP-9, MMP-10,

MMP-11 and MMP-13) as well as of the metallo-elastase (MMP-12) and neutrophil-elastase (HNE), as for example sivelestat or DX-890;

- agents, that block the binding of serotonin to its receptor, for example and with preference antagonists of the 5-HT2b-receptor;
- anti-fibrotic agents, for example and with preference, nintedanib, pirfenidone, adenosine A2b receptor antagonists, sphingosine-1-phosphate receptor 3 (S1P3) antagonists, autotaxin-inhibitors, lysophosphatidic acid receptor 1 (LPA-1) and lysophosphatidic acid receptor 2 (LPA-2) antagonists, lysyloxidase (LOX) inhibitors, lysyloxidase-like-2 inhibitors, CTGF inhibitors, IL-13 antagonists, integrin antagonists, TGF-beta antagonists, inhibitors of wnt signaling, CCR2-antagonists;
- agents, that act as bronchodilators, for example and with preference antagonists of the 5-HT2b-receptor; β2("beta two")-adrenergic agonists (short- and long-acting), anticholinergics, and theophylline;
- agents that are antagonists of cytokines and chemokines, for example and with preference antagonists of TGF-beta, CTGF, IL-1, IL-4, IL-5, IL-6, IL-8, IL-13, IL-25, IL-33, TSLP and integrins;
- organic nitrates and NO-donators, for example and with preference sodium nitroprussid, nitroglycerine, isosorbid mononitrate, isosorbid dinitrate, molsidomine or SIN-1, as well as inhaled NO;
- NO-independent, but heme-dependent stimulators of the soluble guanylate cyclase, for example and with preference the compounds described in WO 00/06568, WO 00/06569, WO 02/42301, WO 03/095451, WO 2011/147809, WO 2012/004258, WO 2012/028647 and WO 2012/059549;
- NO-independent and heme-independent activators of the soluble guanylate cyclase, for example and with preference the compounds described in WO 01/19355, WO 01/19776, WO 01/19778, WO 01/19780, WO 02/070462 and WO 02/070510;
- agents, that stimulate the synthesis of cGMP, for example sGC modulators, for example and with preference riociguat, cinaciguat, vericiguat;
- prostacyclin-analogs or IP receptor agonists, for example and with preference iloprost, beraprost, treprostinil, epoprostenol or Selexipag;
- endothelin receptor antagonists, for example and with preference Bosentan, Darusentan, Ambrisentan oder Sitaxsentan;
- agents, that inhibit soulble epoxidhydrolase (sEH), for example and with preference N,N'-Dicyclohexyl urea, 12-(3-Adamantan-1-yl-ureido)-dodecanic acid or 1-Adamantan-1-yl-3-{5-[2-(2-ethoxyethoxy)ethoxy]pentyl}-urea;
- agents that interact with glucose metabolism, for example and with preference insuline, biguanide, thiazolidinedione, sulfonyl urea, acarbose, DPP4 inhibitors, GLP-1 analogs or SGLT-1 inhibitors;

- natriuretic peptides, for example and with preference Atrial Natriuretic Peptide (ANP, Carperitide), Brain Natriuretic Peptide (BNP, Nesiritide), C-Type Natriuretic Peptide (CNP) or urodilatin;
- natriuretic peptide derivatives, for example and with preference vosoritide, cenderitide, PL 3994
- activators of the cardiac myosin, for example and with preference omecamtiv mecarbil (CK-1827452);
- calcium-sensitizers, for example and with preference levosimendan;
- agents that affect the energy metabolism of the heart, for example and with preference etomoxir, dichloroacetat, ranolazine or trimetazidine, full or partial adenosine A1 receptor agonists such as GS-9667 (formerly known as CVT-3619), capadenoson and neladenoson;
- agents that affect the heart rate, for example and with preference ivabradin.

Antithrombotic agents are preferably understood to mean compounds from the group of the platelet aggregation inhibitors, the anticoagulants or the profibrinolytic substances.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a platelet aggregation inhibitor, by way of example and with preference aspirin, clopidogrel, prasugrel, ticagrelor, ticlopidin or dipyridamole.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a thrombin inhibitor, by way of example and with preference ximelagatran, dabigatran, melagatran, bivalirudin or clexane.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a GPIIb/IIIa antagonist such as, by way of example and with preference, tirofiban or abciximab.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a factor Xa inhibitor, by way of example and with preference rivaroxaban, DU-176b, apixaban, betrixaban, otamixaban, fidexaban, razaxaban, letaxaban, eribaxaban, fondaparinux, idraparinux, PMD-3112, darexaban (YM-150), KFA-1982, EMD-503982, MCM-17, MLN-1021, DX 9065a, DPC 906, JTV 803, SSR-126512 or SSR-128428.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with heparin or with a low molecular weight (LMW) heparin derivative.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a vitamin K antagonist, by way of example and with preference coumarin.

Hypotensive agents are preferably understood to mean compounds from the group of the calcium antagonists, angiotensin AII antagonists, ACE inhibitors, endothelin antagonists, renin inhibitors, alpha-receptor blockers, beta-receptor blockers, mineralocorticoid receptor antagonists, rho-kinase inhibitors and the diuretics.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a calcium antagonist, by way of example and with preference nifedipine, amlodipine, verapamil or diltiazem.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with an alpha-1-receptor blocker, by way of example and with preference prazosin.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a beta-receptor blocker, by way of example and with preference propranolol, atenolol, timolol, pindolol, alprenolol, oxprenolol, penbutolol, bupranolol, metipranolol, nadolol, mepindolol, carazalol, sotalol, metoprolol, betaxolol, celiprolol, bisoprolol, carteolol, esmolol, labetalol, carvedilol, adaprolol, landiolol, nebivolol, epanolol or bucindolol.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with an angiotensin AII antagonist, by way of example and with preference losartan, candesartan, valsartan, telmisartan or embusartan or a dual angiotensin AII antagonist/neprilysin-inhibitor, by way of example and with preference LCZ696 (valsartan/sacubitril).

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with an ACE inhibitor, by way of example and with preference enalapril, captopril, lisinopril, ramipril, delapril, fosinopril, quinopril, perindopril or trandopril.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with an endothelin antagonist, by way of example and with preference bosentan, darusentan, ambrisentan or sitaxsentan.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a renin inhibitor, by way of example and with preference aliskiren, SPP-600 or SPP-800.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a mineralocorticoid receptor antagonist, by way of example and with preference finerenone, spironolactone or eplerenone.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a loop diuretic, for example furosemide, torasemide, bumetanide and piretanide, with potassium-sparing diuretics, for example amiloride and triamterene, with aldosterone antagonists, for example spironolactone, potassium canrenoate and eplerenone, and also thiazide diuretics, for example hydrochlorothiazide, chlorthalidone, xipamide and indapamide.

Lipid metabolism modifiers are preferably understood to mean compounds from the group of the CETP inhibitors, thyroid receptor agonists, cholesterol synthesis inhibitors such as HMG-CoA reductase inhibitors or squalene synthesis inhibitors, the ACAT inhibitors, MTP inhibitors, PPAR-alpha, PPAR-gamma and/or PPAR-delta agonists, cholesterol absorption inhibitors, polymeric bile acid adsorbents, bile acid reabsorption inhibitors, lipase inhibitors and the lipoprotein(a) antagonists.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a CETP inhibitor, by way of example and with preference dalcetrapib,anacetrapib, torcetrapib (CP-529 414), JJT-705 or CETP vaccine (Avant).

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a thyroid receptor agonist, by way of example and with preference D-thyroxine, 3,5,3'-triiodothyronine (T3), CGS 23425 or axitirome (CGS 26214).

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with an HMG-CoA reductase inhibitor from the class of statins, by way of example and with preference lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin or pitavastatin.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a squalene synthesis inhibitor, by way of example and with preference BMS-188494 or TAK-475.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with an ACAT inhibitor, by way of example and with preference avasimibe, melinamide, pactimibe, eflucimibe or SMP-797.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with an MTP inhibitor, by way of example and with preference implitapide, BMS-201038, R-103757 or JTT-130.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a PPAR-gamma agonist, by way of example and with preference pioglitazone or rosiglitazone.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a PPAR-delta agonist, by way of example and with preference GW 501516 or BAY 68-5042.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a cholesterol absorption inhibitor, by way of example and with preference ezetimibe, tiqueside or pamaqueside.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a lipase inhibitor, a preferred example being orlistat.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a polymeric bile acid adsorbent, by way of example and with preference cholestyramine, colestipol, colesolvam, CholestaGel or colestimide.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a bile acid reabsorption inhibitor, by way of example and with preference ASBT (= IBAT) inhibitors, for example AZD-7806, S-8921, AK-105, BARI-1741, SC-435 or SC-635.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a lipoprotein(a) antagonist, by way of example and with preference, gemcabene calcium (CI-1027) or nicotinic acid.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a lipoprotein(a) antagonist, by way of example and with preference, gemcabene calcium (CI-1027) or nicotinic acid.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with sGC modulators, by way of example and with preference, riociguat, cinaciguat or vericiguat.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with an agent affecting the glucose metabolism, by way of example and with preference, insulin, a sulfonyl urea, acarbose, DPP4 inhibitors, GLP-1 analogs or SGLT-1 inhibitors.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a TGFbeta antagonist, by way of example and with preference pirfenidone, nintedanib or fresolimumab.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a CCR2 antagonist, by way of example and with preference CCX-140.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a TNFalpha antagonist, by way of example and with preference adalimumab.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a galectin-3 inhibitor, by way of example and with preference GCS-100.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a Nrf-2 inhibitor, by way of example and with preference bardoxolone.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a BMP-7 agonist, by way of example and with preference THR-184.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a NOX1/4 inhibitor, by way of example and with preference GKT-137831.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a medicament which affects the vitamin D metabolism, by way of example and with preference calcitriol, alfacalcidol, doxercalciferol, maxacalcitol, paricalcitol, cholecalciferol or paracalcitol.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a cytostatic agent, by way of example and with preference cyclophosphamide.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with an immunosuppressive agent, by way of example and with preference ciclosporin.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a phosphate binder, by way of example and with preference colestilan, sevelamer hydrochloride and sevelamer carbonate, Lanthanum and lanthanum carbonate.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with renal proximal tubule sodium-phosphate co-transporter, by way of example and with preference, niacin or nicotinamide.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a calcimimetic for therapy of hyperparathyroidism.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with agents for iron deficit therapy, by way of example and with preference iron products.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with agents for the therapy of hyperurikaemia, by way of example and with preference allopurinol or rasburicase.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with glycoprotein hormone for the therapy of anaemia, by way of example and with preference erythropoietin.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with biologics for immune therapy, by way of example and with preference abatacept, rituximab, eculizumab or belimumab.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with vasopressin antagonists (group of the vaptanes) for the treatment of heart failure, by way of example and with preference tolvaptan, conivaptan, lixivaptan, mozavaptan, satavaptan or relcovaptan.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with Jak inhibitors, by way of example and with preference ruxolitinib, tofacitinib, baricitinib, CYT387, GSK2586184, lestaurtinib, pacritinib (SB1518) or TG101348.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with prostacyclin analogs for therapy of microthrombi.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with an alkali therapy, by way of example and with preference sodium bicarbonate.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with an mTOR inhibitor, by way of example and with preference everolimus or rapamycin.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with an NHE3 inhibitor, by way of example and with preference AZD1722 or tenapanor.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with an eNOS modulator, by way of example and with preference sapropterin.

In particular embodiments, the antibody or fragment thereof according to the present invention is administered in combination with a CTGF inhibitor, by way of example and with preference FG-3019.

The antibody or fragment thereof for use in a method for treatment according to the present invention may be formulated in any conventional manner using one or more physiologically acceptable carriers or excipients. The antibody or fragment thereof according to the present invention may be administered by any suitable means, which can vary, depending on the type of disorder to be treated. Possible administration routes include enteral (e.g., oral), parenteral (e.g., intravenous, intra-arterial, intraperitoneal, intramuscular, subcutaneous, intracardiac, intraventricular, intrathecal, intramedullary, intralesional), intrapulmonary and intranasal administration. In addition, an antibody or fragment thereof according to the present invention may be administered by pulse infusion, with, e.g., declining doses of the antibody or fragment thereof. Preferably, the dosing is given by injections, most preferably intravenous or subcutaneous injections, depending in part on whether the condition is acute or chronic. The amount to be administered will depend on a variety of factors such as the clinical symptoms, sex, age, and/or weight of the individual, whether other drugs are administered, and others. The skilled artisan will recognize that the route of administration will vary depending on the disorder or condition to be treated.

Methods of parenteral delivery include topical, intra-arterial, intratumoral, intramuscular, subcutaneous, intramedullary, intrathecal, intraventricular, intravenous, intraperitoneal, or intranasal administration.

In particular embodiments, the method for treatment comprises a single or multiple administrations of the antibody or fragment thereof or the pharmaceutical composition comprising the same. The single dose of the administrations may be the same or different. In particular, the method for treatment comprises 1, 2, 3, 4, 5 or 6 administrations of the antibody or fragment thereof according to the present invention, preferably wherein the multiple administrations occur within one to six consecutive months. The antibody or fragment thereof according to the present invention may for instance be administered every 3 to 4 days, every week, once every two weeks, or once every three weeks, depending on its half-life and clearance rate.

Short Description of Figures

Figure 1: Mean plasma concentrations of TPP-10992 and TPP-5661 after intravenous administration of 5 mg/kg in rat.

Figure 2: Mean plasma concentrations of TPP-12897 after intraperitoneal administration of 5 mg/kg in mice.

Figure 3: Stability of ANP (A-C), TPP-10992 (D-F) and TPP-5661 (G-I) against proteolytic degradation. ANP, TPP-10992 and TPP-5661 activity were tested on the stable rat ANP receptor cell line directly (A, D, G), or after 4h incubation at 37°C with 0.6 µg/ml NEP (B, E, H) or 0.6 µg/ml IDE (C, F, I).

Figure 4: Stability of BNP (A-C) and TPP-11155 (D-F) against proteolytic degradation. BNP and TPP-11155 activity were tested on the stable rat BNP receptor cell line directly (A, D), or after 4h incubation at 37°C with 0.6 µg/ml NEP (B, E) or 0.6 µg/ml IDE (C, F).

Figure 5: Stability of CNP (A-C) and TPP-12897 (D-F) against proteolytic degradation. CNP and TPP-11155 activity were tested on the stable rat CNP receptor cell line directly (A, D), or after 4h incubation at 37°C with 0.6 µg/ml NEP (B, E) or 0.6 µg/ml IDE (C, F).

Figure 6: ANP Peptide and TPP-10992 induced vasodilation dose-response curves in PE-contracted aortic rings. Concentration-response curves (0.0001-10 µM; n = 3 Rats) to the ANP peptide (open circles) and TPP-10992 (closed circles) in endothelium-intact rat aortic rings contracted by phenylephrine (1 µM). Experimental values were calculated relative to the maximal changes from the contraction produced by phenylephrine in each tissue, which was taken as 100%. Potency of ANP peptide and TPP-10992 were -7.4 and -6.7 respectively ($logEC_{50}$ values). Data represent the mean ± S.E.M. of 2 experiments.

Figure 7: ANP Peptide and TPP-5661 induced vasodilation dose-response curves in PE-contracted aortic rings. Concentration-response curves (0.0001-10 µM; n = 3 Rats) to the ANP peptide (open circles) and TPP-5661 (closed circles) in endothelium-intact rat aortic rings contracted by phenylephrine (1 µM). Experimental values were calculated relative to the maximal changes from the contraction produced by phenylephrine in each tissue, which was taken as 100%. Potency of ANP peptide and TPP-5661 were -7.4 and -6.5 respectively ($logEC_{50}$ values). Data represent the mean ± S.E.M. of 2 experiments.

Figure 8: Hemodynamic effect of ANP in conscious rats. Rat ANP was given intraperitoneally at 0 hours. A 500 µg dose of ANP resulted in an approximately 25% drop in mean arterial blood pressure (MAP) with a duration of effect around 6-8 hours.

Figure 9: Hemodynamic effect TPP-5661 in conscious rats. TPP-5661 was given intraperitoneally at 0 hours. A 15 mg/kg dose resulted in an approximately 20% reduction in mean arterial blood pressure (MAP) with maximum effect at 24-48 hours post application and a duration of effect greater than 6 days.

Figure 10: Hemodynamic effect TPP-10992 in conscious rats. TPP-10992 was given intraperitoneally at 0 hours. A 30 mg/kg dose resulted in an approximately 20% reduction in mean arterial blood pressure (MAP) with maximum effect at 48 hours post application and a duration of effect greater than 6 days.

Figure 11: Activity of BNP engrafted antibody constructs on hNPRA cells. The activity of purified compound samples on stable hNPRA-CHO k1 cells was assessed by comparison to reference sample TPP-5661 and TPP-5657. Samples were tested in dilution series in quadruplets.

Figure 12: Different human IgG isotypes provide equally suitable antibody scaffolds. Exemplary activity determination of compounds 9, 33, 65, 91, 127 and 191 IgG1 (TPP-10294, TPP-10277, TPP-10279, TPP-10282, TPP-10269 and TPP-10355, respectively), IgG2 and IgG4 isotypes. The activity of purified compound samples on stable hNPRA-CHO k1 cells was assessed by comparison to reference samples compound 117 human IgG1 TPP-5661 and compound 209 human IgG1 TPP-5657. Samples were tested in dilution series in quadruplets.

Figure 13: Equally suitable IgG antibody scaffolds originated from different species. Exemplary activity determination of compound 117 human IgG1 (TPP-5661) and compound 9 human IgG1 (TPP-10294) and their non-human IgG1 counterparts. The activity of purified compound samples on stable hNPRA-CHO k1 cells was assessed by comparison to reference sample compound 209 human IgG1 (TPP-5657). Samples were tested in dilution series in quadruplets.

Figure 14: Equally suitable human IgG antibody scaffolds originated from different germline sequences. The activity of purified compound samples on stable hNPRA-CHO k1 cells was assessed by comparison to reference sample TPP-10992. Samples were tested in dilution series in quadruplets.

Figure 15: Protective effects of TPP-12899 against LPS, IL-1ß and thrombin induced endothelial barrier permeability as assessed by real-time impedance measurement.

Figure 16: Therapeutic effects of TPP-13992 on survival (A), body weight gain (B), urinary protein/creatinine ratio (C) and left atrial weight (D); (n=8-12 (healthy control n=5), mean ±SEM, One-Way ANOVA vs TPP-10155 (isotype specific control antibody).

Figure 17: Hemodynamic assessment after Placebo, 0.1, 0.3 and 1.0 mg/kg of TPP-10992. TPP-10992 shows a dose-dependent and long-lasting (>5d) reduction in blood pressure.**$p<0.01$, ****$p<0.0001$ in comparison to placebo group using an One-way ANOVA test for repeated measurements followed by Tukey`s multiple comparison test.

Examples

Example 1: Construction of candidate TPP-5661

Candidate TPP-5661 was designed by fusion of a heterologous amino acid sequence comprising a Ntls, wild type rat ANP and a Ctls to the C-terminus of HV 3-23 (SEQ ID NO 85) by substituting the two C-terminal residues of HV 3-23 by the two N-terminal residues of the heterologous amino acid sequence and to the N-terminus of IGHJ1 (SEQ ID NO 86) by substituting the nine N-terminal residues of IGHJ1 by the 9 C-terminal residues of the heterologous amino acid sequence. The corresponding full length heavy chain sequence of SEQ ID NO 67 further comprises amino acid sequence Constant-H (SEQ ID NO 87).

Pairing of the full length heavy chain sequence of SEQ ID NO 67 harboring the inserted rat ANP (rANP) with the full length light chain sequence of SEQ ID NO 66 built by combining sequences LV 1-40 (SEQ ID NO 88), IGLJ2 (SEQ ID NO 89) and Constant-L (SEQ ID NO 90) yields the full IgG candidate TPP-5661 (see Table 1).

Shown below is the full length heavy chain sequence (SEQ ID NO 67); the incorporated heterologous amino acid sequence (Ntls-rANP-Ctls) is underlined; sequences derived from HV 3-23 and IGHJ1 are shown in bold:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYY ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC*TSVHQETKKYQSSPDGGSGGSLRRSSC FGGRIDRIGAQSGLGCNSFRYGSYSYTYNYEWHVDVWGQ***GTLVTVSS**ASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

The designed and synthesized antibody construct was cloned according to well-known methods in the art and confirmed by DNA sequencing using plasmid specific oligonucleotides.

Example 2: Insertion of NPs within antibody-CDRs results in an increased serum half-life

Determination of *in vivo* Pharmacokinetic Parameters

Pharmacokinetic parameters of TPP-10992 (SEQ ID NO 76 and SEQ ID NO 66) and TPP-5661 (SEQ ID NO 67 and SEQ ID NO 66) were determined after intravenous administration of 5 mg/kg to male Wistar rats (n=3). TPP-10992 and TPP-5661 were given as a bolus injection via the tail vein. Blood samples were collected from the jugular vein via previously implanted catheters in time intervals up to 14 days (336 hours). Generated EDTA-plasma was stored at -20°C until further analysis.

The quantification of TPP-10992 and TPP-5661 in plasma samples was performed employing an anti-human IgG ELISA (enzyme-linked immunosorbent assay) format. Pharmacokinetic parameters were calculated from plasma concentration time profiles using non-compartmental data analysis.

Mean plasma concentrations of TPP-10992 and TPP-5661 after intravenous administration over time are graphically depicted in Figure 1.

Mean clearance and terminal half-life of TPP-10992 and TPP-5661 are summarized in Table 2 below.

Table 2: Mean clearance (CL) and terminal half-life ($t_{1/2}$) of TPP-10992 and TPP-5661 after intravenous administration of 5 mg/kg in rat.

Analyte		**TPP-5661**	**TPP-10992**
CL	[mL/h/kg]	0.62	0.27
$t_{1/2}$	[h]	297	184

Determination of *in vivo* Pharmacokinetic Parameters

Pharmacokinetic parameters of TPP-12897 were determined after intraperitoneal administration to female Balb/c mice (n=3). Blood samples were collected from 15 minutes up to 72 hours post application. Generated EDTA-plasma was stored at -20°C until further analysis. The quantification of TPP-12897 in plasma samples was performed by an anti-human IgG (Immunoglobulin G) ELISA format.

Pharmacokinetic parameters were calculated from plasma concentration time profiles using non-compartmental data analysis.

Mean plasma concentrations of TPP-12897 after intraperitoneal administration over time are graphically depicted in Figure 2.

Mean area under the curve (AUC) and terminal half-life of TPP-12897 are summarized in Table 3 below.

Table 3: Mean area under the curve (AUC) and terminal half-life ($t_{1/2}$) of TPP-12897 after intraperitoneal administration of 5 mg/kg in mice.

Analyte		**TPP-12897**
AUC	[mg·h/L]	7705
$t_{1/2}$	[h]	194

Example 3: In vitro, ex vivo and in vivo potency of NP engrafted antibodies

Activity data of ANP engrafted antibodies in NPR-A receptor cell line

A luminescence-based rat ANP receptor (NPR-A) cell line was generated as described previously (Wunder *et al.* (2013), *Eur J Pharmacol.* 698: 131). Accordingly, a fluorescence-based rat ANP receptor (NPR-A) cell line was generated by co-transfecting a CHO cell line, stably expressing the fluorescent calcium sensor protein GCaMP6, with plasmid constructs encoding CNGA2 (cGMP biosensor) and rat NPR-A.

ANP receptor GCaMP6 cells were cultured for one day on black, clear-bottom 384-well microtiter plates (2500 cells/well). After removal of the cell culture medium reporter cells were loaded for 20 min with Tyrode (130 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 20 mM HEPES, 1 mM $MgCl_2$, 4.8 mM $NaHCO_3$ at pH 7.4) containing a black masking dye at 37°C and 5% CO_2. IBMX (0.2 mM) was used to prevent cGMP degradation by endogenous phosphodiesterases.

Fluorescence measurements (3 min, kinetic mode) were directly started upon agonist addition. Receptor ligands were added in Tyrode containing a black masking dye and 0.1% BSA. Measurements were done on a FLIPR Tetra®.

ANP (Bachem, H-2100) stimulated concentration-dependent fluorescence signals on the NPR-A cell line with an EC_{50} values of 0.22 nM. TPP-5661 and TPP-10992 stimulated the rat ANP receptor reporter cell line with EC_{50} values of 17 nM and 180 nM, respectively. The control antibody construct TPP-5657 did not significantly stimulate the NPR-A cell line (tested up to the max. concentration of 460 nM).

To determine the sensitivity towards proteolytic degradation, the activity of receptor ligands was also characterized after 4 hours incubation with 0.6 µg/ml neutral endopeptidase (NEP, R&D Systems, 1182-ZNC) or 0.6 µg/ml insulin degrading enzyme (IDE, Merck, 407241-50UG) at 37°C.

Figure 3 graphically depicts the stability of ANP (A-C), TPP-10992 (D-F) and TPP-5661 (G-I) against proteolytic degradation. As shown in Figure 3, the natriuretic peptide ANP (Bachem, H-2100) showed high sensitivity towards degradation by NEP and IDE. In contrast, TPP-5661 and TPP-10992 showed high resistance to proteolytic degradation by NEP and IDE.

Activity data of BNP engrafted antibodies in NPR-A receptor cell line

A luminescence-based rat BNP receptor (NPR-A) cell line was generated as described previously (Wunder *et al.* (2013), *Eur J Pharmacol.* 698: 131). Accordingly, a fluorescence-based rat BNP receptor (NPR-A) cell line was generated by co-transfecting a CHO cell line, stably expressing the fluorescent calcium sensor protein GCaMP6, with plasmid constructs encoding CNGA2 (cGMP biosensor) and rat NPR-A.

BNP receptor GCaMP6 cells were cultured for one day on black, clear-bottom 384-well microtiter plates (2500 cells/well). After removal of the cell culture medium reporter cells were loaded for 20 min with Tyrode (130 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 20 mM HEPES, 1 mM $MgCl_2$, 4.8 mM $NaHCO_3$ at pH 7.4) containing a black masking dye at 37°C and 5% CO_2. IBMX (0.2 mM) was used to prevent cGMP degradation by endogenous phosphodiesterases.

Fluorescence measurements (3 min, kinetic mode) were directly started upon agonist addition. Receptor ligands were added in Tyrode containing a black masking dye and 0.1% BSA. Measurements were done on a FLIPR Tetra®.

BNP (Bachem, H-5968) stimulated concentration-dependent fluorescence signals on the NPR-A cell line with an EC_{50} value of 2.9 nM. TPP-9902, TPP-11153, TPP-1154, TPP-11155, TPP-11156 and TPP-11157 stimulated the rat BNP receptor reporter cell line with EC_{50} values of 2.3 µM, >1.9 µM, 7 nM, 12 nM, 1.2 µM and 11 nM, respectively. The control antibody construct TPP-5657 did not significantly stimulate the NPR-A cell line (tested up to the max. concentration of 460 nM).

To determine the sensitivity towards proteolytic degradation, the activity of receptor ligands was also characterized after 4 hours incubation with 0.6 µg/ml neutral endopeptidase (NEP, R&D Systems, 1182-ZNC) or 0.6 µg/ml insulin degrading enzyme (IDE, Merck, 407241-50UG) at 37°C. The natriuretic peptide BNP (Bachem, H-5968) showed high sensitivity towards degradation by NEP and IDE. In contrast, TPP-11155 and TPP-11157 showed high resistance to proteolytic degradation by NEP and IDE.

Figure 4 graphically depicts the stability of BNP (A-C) and TPP-11155 (D-F) against proteolytic degradation.

Activity data of CNP engrafted antibodies in NPR-B receptor cell line

A luminescence-based rat CNP receptor (NPR-B) reporter cell line was generated and luminescence measurements were performed as described previously (Wunder *et al.* (2013), *Eur J Pharmacol.* 698: 131).

CNP receptor cells (2500 cells/well) were cultured for 1 day on opaque 384-well microtiter plates. After removal of the cell culture medium, cells were loaded for 3 h with 2.5 µg/ml coelenterazine in Ca^{2+}-free Tyrode (130 mM NaCl, 5 mM KCl, 20 mM HEPES, 1 mM $MgCl_2$, 4.8 mM $NaHCO_3$ at pH 7.4) at 37°C and 5% CO_2. Receptor ligands were added for 10 min in Ca^{2+}-free Tyrode containing 0.1% BSA. IBMX (0.2 mM) was used to prevent cGMP degradation by endogenous phosphodiesterases. Immediately before adding calcium ions (final concentration 3 mM), luminescence measurements were started by using a charge-coupled device (CCD) camera in a light tight box. Luminescence was monitored continuously for 50 s.

CNP (Bachem, H-1296) stimulated concentration-dependent luminescence signals on the rat NPR-B cell line with an EC_{50} value of 0.024 nM. TPP-9465, TPP-12377, TPP-12378, TPP-12897 and TPP-12899 stimulated the rat CNP receptor reporter cell line with EC_{50} values of 5.2 nM, 4.1 nM, 25 nM, 10 nM and 3.2 nM, respectively. TPP-12374 stimulated the rat CNP receptor reporter cell line with EC_{50} values of 150 nM, and TPP-12375, TPP-12376 showed only weak indication of activity.

To determine the sensitivity towards proteolytic degradation, the activity of receptor ligands was also characterized after 4 hours incubation with 0.6 µg/ml neutral endopeptidase (NEP, R&D Systems, 1182-ZNC) or 0.6 µg/ml insulin degrading enzyme (IDE, Merck, 407241-50UG) at 37°C.

In contrast to the natriuretic peptide CNP (Bachem, H-1296), TPP-12377, TPP-12897 and TPP-12899 showed high resistance to proteolytic degradation by NEP and IDE.

Figure 5 graphically depicts the stability of CNP (A-C) and TPP-12897 (D-F) against proteolytic degradation.

Activity data of ANP engrafted antibodies determined with isolated rat aortic rings

All experiments were conducted in accordance with institutional guidelines and approved by the local committee on animal experiments. Male Sprague-Dawley rats (weighing 250-300 g) were anesthetized with pentobarbital sodium (40 mg/kg i.p.), killed by decapitation, and exsanguinated. The thoracic aorta was excised and placed in ice-cold Krebs buffer of the following composition: 130 mM NaCl, 14.9 mM $NaHCO_3$, 5.5 mM dextrose, 4.7 mM KCl, 1.18 mM KH_2PO_4, 1.17 mM $MgSO_47H_2O$, and 1.6 mM $CaCl_22H_2O$. The vessel was pinned in a Sylgard Petri dish filled with chilled Krebs' solution, cleaned of fat and connective tissue, and cut into ring segments of approximately 3 to 4 mm in length. Aortic rings were vertically mounted in 50-ml chambers (ADInstruments) containing Krebs' solution at 37°C continuously bubbled with a mixture of 95% O_2 and 5% CO_2. Changes in isometric force were recorded using a PowerLab data acquisition system (software Lab Chart 7.0)

After the equilibration period, aortic rings were challenged with 80 mM KCl to check tissue viability. Next, the endothelial integrity of the preparations was determined by verifying the responsiveness to acetylcholine (ACh, 1 µM) in vessels pre-contracted with Phenylephrine (PE, 1 µM). After wash-out and a period of equilibration, Phenylephrine (PE, 1 µM) was used to induce contraction, thereafter natriuretic peptides and natriuretic peptide engrafted IgGs were evaluated for vasorelaxation. Rat ANP peptide (ADH-GM-10057T, Santai Labs) was used as a reference.

As shown in Figure 6, both ANP peptide and TPP-10992 induced dose-dependent vasodilation in PE-contracted aortic rings.

As shown in Figure 7, both ANP peptide and TPP-5661 induced dose-dependent vasodilation in PE-contracted aortic rings.

Activity data of ANP engrafted antibodies obtained in conscious rats

Blood pressure and heart rate were monitored in freely moving conscious animals by radiotelemetry (Data Sciences International). Female spontaneously hypertensive rats (SHR/N Crl BR, Charles River) with a body weight of 210-300 g were used for these studies. All animals were housed in individual cages at 22-24 °C ambient temperature and maintained on a 12-hour light/dark cycle with free access to standard laboratory rat chow and water ad libitum. Telemeter (HD-10, DSI) implantation was performed a minimum of 14 days before animals were used for blood pressure measurements. Surgery was performed under aseptic conditions. After shaving the abdominal wall, a midline abdominal incision was made, and the fluid-filled sensor catheter was inserted upstream into the exposed descending aorta between the iliac bifurcation and the renal arteries. According to the DSI guidelines the tip of the telemetric catheter was located caudal to the renal arteries and secured by tissue adhesive. The transmitter body was affixed to the inner peritoneal wall before closure of the abdomen. For postsurgical protection against infections and pain a single dosage of an antibiotic (Oxytetracyclin® 10%, 60 mg/kg s.c., 0.06 ml/ 100g body weight, Beta-Pharma GmbH & Co, Germany) and analgesic were injected (Rimadyl®, 4 mg/kg s.c., Pfizer, Germany). Telemetric data acquisition was performed by DSI software was predefined to sample hemodynamic data for 10 seconds repeated every 5 minutes. Data collection was started at least 2 hours before drug administration and finished after completion of measurement cycles. Data are expressed as % of basal values ± SEM of at least 4 animals per group. The basal value for each animal was calculated as the average of the values measured in two hours prior to substance application (7:00 – 9:00 AM). Data are then expressed as averages every half hour, starting 15 minutes post application. All animals were treated with a single intraperitoneal (ip) application of test substances dissolved in phosphate buffered saline (PBS). Drug administration took place at 9:00 AM (0 hours).

The hemodynamic effect of ANP peptide is graphically depicted in Figure 8. The hemodynamic effect of TPP-5661 is graphically depicted in Figure 9. The hemodynamic effect of TPP-10992 is graphically depicted in Figure 10.

Example 4: Generation of different NP engrafted antibody constructs

For constructs with a natriuretic peptide incorporation in a CDR region other than CDRH3 a presumably functionally neutral CDRH3 was designed by fusion of the three residues stretch Leu Thr Gly (IGHD7-27*01) to the C-terminus of HV 3-23 and the N-terminus of IGHJ1 (compare Example 1). The corresponding full length heavy chain sequence of SEQ ID NO 65 further comprises amino acid sequence Constant-H (SEQ ID NO 87).

Pairing of the full length heavy chain sequence of SEQ ID NO 65 without any natriuretic peptide insertion with the full length light chain sequence of SEQ ID NO 66 described in Example 1 yields the synthetic and presumably neutral IgG negative control TPP-5657.

The designed and synthesized antibody construct was cloned according to well-known methods in the art and confirmed by DNA sequencing using plasmid specific oligonucleotides.

Starting from this antibody scaffold, the following ANP engrafted antibody constructs were generated.

Table 4: Design of ANP engrafted antibody constructs

Cmpd	TPP	Insertion Site	SEQ ID NO comprised in Ntls	SEQ ID NO comprised in Ctls	# aa N-term[1]	# aa C-term[2]
1	TPP-13057	CDRH1			6	2
2	TPP-13056	CDRH1			9	5
3	TPP-13055	CDRH1			12	8
4	TPP-13054	CDRH1			15	11
5	TPP-12545	CDRH1			18	10
6	TPP-10454	CDRH1			19	17
7	TPP-10453	CDRH1			19	17
8	TPP-11172	CDRH1	6		20	17
9	TPP-10294	CDRH1			23	14
10	TPP-12547	CDRH1			23	14
11	TPP-11171	CDRH1	6		24	13

12	TPP-10841	CDRH2			3	3
13	TPP-10842	CDRH2			7	7
14	TPP-11009	CDRH2			8	9
15	TPP-11008	CDRH2			10	11
16	TPP-11018	CDRH2			11	14
17	TPP-10775	CDRH2			12	8
18	TPP-10767	CDRH2			13	12
19	TPP-11012	CDRH2	9		14	9
20	TPP-10774	CDRH2	13	14	14	10
21	TPP-11007	CDRH2			14	11
22	TPP-11179	CDRH2			14	14
23	TPP-10773	CDRH2	13	14	15	10
24	TPP-10770	CDRH2	1	1	15	12
25	TPP-10766	CDRH2			15	14
26	TPP-10772	CDRH2	13	14	16	11
27	TPP-11005	CDRH2			16	11
28	TPP-11006	CDRH2			16	11
29	TPP-11017	CDRH2			16	14
30	TPP-11169	CDRH2	9	10	16	15
31	TPP-11181	CDRH2			16	15
32	TPP-11182	CDRH2			16	17
33	TPP-10277	CDRH2	9	10	17	11
34	TPP-12553	CDRH2	9	10	17	11
35	TPP-12554	CDRH2	9	10	17	11
36	TPP-12555	CDRH2	9	10	17	11
37	TPP-12542	CDRH2	9	10	17	11
38	TPP-	CDRH2	9	10	17	11

	12543					
39	TPP-12544	CDRH2	9	10	17	11
40	TPP-13058	CDRH2	9	10	17	11
41	TPP-13059	CDRH2	9	10	17	11
42	TPP-13060	CDRH2	9	20	17	11
43	TPP-13061	CDRH2	9	20	17	11
44	TPP-13062	CDRH2	9	10	17	11
45	TPP-13063	CDRH2	9	10	17	11
46	TPP-13064	CDRH2	9	10	17	11
47	TPP-13065	CDRH2	9	10	17	11
48	TPP-13066	CDRH2	9	10	17	11
49	TPP-12546	CDRH2	9	10	17	11
50	TPP-10452	CDRH2	13	14	17	12
51	TPP-10846	CDRH2	4	5	17	12
52	TPP-10852	CDRH2			17	12
53	TPP-10851	CDRH2	6		17	13
54	TPP-10769	CDRH2	1	1	17	14
55	TPP-10765	CDRH2			17	14
56	TPP-11180	CDRH2			17	15
57	TPP-11177	CDRH2			17	17
58	TPP-11178	CDRH2			17	17
59	TPP-11176	CDRH2	17	18	17	17
60	TPP-10278	CDRH2	9	10	18	12
61	TPP-10847	CDRH2	4	5	18	13
62	TPP-11004	CDRH2			18	13
63	TPP-10844	CDRH2	2	3	18	13
64	TPP-10853	CDRH2			18	13

65	TPP-10279	CDRH2	9	10	18	13
66	TPP-11170	CDRH2	9	10	18	13
67	TPP-11010	CDRH2	9		18	13
68	TPP-11011	CDRH2	9		18	13
69	TPP-10764	CDRH2			18	14
70	TPP-11183	CDRH2			18	17
71	TPP-11175	CDRH2	16	17	18	17
72	TPP-11016	CDRH2	15		19	12
73	TPP-11015	CDRH2	15		19	14
74	TPP-10451	CDRH2	13	14	19	14
75	TPP-10768	CDRH2	1	1	19	14
76	TPP-10848	CDRH2	4	5	19	14
77	TPP-11003	CDRH2			19	14
78	TPP-11002	CDRH2			19	14
79	TPP-10843	CDRH2	2	3	19	14
80	TPP-10845	CDRH2	2	3	19	14
81	TPP-10284	CDRH2			19	14
82	TPP-10446	CDRH2	11	12	19	14
83	TPP-10447	CDRH2			19	14
84	TPP-10854	CDRH2			19	14
85	TPP-11014	CDRH2	15		19	15
86	TPP-10849	CDRH2	6	6	19	15
87	TPP-10850	CDRH2	6		19	15
88	TPP-11013	CDRH2			20	14
89	TPP-10771	CDRH2	1	1	20	15
90	TPP-10287	CDRH2	1	1	20	15
91	TPP-	CDRH2			20	15

	10282					
92	TPP-10285	CDRH2			20	15
93	TPP-10286	CDRH2			20	15
94	TPP-10283	CDRH2			20	15
95	TPP-11168	CDRH2	9	10	20	15
96	TPP-10857	CDRH2			20	15
97	TPP-10856	CDRH2			20	15
98	TPP-10855	CDRH2			20	15
99	TPP-10281	CDRH3			10	3
100	TPP-10280	CDRH3			10	8
101	TPP-10583	CDRH3			12	10
102	TPP-10582	CDRH3	7		14	12
103	TPP-10270	CDRH3	7	8	15	18
104	TPP-10264	CDRH3	7	8	16	14
105	TPP-10581	CDRH3			16	14
106	TPP-10263	CDRH3	7	8	17	15
107	TPP-10271	CDRH3	7	8	17	18
108	TPP-10262	CDRH3	7	8	18	16
109	TPP-10272	CDRH3	7	8	18	18
110	TPP-10261	CDRH3	7	8	19	17
111	TPP-10289	CDRH3			19	17
112	TPP-10273	CDRH3	7	8	19	18
113	TPP-10260	CDRH3	7	8	20	17
114	TPP-10275	CDRH3	9	10	20	17
115	TPP-10580	CDRH3			20	18
116	TPP-10274	CDRH3	7	8	20	18
117	TPP-5661	CDRH3	7	8	20	18
118	TPP-	CDRH3	7	8	18	16

	13226					
119	TPP-13227	CDRH3	7	8	18	16
120	TPP-13228	CDRH3	7	22	20	18
121	TPP-13229	CDRH3	7	22	20	18
122	TPP-13230	CDRH3	21	22	20	18
123	TPP-13231	CDRH3	21	22	20	18
124	TPP-10276	CDRH3	9	10	20	18
125	TPP-10290	CDRH3			20	18
126	TPP-10445	CDRH3	11	12	20	18
127	TPP-10269	CDRH3	7	8	20	18
128	TPP-10288	CDRH3	2	3	20	18
129	TPP-10265	CDRH3	7	8	20	19
130	TPP-10268	CDRH3	7	8	21	19
131	TPP-10593	CDRH3	19		22	20
132	TPP-11174	CDRH3	6	12	22	20
133	TPP-10266	CDRH3	7	8	22	20
134	TPP-11173	CDRH3	6	12	22	20
135	TPP-10444	CDRH3	11	12	22	20
136	TPP-10267	CDRH3	7	8	24	22
137	TPP-10443	CDRH3	11	12	24	22
138	TPP-11163	CDRL1	6		16	14
139	TPP-10360	CDRL1			19	13
140	TPP-10462	CDRL1			20	18
141	TPP-10460	CDRL1			21	19
142	TPP-10461	CDRL1			21	19
143	TPP-11161	CDRL1	6	6	21	19
144	TPP-11162	CDRL1	6		21	19

145	TPP-10359	CDRL1			23	14
146	TPP-10824	CDRL2			1	6
147	TPP-10825	CDRL2			5	10
148	TPP-11019	CDRL2			12	16
149	TPP-11021	CDRL2			13	17
150	TPP-11020	CDRL2			13	17
151	TPP-10789	CDRL2			14	14
152	TPP-11022	CDRL2			15	19
153	TPP-10829	CDRL2	4	5	16	15
154	TPP-10835	CDRL2			16	15
155	TPP-10788	CDRL2			16	16
156	TPP-10571	CDRL2	15	15	17	16
157	TPP-10830	CDRL2	4	5	17	16
158	TPP-10790	CDRL2			17	16
159	TPP-10573	CDRL2		19	17	16
160	TPP-10827	CDRL2	2	3	17	16
161	TPP-10572	CDRL2	19		17	16
162	TPP-10836	CDRL2			17	16
163	TPP-10834	CDRL2	6		17	17
164	TPP-10787	CDRL2			18	16
165	TPP-10831	CDRL2	4	5	18	17
166	TPP-10828	CDRL2	2	3	18	17
167	TPP-10826	CDRL2	2	3	18	17
168	TPP-10837	CDRL2			18	17
169	TPP-10361	CDRL2			19	17
170	TPP-11023	CDRL2	11	12	19	18
171	TPP-	CDRL2			19	18

	10838					
172	TPP-10840	CDRL2			19	18
173	TPP-10839	CDRL2			19	18
174	TPP-10832	CDRL2	6		19	19
175	TPP-10833	CDRL2	6		19	19
176	TPP-11024	CDRL2	11	12	20	19
177	TPP-10353	CDRL3			2	2
178	TPP-10780	CDRL3			14	9
179	TPP-10786	CDRL3			16	10
180	TPP-10779	CDRL3			16	11
181	TPP-10778	CDRL3			16	13
182	TPP-10783	CDRL3	11	12	17	11
183	TPP-10785	CDRL3			18	12
184	TPP-10776	CDRL3			18	13
185	TPP-10777	CDRL3			18	13
186	TPP-10784	CDRL3			18	14
187	TPP-10782	CDRL3	11	12	19	13
188	TPP-10352	CDRL3	7	8	19	14
189	TPP-10356	CDRL3			19	14
190	TPP-10354	CDRL3			19	14
191	TPP-10355	CDRL3			19	14
192	TPP-10781	CDRL3	11	12	19	15
193	TPP-10436	CDRL3	7	8	20	14
194	TPP-10440	CDRL3	11	12	20	14
195	TPP-10442	CDRL3			20	14
196	TPP-10351	CDRL3	7	8	20	15
197	TPP-10348	CDRL3	7	8	20	15

198	TPP-10358	CDRL3			20	15
199	TPP-11167	CDRL3	6	12	21	15
200	TPP-10438	CDRL3	11	12	21	15
201	TPP-10439	CDRL3	11	12	21	15
202	TPP-10441	CDRL3			21	15
203	TPP-10349	CDRL3	7	8	21	16
204	TPP-10350	CDRL3	7	8	22	17
205	TPP-10437	CDRL3	11	12	23	17
206	TPP-11166	CDRL3	6	12	24	18
207	TPP-10362	CDRL3	6	6	24	20
208	TPP-10363	CDRL3	6	6	24	20
209	TPP-5657	no			na	na

[1] The number of amino acid residues present between the respective N-terminal reference amino acid residue and the first amino acid of the inserted natriuretic peptide;

[2] The number of amino acid residues present between the last amino acid of the inserted natriuretic peptide and the respective C-terminal reference amino acid residue

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Table 4 cont.: Design of ANP engrafted antibody constructs

Cmpd	TPP	N-terminal sequence[3]	C-terminal sequence[4]
1	TPP-13057	SGFTFSS	YAM
2	TPP-13056	SGFTFGSGSG	GSGSGM
3	TPP-13055	SGFTFGSGSGSGS	SGSGSGSGM
4	TPP-13054	SGFTFGSGSGSGGSGG	GGSGGSGSGSGM
5	TPP-12545	SGFTFGSGSGSGSGGGSGG	GSGSGGSGSGM
6	TPP-10454	SPAVVYIEILDRHPDGGSGG	GSGREVPISNGSGFVVAM
7	TPP-10453	SGAVVYIEILDRHPDGGSGG	GSGREVPISNGSGFVVAM
8	TPP-11172	SSSDRSALLKSKLRALLTAPR	GSGREVPISNGSGFVVAM
9	TPP-10294	SGFTFGSGSGSGSGSGSPDGGSGG	GSYGSGSGSGSGSGM
10	TPP-12547	SGFTFGSGSGSGSGSGSPDGGSGG	GSYGSGSGSGSGSGM
11	TPP-	SGFTFSSDRSALLKSKLRALLTAPR	GSGSGSGSGSGSGM

	11171		
12	TPP-10841	ISGS	GGST
13	TPP-10842	ISGSGSGS	GSGSGGST
14	TPP-11009	ISGSGSGSG	GSSGSGSGST
15	TPP-11008	ISGSGSGSGSG	GSSGSGSGSGST
16	TPP-11018	ISGSGSGSGSGG	GEKEKEKVSTAVGST
17	TPP-10775	ISGSAVVNGGSGG	GKIAIGGST
18	TPP-10767	ISGPNPNKNPNPGG	GSNENPNPNPGST
19	TPP-11012	ISGSVVVTSHGGSGG	GGSGSGSGST
20	TPP-10774	ISGSAVVNVRGGSGG	GGDKIAIGGST
21	TPP-11007	ISGSGSGSGSGSSGG	GSSGSGSGSGST
22	TPP-11179	ISGLAVQIRRGGSGG	GGSGRETLTLYVGST
23	TPP-10773	ISGSAVVNVRAGGSGG	GGDKIAIGGST
24	TPP-10770	ISGSYAMSWVRGGSGG	GSYAMSWVRQGST
25	TPP-10766	ISGPNPNKNPNPNPGG	GSNPNENPNPNPGST
26	TPP-10772	ISGSAVVNVRADGGSGG	GSGDKIAIGGST
27	TPP-11005	ISGSGSGSGSPDGGSGG	GSSGSGSGSGST
28	TPP-11006	ISGSGSGSGSGSGGSGG	GSSGSGSGSGST
29	TPP-11017	ISGSGSGSGSGSGGSGG	GEKEKEKVSTAVGST
30	TPP-11169	ISGSVVVTSHQAPGSGG	GSGEKKKLKSLAYGST
31	TPP-11181	ISGRYNILKIQKVGSGG	GGSGEYLITYQIMGST
32	TPP-11182	ISGRQLLFCRVTLGSGG	GGSGEQAYPEYLITYGST
33	TPP-10277	ISVVVTSHQAPGEGGSGG	GEKKKLKSLAST
34	TPP-12553	ISGVVTSHQAPGEGGSGG	GEKKKLKSLAST
35	TPP-12554	ISVVVTSHQAPGEGGSGG	GEKKKLKSLGST
36	TPP-12555	ISVVVTSHQAPGEGGSGG	GEKKKLKSGGST
37	TPP-12542	ISGVVTSHQAPGEGGSGG	GEKKKLKSGGST

38	TPP-12543	ISGSVTSHQAPGEGGSGG	GEKKKLKSGGST
39	TPP-12544	ISGSVTSHQAPGEGGSGG	GEKKKGKSGGST
40	TPP-13058	ISVVVTSHQAPGSGGSGG	GEKKKLKSLAST
41	TPP-13059	ISVVVTSHQAPTSGGSGG	GEKKKLKSLAST
42	TPP-13060	ISVVVTSHQSPTPGGSGG	GGSTPLKSLAST
43	TPP-13061	ISVVVTSHQAPGEGGSGG	GGSTPLKSLAST
44	TPP-13062	ISVVVTSHQAPGEGGSGG	GSTPKLKSLAST
45	TPP-13063	ISVVVTSHQSPTPGGSGG	GEKKKLKSLAST
46	TPP-13064	ISVVVTSHPTPGEGGSGG	GEKKKLKSLAST
47	TPP-13065	ISVVVTSHQAPSPGSTGG	GEKKKLKSLAST
48	TPP-13066	ISVVVTSHQANGSGGSGG	GEKKKLKSLAST
49	TPP-12546	ISVVVTSHQAPGEGGSGG	GEKKKLKSLAST
50	TPP-10452	ISGSAVVNVRAPDGGSGG	GSKGDKIAIGGST
51	TPP-10846	ISTSASLAITGPDGGSGG	GSDRFSGSKSGST
52	TPP-10852	ISGFILPIEVYPDGGSGG	GSKVRFDYDLFST
53	TPP-10851	ISSALLKSKLRALLTAPG	GGSGSGSGSGSGST
54	TPP-10769	ISGSYAMSWVRQAGGSGG	GSSSYAMSWVRQGST
55	TPP-10765	ISGPNPNKNPNPNPGSGG	GSNPNENPNPNPGST
56	TPP-11180	IHPLQNRWALWFFKGSGG	GGSGNLRLISKFDTVT
57	TPP-11177	ISGSVTIFSLATNEGSGG	GGSGKTTWHRISVFGGST
58	TPP-11178	IYLEGKIDYGEYMDGSGG	GGSNVRRQATTIIADNIT
59	TPP-11176	ISGSVQGIINFEQKGSGG	GGSGPVKVWGSIKGGGST
60	TPP-10278	ISGVVVTSHQAPGEGGSGG	GEKKKLKSLAGST
61	TPP-10847	ISGTSASLAITGPDGGSGG	GSDRFSGSKSGGST
62	TPP-11004	ISGSGSGSGSGSPDGGSGG	GSSGSGSGSGSGST
63	TPP-10844	ISGTYISNVNHKPDGGSGG	GSNTKVDKKVEGST
64	TPP-	ISGGFILPIEVYPDGGSGG	GSKVRFDYDLFGST

	10853		
65	TPP-10279	ISGSVVVTSHQAPGGGSGG	GEKKKLKSLAYGST
66	TPP-11170	ISGSVVVTSHQAPGGGSGG	GEKPKPKPLAYGST
67	TPP-11010	ISGSVVVTSHQAPGGGSGG	GSSGSGSGSGSGST
68	TPP-11011	ISGSVVVTSHQAPGGGSGG	GSGSGSGSGSGGST
69	TPP-10764	ISGPNPNKNPNPNPGGSGG	GSNPNENPNPNPGST
70	TPP-11183	ISGDIYLAINITNGEGSGG	GGSGDIYLAINITNGEST
71	TPP-11175	ISGSATKAVSVLKGDGSGG	GGSGVQGIINFEQKGGST
72	TPP-11016	ISGSVPKEKEKEKVSTAVGG	GSGSGSGSGSGST
73	TPP-11015	ISGSVPKEKEKEKVSTAVGG	GSGSGSGSGSGSGST
74	TPP-10451	ISGSSGAVVNVRAPDGGSGG	GSKGDKIAIWTTGST
75	TPP-10768	ISGSYAMSWVRQAPDGGSGG	GSSSYAMSWVRQGST
76	TPP-10848	ISGSTSASLAITGPDGGSGG	GSDRFSGSKSGGGST
77	TPP-11003	ISGSGSGSGSGSGPDGGSGG	GSGSGSGSGSGSGST
78	TPP-11002	ISGSGSGSGSGSSPDGGSGG	GSYSGSGSGSGSGST
79	TPP-10843	ISTQTYISNVNHKPDGGSGG	GSNTKVDKKVEPKST
80	TPP-10845	ISGSTYISNVNHKPDGGSGG	GSNTKVDKKVEGGST
81	TPP-10284	ISGPNPNPNPNPNPDGGSGG	GSNPNPNPNPNPGST
82	TPP-10446	ISAVQVKLELGHRPDGGSGG	GSNHLRSEKLTFNST
83	TPP-10447	ISGFILPIEVYFKPDGGSGG	GSPRKVRFDYDLFST
84	TPP-10854	ISGSGFILPIEVYPDGGSGG	GSKVRFDYDLFGGST
85	TPP-11014	ISGSVPKEKEKEKVSTAVGG	GSYGSGSGSGSGSGST
86	TPP-10849	ISDRSALLKSKLRALLTAPR	GSDRSALLKSKLRAST
87	TPP-10850	ISDRSALLKSKLRALLTAPG	GGSGSGSGSGSGSGST
88	TPP-11013	ISGSSDKTHTSPPSPDGGSGG	GSKTHTSPPSPGGST
89	TPP-10771	ISGSYAMSWVRQASPDGGSGG	GSYSSYAMSWVRGGST
90	TPP-10287	ISGSYAMSWVRQASPDGGSGG	GSYSSYAMSWVRQGST

91	TPP-10282	ISGSGSGSGSGSGSPDGGSGG	GSYGSGSGSGSGSGST
92	TPP-10285	ISGSPNPNPNPNPSPDGGSGG	GSYPNPNPNPNPSGST
93	TPP-10286	ISGPNPNKNPNPNSPDGGSGG	GSYNPNENPNPNPGST
94	TPP-10283	ISGPNPNPNPNPNSPDGGSGG	GSYNPNPNPNPNPGST
95	TPP-11168	ISGSVVVTSHQAPGGSGGSGG	GSGEKKKLKSLAYGST
96	TPP-10857	ISGSVVYIEILDRHPDGGSGG	GSGREVPISNGSGGST
97	TPP-10856	ISGAVVYIEILDRHPDGGSGG	GSGREVPISNGSGGST
98	TPP-10855	ISPAVVYIEILDRHPDGGSGG	GSGREVPISNGSGFST
99	TPP-10281	CAKSPDGGSGG	GSYG
100	TPP-10280	CAKSPDGGSGG	GSYQHWGQG
101	TPP-10583	CAKVHQETGGSGG	GSWHVQHWGQG
102	TPP-10582	CAKVHQETPDGGSGG	GSYEWHVQHWGQG
103	TPP-10270	CTSVHQETKKYQSSGG	GSYSYTYNYEWHVDVWGQG
104	TPP-10264	CTSVHQETSSPDGGSGG	GSYSYEWHVDVWGQG
105	TPP-10581	CAKTHTSPPSPDGGSGG	GSSPPSPYFQHWGQG
106	TPP-10263	CTSVHQETKSSPDGGSGG	GSYSNYEWHVDVWGQG
107	TPP-10271	CTSVHQETKKYQSSPDGG	GSYSYTYNYEWHVDVWGQG
108	TPP-10262	CTSVHQETKKSSPDGGSGG	GSYSYNYEWHVDVWGQG
109	TPP-10272	CTSVHQETKKYQSSGGSGG	GSYSYTYNYEWHVDVWGQG
110	TPP-10261	CTSVHQETKKQSSPDGGSGG	GSYSYYNYEWHVDVWGQG
111	TPP-10289	CAKVHPNPNPNPNPDGGSGG	GSNPNPNPNPHVDVWGQG
112	TPP-10273	CTSVHQETKKYQSSPDGGSG	GSYSYTYNYEWHVDVWGQG
113	TPP-10260	CTSVHQETKKYQSSPDGGSGG	GSYSYYNYEWHVDVWGQG
114	TPP-10275	CAKLTVVVTSHQAPGEGGSGG	GEKKKLKSLAYFQHWGQG
115	TPP-10580	CAKSSDKTHTSPPSPDGGSGG	GSKTHTSPPSPYFQHWGQG
116	TPP-10274	CTSVHQETKKYQSSPDGGSGG	GSYSYTYNYEWHVDVWGQG
117	TPP-5661	CTSVHQETKKYQSSPDGGSGG	GSYSYTYNYEWHVDVWGQG

118	TPP-13226	CAKVETKKYQSSPDGGSGG	GSYSYTYNYEVQHWGQG
119	TPP-13227	CAKVHTKKYQSSPDGGSGG	GSYSYTYNYHVQHWGQG
120	TPP-13228	CAKLTVETKKYQSSPDGGSGG	GSYSYTYNYEWHVQHWGQG
121	TPP-13229	CAKLTAETKKYQSSPDGGSGG	GSYSYTYNYENYFQHWGQG
122	TPP-13230	CAKGITGTKKYQSSPDGGSGG	GSYSYTYNYAEYFQHWGQG
123	TPP-13231	CAKGITGTKKYQSSPDGGSGG	GSYDYVWGSYAYFQHWGQG
124	TPP-10276	CAKLTSVVVTSHQAPGGGSGG	GEKKKLKSLAYYFQHWGQG
125	TPP-10290	CAKVHPNPNPNPNSPDGGSGG	GSYNPNPNPNPHVDVWGQG
126	TPP-10445	CAKLTQVKLELGHRPDGGSGG	GSNHLRSEKLTYFQHWGQG
127	TPP-10269	CAKVHQETKKYQSSPDGGSGG	GSYSYTYNYEWHVQHWGQG
128	TPP-10288	CAKTQTYISNVNHKPDGGSGG	GSNTKVDKKAEYFQHWGQG
129	TPP-10265	CTSVHQETKKYQSSPDGGSGG	GSYSYTTYNYEWHVDVWGQG
130	TPP-10268	CATSVHQETKKYQSSPDGGSGG	GSYSYTYNYEWHVDVHWGQG
131	TPP-10593	CAKLTAEEWKKKYEKEKEKNKGS	GGSGGSGGSGGAEYFQHWGQG
132	TPP-11174	CADSSDRSALLKSKLRALLTAPR	GSNHLRSEKLTFNYFQHWGQG
133	TPP-10266	CTSVHQETKKYQYQSSPDGGSGG	GSYSYTYTYNYEWHVDVWGQG
134	TPP-11173	CAKLTDRSALLKSKLRALLTAPR	GSNHLRSEKLTFNYFQHWGQG
135	TPP-10444	CAKLTAVQVKLELGHRPDGGSGG	GSNHLRSEKLTFNYFQHWGQG
136	TPP-10267	CTSVHQETKKYQSSYQSSPDGGSGG	GSYSYTYSYTYNYEWHVDVWGQG
137	TPP-10443	CAKLTAVQVKLELGHRAQPDGGSGG	GSPVNHLRSEKLTFNYFQHWGQG
138	TPP-11163	SSSNIGSKLRALLTAPR	GSGSGGSGGSGSGYD
139	TPP-10360	SGSGSGSGSGSGSPDGGSGG	GSYGSGGSGSGSGD
140	TPP-10462	SSLGQIQLTIRHSSPDGGSGG	GSNKLIVVVHASRNLIGYD
141	TPP-10460	SPLGQIQLTIRHSSQPDGGSGG	GSRNKLIVVVHASRNLIAYD
142	TPP-10461	SSLGQIQLTIRHSSQPDGGSGG	GSRNKLIVVVHASRNLIGYD
143	TPP-11161	SSSNIGSALLKSKLRALLTAPR	GSSDRSALLKSKLRALLTAD
144	TPP-	SSSNIGSALLKSKLRALLTAPR	GSGSGGSGGSGGSGSGSGYD

	11162		
145	TPP-10359	SSSNIGSGSGSGSGSGSPDGGSGG	GSYGSGGSGSGSGYD
146	TPP-10824	YG	NSNRPSG
147	TPP-10825	YGGSGS	GSGSNSNRPSG
148	TPP-11019	YGKTHTSPPSPGG	GGKTHTSPPSPGNRPSG
149	TPP-11021	YGSGSGSGSGSGGG	GGKTHTSPPSPSGNRPSG
150	TPP-11020	YGSKTHTSPPSPGG	GGKTHTSPPSPSGNRPSG
151	TPP-10789	YGSGSGSGSGGGSGG	GSGGSGSGSGNRPSG
152	TPP-11022	YGSSDKTHTSPPSPGG	GGSGSGSGGSGSGSGNRPSG
153	TPP-10829	YTSASLAITGPDGGSGG	GSDRFSGSKSGNRPSG
154	TPP-10835	YGFILPIEVYPDGGSGG	GSKVRFDYDLFNRPSG
155	TPP-10788	YGSGSGSGSGSGGGSGG	GSGSGGSGSGSGNRPSG
156	TPP-10571	YGVPKEKEKEKVSTAVGG	GSAPLEVPKEKEKEKVG
157	TPP-10830	YGTSASLAITGPDGGSGG	GSDRFSGSKSGGNRPSG
158	TPP-10790	YGGSGSGSGSGPDGGSGG	GSGSGGSGSGSGNRPSG
159	TPP-10573	YGSGSGSGSGSGSGSGGG	GSYEKEKEKNKTLKNVG
160	TPP-10827	YGTYISNVNHKPDGGSGG	GSNTKVDKKVEGNRPSG
161	TPP-10572	YGAEEWKKKYEKEKEKGG	GSGSGSGSGSGSGSGSG
162	TPP-10836	YGGFILPIEVYPDGGSGG	GSKVRFDYDLFGNRPSG
163	TPP-10834	YGSALLKSKLRALLTAPG	GSDGSGGSGSGSGNRPSG
164	TPP-10787	YGSGSGSGSGSGPDGGSGG	GSGSGGSGSGSGNRPSG
165	TPP-10831	YGGTSASLAITGPDGGSGG	GSDRFSGSKSGGGNRPSG
166	TPP-10828	YGGTYISNVNHKPDGGSGG	GSNTKVDKKVEGGNRPSG
167	TPP-10826	YTQTYISNVNHKPDGGSGG	GSNTKVDKKVEPKNRPSG
168	TPP-10837	YGGGFILPIEVYPDGGSGG	GSKVRFDYDLFGGNRPSG
169	TPP-10361	YGSGSGSGSGSGSPDGGSGG	GSYGSGGSGSGSGNRPSG
170	TPP-11023	YGSQVKLELGHRAPDGGSGG	GSVNHLRSEKLTSGNRPSG

171	TPP-10838	YPAVVYIEILDRHPDGGSGG	GSGREVPISNGSGFNRPSG
172	TPP-10840	YGGVVYIEILDRHPDGGSGG	GSGREVPISNGSGGNRPSG
173	TPP-10839	YGAVVYIEILDRHPDGGSGG	GSGREVPISNGSGGNRPSG
174	TPP-10832	YGSRSALLKSKLRALLTAPR	GSDGSGSGGSGSGSGNRPSG
175	TPP-10833	YGSRSALLKSKLRALLTAPG	GSDGSGSGGSGSGSGNRPSG
176	TPP-11024	YGSAVQVKLELGHRPDGGSGG	GSNHLRSEKLTFNSGNRPSG
177	TPP-10353	CQS	VVF
178	TPP-10780	CGSGSGSGPDGGSGG	GSGSGSGSGF
179	TPP-10786	CQSYDILPIEPDGGSGG	GSRFDYDGVVF
180	TPP-10779	CGSGSGSGSGPDGGSGG	GSGSGSGSGSGF
181	TPP-10778	CGSGSGSGSGSGGGSGG	GSGSGSGSGSGSGF
182	TPP-10783	CQSYDKLELGHPDGGSGG	GSHLRSEKGVVF
183	TPP-10785	CQSYDILPIEVYPDGGSGG	GSKVRFDYDGVVF
184	TPP-10776	CGSGSGSGSGSGPDGGSGG	GSGSGSGSGSGSGF
185	TPP-10777	CGSGSGSGSGSGSDGGSGG	GSGSGSGSGSGSGF
186	TPP-10784	CQSYDGFILPIEVYGGSGG	GSKVRFDYDLFGVVF
187	TPP-10782	CQSYDKLELGHRAPDGGSGG	GSVNHLRSEKGVVF
188	TPP-10352	CQVHQETKKYQSSPDGGSGG	GSYSYTYNYEWHVVF
189	TPP-10356	CGSGSGSGSGSGSPDGGSGG	GSYGSGSGSGSGSGF
190	TPP-10354	CQSYDPNPNPNPNPDGGSGG	GSNPNPNPNPSGVVF
191	TPP-10355	CAAWNPNPNPNPNPNGGSGG	GSNPNPNPNPNPNVF
192	TPP-10781	CQSYDQVKLELGHRAGGSGG	GSVNHLRSEKLTGVVF
193	TPP-10436	CQSVHQETKKYQSSPDGGSGG	GSYSYTYNYEWHVVF
194	TPP-10440	CQSYDQVKLELGHRPDGGSGG	GSNHLRSEKLTGVVF
195	TPP-10442	CQSYDGFILPIEVYPDGGSGG	GSKVRFDYDLFGVVF
196	TPP-10351	CTSVHQETKKYQSSPDGGSGG	GSYSYTYNYEWHVDVF
197	TPP-	CQSVHQETKKYQSSPDGGSGG	GSYSYTYNYEWHVVVF

	10348		
198	TPP-10358	CGGSGSGSGSGSGSPDGGSGG	GSYGSGSGSGSGSGGF
199	TPP-11167	CQSYDSSALLKSKLRALLTAPR	GSVNHLRSEKLTGVVF
200	TPP-10438	CQSAVQVKLELGHRAPDGGSGG	GSVNHLRSEKLTFNVF
201	TPP-10439	CQSYDQVKLELGHRAPDGGSGG	GSVNHLRSEKLTGVVF
202	TPP-10441	CQSYDGFILPIEVYFPDGGSGG	GSRKVRFDYDLFGVVF
203	TPP-10349	CQSYVHQETKKYQSSPDGGSGG	GSYSYTYNYEWHVGVVF
204	TPP-10350	CQSYDVHQETKKYQSSPDGGSGG	GSYSYTYNYEWHVSGVVF
205	TPP-10437	CQSYDAVQVKLELGHRAPDGGSGG	GSVNHLRSEKLTFNGVVF
206	TPP-11166	CQSYDSSDRSALLKSKLRALLTAPR	GSGGSVNHLRSEKLTGVVF
207	TPP-10362	CQSYDSSDRSALLKSKLRALLTAPR	GSDRSALLKSKLRALLTAVVF
208	TPP-10363	CQSYDSSDRSALLKSKLRALLTAPE	GSDRSALLKSKLRALLTAVVF
209	TPP-5657		

[3] The N-terminal sequence corresponds to the nearest neighboring reference aa N-terminal from the inserted natriuretic peptide plus the amino acid stretch present between said reference aa and the first amino acid residue of the inserted natriuretic peptide

[4] The C-terminal sequence corresponds the amino acid stretch present between the last amino acid residue of the inserted natriuretic peptide and the nearest neighboring reference aa C-terminal from the inserted natriuretic peptide plus and said reference aa

In addition, the following BNP engrafted human IgG1 antibody constructs were generated starting from the antibody scaffold TPP-5657.

Table 5: Design of BNP engrafted antibody constructs

Cmpd	TPP	Insertion Site	# aa N-term[1]	# aa C-term[2]	BNP	Corresp. ANP Cpd[3]
B1	TPP-9902	CDRH3	20	18	Hum28aa	#117
B2	TPP-11153	CDRH3	22	19	Hum25aa	
B3	TPP-11154	CDRH3	20	18	Rat28aa	#117
B4	TPP-11155	CDRH3	17	17	Rat32aa	
B5	TPP-11156	CDRH2	18	13	Hum28aa	#65
B6	TPP-11157	CDRH2	18	13	Rat28aa	#65
B7	TPP-18029	CDRH1	23	14	Hum28aa	#9
B8	TPP-18031	CDRH2	3	3	Hum28aa	#12
B9	TPP-18032	CDRH2	7	7	Hum28aa	#13
B10	TPP-18033	CDRH2	19	14	Hum28aa	#80
B11	TPP-18028	CDRH2	20	15	Hum28aa	#94
B12	TPP-18034	CDRH3	20	18	Hum28aa	#122
B13	TPP-18030	CDRL3	19	14	Hum28aa	#191

[1] The number of amino acid residues present between the respective N-terminal reference amino acid residue and the first amino acid of the inserted natriuretic peptide;
[2] The number of amino acid residues present between the last amino acid of the inserted natriuretic peptide and the respective C-terminal reference amino acid residue
[3]Corresponding ANP Cpd. refers to an ANP engrafted antibody construct with the same integration locus and comprising the same N-terminal and C-terminal sequence

Table 5 cont.: Design of BNP engrafted antibody constructs

Cmpd	TPP	N-terminal sequence[3]	C-terminal sequence[4]
B1	TPP-9902	CTSVHQETKKYQSSPDGGSGG	GSYSYTYNYEWHVDVWGQG
B2	TPP-11153	CTSVHQETKKYQSSPDGGSGGSG	GGSYSYTYNYEWHVDVWGQG
B3	TPP-11154	CTSVHQETKKYQSSPDGGSGG	GSYSYTYNYEWHVDVWGQG
B4	TPP-11155	CTSVHQETKKYQSSPDGG	SYSYTYNYEWHVDVWGQG
B5	TPP-	ISGSVVVTSHQAPGGGSGG	GEKKKLKSLAYGST

	11156		
B6	TPP-11157	ISGSVVVTSHQAPGGGSGG	GEKKKLKSLAYGST
B7	TPP-18029	SGFTFGSGSGSGSGSGSPDGGSGG	GSYGSGSGSGSGSGM
B8	TPP-18031	ISGS	GGST
B9	TPP-18032	ISGSGSGS	GSGSGGST
B10	TPP-18033	ISGSTYISNVNHKPDGGSGG	GSNTKVDKKVEGGST
B11	TPP-18028	ISGPNPNPNPNPNSPDGGSGG	GSYNPNPNPNPNPGST
B12	TPP-18034	CAKGITGTKKYQSSPDGGSGG	GSYSYTYNYAEYFQHWGQG
B13	TPP-18030	CAAWNPNPNPNPNPNGGSGG	GSNPNPNPNPNPNVF

[3] The N-terminal sequence corresponds to the nearest neighboring reference aa N-terminal from the inserted natriuretic peptide plus the amino acid stretch present between said reference aa and the first amino acid residue of the inserted natriuretic peptide

[4] The C-terminal sequence corresponds the amino acid stretch present between the last amino acid residue of the inserted natriuretic peptide and the nearest neighboring reference aa C-terminal from the inserted natriuretic peptide plus and said reference aa

In addition, the following CNP engrafted human IgG1 antibody constructs were generated.

Table 6: Design of CNP engrafted antibody constructs

Cmpd	TPP	Insertion Site	SEQ ID NO comprised in Ntls	SEQ ID NO comprised in Ctls	# aa N-term[1]	# aa C-term[2]	µg/ml pcs	% purity pcs	Corresp. ANP Cpd[3]
C1	TPP-9465	CDRH3	7	8	21	23	69-242	97	
C2	TPP-12374	CDRL3	11	12	20	20	212		
C3	TPP-12375	CDRH3	7	8	21	23	6		
C4	TPP-12376	CDRH3	7	8	20	22	7		
C5	TPP-12377	CDRH3		8	21	23	7		
C6	TPP-12378	CDRH2	9	10	19	18	3		
C13	TPP-18036	CDRH1			23	14	259	100	#9
C14	TPP-18038	CDRH2			3	3	0		#12
C15	TPP-18039	CDRH2			7	7	301	100	#13
C16	TPP-18040	CDRH2	2	3	19	14	300	100	#80
C17	TPP-18035	CDRH2			20	15	243	100	#94
C18	TPP-18041	CDRH3	21	22	20	18	287	100	#122
C19	TPP-18037	CDRL3			19	14	246	100	#191
Cmpds based on TPP-12377:		**Difference vs. TPP-12377**							
C7	TPP-12895	LC_G99E							
C8	TPP-12896	LC_G99L					101-131		
C9	TPP-12897	LC_S98D					198-304		
C10	TPP-12898	LC_S98G					147-258		
C11	TPP-12899	LC_A33Y					165-197	82	
C12	TPP-12900	LC_A33E					109-195		

[1] The number of amino acid residues present between the respective N-terminal reference amino acid residue and the first amino acid of the inserted natriuretic peptide;

[2] The number of amino acid residues present between the last amino acid of the inserted natriuretic peptide and the respective C-terminal reference amino acid residue

[3]Corresponding ANP Cpd. refers to an ANP engrafted antibody construct with the same integration locus and comprising the same N-terminal and C-terminal sequence

Table 6 cont.: Design of CNP engrafted antibody constructs

Cmpd	TPP	N-terminal sequence[3]	C-terminal sequence[4]
C1	TPP-9465	CTSVHQETKKYQSSPDGGSGGS	GSGGYGSYSYTYNYEWHVDVWGQG
C2	TPP-12374	CQSYDQVKLELGHRAGGSGGS	GSGGSGSVNHLRSEKLTGVVF
C3	TPP-12375	CTSVHQETKKYQSSPDGGSGGS	GSGGSGSYSYTYNYEWHVDVWGQG
C4	TPP-12376	CTSVHQETKKYQSSPDGGSGG	GGGSGSYSYTYNYEWHVDVWGQG
C5	TPP-12377	CTSVHQETKKYQSSPYKGANKK	GSGGSGSYSYTYNYEWHVDVWGQG
C6	TPP-12378	ISGSVVVTSHQAPGGGSGGS	GSGGSGEKKKLKSLAYGST

[3] The N-terminal sequence corresponds to the nearest neighboring reference aa N-terminal from the inserted natriuretic peptide plus the amino acid stretch present between said reference aa and the first amino acid residue of the inserted natriuretic peptide

[4] The C-terminal sequence corresponds the amino acid stretch present between the last amino acid residue of the inserted natriuretic peptide and the nearest neighboring reference aa C-terminal from the inserted natriuretic peptide plus and said reference aa

Example 5: In vitro activities of generated constructs

All constructs were expressed transiently in HEK293 cells according to well-known methods in the art, targeting a cell density of about 2x10^6 cells/ml, a total DNA concentration of about 1µg/ml for the two plasmids encoding the light and heavy chain and a 5 day incubation for the expression.

Raw compound samples (rcs) were expressed in a culture volume of 0.4ml, and the supernatant separated by centrifugation was directly used for testing. The compound concentration was assessed by an IgG-Fc quantification ELISA according to well-known methods in the art. Briefly, 1:1500 diluted supernatant and a 2-fold dilution series of Human Reference Serum (Bethyl, RS-110-4) starting with 400ng/ml were immobilized in black Maxisorp 384 micro titer plates (MTP) coated with anti-human Fc [Sigma I2136] in a 1:440 dilution in 1x coating buffer (Candor, 121125) for 1h, 37°C. After blocking with 100% SMART Block (Candor, 113125) anti-human Fc-HRP [Sigma, A0170] was applied in a 1:10000 dilution for the detection of antibodies in rcs and reference samples. Dose curves of the reference sample were used for the quantitative assessment of compound concentrations shown in Tables 7 and 8, column "µg/ml rcs". All samples were applied in quadruplets.

Isolated compound samples (ics) were generated by 1-step purification via protein-A from 6 ml expression culture and according to well-known methods in the art. Acid eluates were neutralized by addition of 8% (v/v) 1M Tris/HCl pH 9.0, quantified via absorption at 280nm and normalized to a concentration of 125nM.

Purified compound samples (pcs) were generated by 2-step purification via protein-A and subsequent SEC in PBS buffer from expression culture of at least 35ml. Values shown in Tables 7 and 8, column "µg/ml pcs", refer to the compound concentration in the expression culture supernatant determined by analytical Protein A chromatography.

All activities shown in Tables 7 and 8 were measured on cells with heterologous over expression of human NPRA (hNPRA) by use of a cGMP quantification assay conducted according to manufacturer's instructions (cisbio; 62GM2PEH). In brief, the assay quantifies cGMP in buffered solution or cell–culture supernatants based on the competition between cGMP produced by the cell as result of the NPRA stimulation through the (natriuretic peptide) sample and d2 labelled cGMP for binding to a Cryptate labelled antibody. Sample cGMP and d2 labeled cGMP compete for binding to a limited number of sites on Cryptate labeled anti-cGMP antibodies, and consequently, HTRF® specific fluorescent signal (i.e. energy transfer) is inversely proportional to the concentration of cGMP in the sample.

Dose-response curve data were analyzed with GraphPad Prism (version 7.00 for Windows, GraphPad Software, La Jolla California USA) and EC50 were fitted according to *Y=Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*HillSlope))* applying constraints for bottom, top and slope (shared value for all data sets of the respective experiment).

The raw compound sample activity on stable hNPRA-CHO k1 cells was first assessed by comparison to the negative control TPP-5657 and to a positive sample, in particular TPP-5661. Controls and rcs were tested in quadruplets in two concentrations with a relative dilution factor of 5 aiming for a fluorescent signal (s) in the dynamic range of the assay. The assay window was defined as the difference in signal of inactive (max. signal, s_max) and highly active samples (min. signal, s_min), and for both compound concentrations the activity in % was calculated as 100*(s_max – s) / (s_max – s_min). Values listed in Table 7, columns "activity rcs" and "stdev activity rcs", represent the average of the results for the two concentrations and the respective standard deviation. Rcs signals less than half of the signal of the reference compound TPP-5661 (36%) were assessed as not active (n.a.).

The activity of several raw compound samples on stable hNPRA-CHO k1 cells was reassessed by comparison to reference sample TPP-5661 in 2.5-fold dilution series (8 concentrations) starting with a 5-fold dilution. The "logEC50" fit value as activity measure of the rcs was set in relation to the corresponding value of the reference rcs TPP-5661 by calculating the delta "logEC50"_compound – "logEC50"_TPP-5661; resulting values are listed in Table 7, column "rel. activity rcs". Notably, the compound concentrations in the rcs was not considered, and consequently given values are influenced by compound activity and concentration in equal measure. All samples were applied in quadruplets.

The activity of isolated compound samples on stable hNPRA-CHO k1 cells was assessed by EC50 determination and comparison to reference sample TPP-5661. Samples were tested in 2.5-fold dilution series from 80nM to 0.13nM. The logEC50 fit value as activity measure of the ics was set in relation to the corresponding value of the reference ics TPP-5661 (-8.8) by calculating the delta logEC50_compound – logEC50_TPP-5661; resulting values are listed in Table 7, column "rel. logEC50 ics". All samples were applied in quadruplets.

The activity of purified compound samples on stable hNPRA-CHO k1 cells was assessed in multiple experiments by EC50 determination and comparison to reference sample TPP-5661. Samples were tested in dilution series at least in quadruplets. Values listed in Table 7, columns "rel. logEC50 pcs 1, 3 and 4" result from 5-fold dilution series (≥4 concentrations) starting with 20 or 25nM. Values listed in Table 7, column "rel. logEC50 pcs 2" result from 10-fold dilution series (4 concentrations) starting with

25nM. Values listed in Table 7, columns "rel. logEC50 pcs 5, 6, 7, 8 and 9" result from 2.5-fold dilution series, with 8 or 12 concentrations starting with 40 to 200nM, respectively. The logEC50 fit value as activity measure of the pcs was set in relation to the corresponding value of the reference TPP-5661 in the respective experiment (in average -9.2, standard deviation 0.5) by calculating the delta logEC50_compound – logEC50_TPP-5661.

The activity of purified compound samples on transient hNPRA-HEK293 cells was assessed in three experiments by EC50 determination and comparison to reference sample TPP-5661. Samples were tested in 5-fold dilution series from 1000nM to 0.013nM. The logEC50 fit value as activity measure of the pcs was set in relation to the corresponding value of the reference TPP-5661 in the respective experiment (average of three experiments -9.0, standard deviation 0.4) by calculating the delta logEC50_compound – logEC50_TPP-5661; resulting values are listed in Table 7, columns "rel. logEC50* pcs". All samples were applied in duplicates.

A summarized qualitative assessment of the activity of compounds is given in the column "qualit. activity", values listed in column "average rel. logEC50" were calculated as average of given rel. logEC50 values. Compounds showing an EC50 values >50-fold of the reference compound TPP-5661, meaning average rel. logEC50 > 1.7, were qualitatively assessed as not active (" - "), compounds showing a relative logEC50 between 0.7 and 1.7 were assessed as active (" + "), compounds showing a relative logEC50 < 0.7 were assessed as very active (" ++ "); highest activities were observed at relative logEC50 below -0.7 (" +++ "). Compounds showing an activity in rcs without confirmation as ics or pcs are marked with an unified " y ", and compounds assessed as not active ("n.a." in column "activity rcs") probably due to their very low expression level (≤1 µg/ml, "n.e." in column "µg/ml rcs") are marked accordingly.

Table 7: Expression levels and activities of atrial natriuretic peptide engrafted antibody constructs

Not determined (n.d.), not active (n.a.), not expressed (n.e.), not applicable (na)

Compound	# aa N-term[1]	# aa C-term[2]	µg/ml res	µg/ml pcs	% purity pcs	activity res	stdev activity res	rel. activity res	rel. logEC50 ics	rel. logEC50 pcs 1	rel. logEC50 pcs 2	rel. logEC50 pcs 3	rel. logEC50 pcs 4	rel. logEC50 pcs 5	rel. logEC50 pcs 6	rel. logEC50 pcs 7	rel. logEC50 pcs 8	rel. logEC50 pcs 9	rel. logEC50* pcs	rel. logEC50* pcs	rel. logEC50* pcs	qualit. activity	average rel logEC50
#1	6	2	n.d.	225	93	n.d.													n.a.	n.a.	n.a.	-	n.a.
#2	9	5	n.d.	179	96	n.d.													n.a.	n.a.	n.a.	-	n.a.
#3	12	8	n.d.	196	97	n.d.													0,2	0,0	0,0	++	0,1
#4	15	10	n.d.	214	96	n.d.													-0,7	-0,8	-0,8	++	-0,8
#5	18	10	n.d.	229	93	n.d.											-0,7		-0,4	-0,4	-0,5	++	-0,5
#6	19	17	1,6	150	76	33%	18%															y	
#7	19	17	n.e	117	70	22%	20%															y	
#9	23	14	4,8	226	97	41%	27%						-0,2			0,0			-0,5	-0,6	-0,4	++	-0,3
#10	23	14	n.d.	265	96	n.d.											0,9		0,2	0,1	0,0	++	0,3
#12	3	3	42,0	n.d.	n.d.	n.a.																-	
#13	7	7	12,0	n.d.	n.d.	n.a.			n.a.													-	n.a.
#14	8	9	14,0	n.d.	n.d.	n.a.			n.a.													-	n.a.
#15	10	11	6,6	n.d.	n.d.	n.a.			n.a.													-	n.a.
#16	11	14	9,8	n.d.	n.d.	n.a.																-	
#17	12	8	7,2	n.d.	n.d.	53%	3%															y	
#18	13	12	12,0	290	98	n.a.		-0,2						0,9								+	0,9
#19	14	9	9,5	n.d.	n.d.	48%	11%															y	
#20	14	10	9,9	n.d.	n.d.	64%	3%															y	
#21	14	11	5,8	n.d.	n.d.	38%	18%		0,7													++	0,7
#22	14	14	23,0	n.d.	n.d.	75%	9%															y	
#23	15	10	2,6	n.d.	n.d.	60%	35%															y	
#24	15	12	n.e	83	52	26%	22%						0,6									++	0,6

#25	15	14	14,0	n.d.	n.d.	25%	5%	-1,0	0,8														+	0,8
#26	16	11	2,0	181	98	n.a.		1,9															-	
#27	16	11	17,0	n.d.	n.d.	37%	23%		1,4														+	1,4
#28	16	11	9,1	n.d.	n.d.	50%	9%	-0,9	0,5														++	0,5
#29	16	14	7,0	n.d.	n.d.	n.a.																	-	
#30	16	15	35,0	n.d.	n.d.	88%	13%																y	
#33	17	11	2,3	229	79	73%	32%	-0,9		-0,1	-1,1		-0,7			-0,9	-0,5	-0,8	++	-0,7				
#34	17	11	n.d.	226	87	n.d.								-0,2					++	-0,2				
#35	17	11	n.d.	215	86	n.d.								-0,6					++	-0,6				
#36	17	11	n.d.	217	86	n.d.								-0,1					++	-0,1				
#37	17	11	n.d.	244	86	n.d.								-0,8					+++	-0,8				
#38	17	11	n.d.	233	88	n.d.								-0,5					++	-0,5				
#39	17	11	n.d.	208	86	n.d.								-0,6					++	-0,6				
#40	17	11	n.d.	154	85	n.d.										-0,5	-0,3	-0,6	++	-0,5				
#41	17	11	n.d.	106	79	n.d.													n.d.					
#42	17	11	n.d.	112	97	n.d.										-0,6	-0,7	-0,7	++	-0,7				
#43	17	11	n.d.	141	96	n.d.										-0,6	-0,8	-0,6	++	-0,7				
#44	17	11	n.d.	166	93	n.d.										-0,7	-0,8	-0,8	+++	-0,8				
#45	17	11	n.d.	135	90	n.d.										-0,4	-0,2	-0,5	++	-0,4				
#46	17	11	n.d.	166	92	n.d.										-0,5	-0,4	-0,6	++	-0,5				
#47	17	11	n.d.	123	83	n.d.										-0,3	-0,3	-0,7	++	-0,4				
#49	17	11	n.d.	203	84	n.d.								-0,6		-0,2	-0,1	-0,6	++	-0,4				
#50	17	12	9,0	87	97	66%	21%	-1,0		0,0	-0,4								++	-0,2				
#51	17	12	6,4	n.d.	n.d.	44%	39%												y					
#52	17	12	7,6	n.d.	n.d.	26%	20%												y					
#53	17	13	n.d.	n.d.	n.d.	69%	5%												y					
#54	17	14	n.e	75	n.d.	n.a.													n.e					
#55	17	14	8,8	271	95	72%	40%	-0,9							-0,9	-0,4	0,2		++	-0,4				
#57	17	17	13,0	n.d.	n.d.	48%	1%												y					
#58	17	17	33,0	n.d.	n.d.	45%	9%												y					
#59	17	17	31,0	n.d.	n.d.	87%	4%	-1,1	0,0										++	0,0				
#60	18	12	4,1	367	90	53%	31%			0,0	-0,5								++	-0,3				

#61	18	13	n.e	334	97	n.a.					0,0	-0,9						++	-0,5
#62	18	13	11,0	n.d.	n.d.	36%	14%		1,5									+	1,5
#63	18	13	9,5	239	96	70%	22%				-0,1							++	-0,1
#64	18	13	5,3	n.d.	n.d.	51%	18%											y	
#65	18	13	1,2	253	86	69%	17%		-0,5	-0,3	-1,2	-0,9						+++	-0,7
#66	18	13	38,0	n.d.	n.d.	87%	4%	-0,5	0,2									++	0,2
#67	18	13	4,8	n.d.	n.d.	35%	17%	-1,1	0,7									++	0,7
#68	18	13	9,2	n.d.	n.d.	48%	13%											y	
#69	18	14	7,1	n.d.	n.d.	66%	11%	-1,0	0,3									++	0,3
#70	18	17	n.e	n.d.	n.d.	30%	2%											y	
#71	18	17	27,0	n.d.	n.d.	89%	2%	-0,5	-0,6									++	-0,6
#72	19	12	11,0	n.d.	n.d.	82%	0%	-1,5	0,1									++	0,1
#73	19	14	9,4	n.d.	n.d.	71%	0%	-1,4	-0,2									++	-0,2
#74	19	14	3,8	142	97	67%	7%	-1,0		0,0	0,3							++	0,2
#75	19	14	4,4	50	49	95%	8%					-0,4						++	-0,4
#76	19	14	11,0	299	97	56%	2%						0,2	-0,8				++	-0,3
#77	19	14	13,0	n.d.	n.d.	38%	6%		1,1									+	1,1
#78	19	14	14,0	n.d.	n.d.	55%	38%		1,0									+	1,0
#79	19	14	5,5	n.d.	n.d.	67%	26%											y	
#80	19	14	5,4	214	95	67%	19%						-0,4	-0,8				++	-0,6
#81	19	14	6,2	n.d.	n.d.	64%	10%											y	
#82	19	14	1,6	n.d.	n.d.	57%	9%											y	
#83	19	14	n.e	n.d.	n.d.	22%	40%											y	
#84	19	14	11,0	n.d.	n.d.	45%	30%											y	
#85	19	15	4,5	n.d.	n.d.	74%	27%	-1,2	-0,9									+++	-0,9
#87	19	15	42,0	n.d.	n.d.	90%	13%											y	
#89	20	15	n.e	85	n.d.	n.a.												n.e	
#90	20	15	n.e	68	50	52%	18%			0,9	0,5		0,4					++	0,6
#91	20	15	3,4	275	99	30%	26%	0,3		0,3	-0,2		0,1	0,2				++	0,1
#92	20	15	2,3	n.d.	n.d.	n.a.		-0,3	0,6									++	0,6
#93	20	15	4,1	286	98	70%	4%	-0,8						-0,8				+++	-0,8
#94	20	15	12,0	318	98	83%	17%	-0,8						-0,8				+++	-0,8

#95	20	15	38,0	n.d.	n.d.	81%	16%																		y		
#96	20	15	7,3	n.d.	n.d.	n.a.																			-		
#97	20	15	8,3	n.d.	n.d.	26%	17%																		y		
#98	20	15	7,7	n.d.	n.d.	40%	14%																		y		
#99	10	3	44,0	257	100	n.a.				n.a.	n.a.														-	n.a.	
#100	10	8	88,0	188	99	n.a.				n.a.	n.a.														-	n.a.	
#101	12	10	83,0	n.d.	n.d.	n.a.																			-		
#102	14	12	16,0	n.d.	n.d.	20%	7%																		y		
#103	15	18	7,7	101	85	50%	8%			0,7		-0,1													++	0,3	
#104	16	14	15,0	137	98	n.a.				1,0	2,3														?	1,7	
#106	17	15	30,0	n.d.	n.d.	20%	2%																		y		
#107	17	18	8,8	n.d.	n.d.	50%	19%																		y		
#108	18	16	37,0	n.d.	n.d.	68%	7%																		y		
#109	18	18	4,6	n.d.	n.d.	62%	20%																		y		
#110	19	17	34,0	238	100	45%	25%			-0,4	1,1														++	0,4	
#111	19	17	41,0	296	98	80%	3%			-0,4	0,2														++	-0,1	
#112	19	18	3,9	n.d.	n.d.	31%	30%																		y		
#113	20	17	44,0	n.d.	n.d.	52%	2%																		y		
#114	20	17	26,0	219	76	94%	4%			0,5	0,1														++	0,3	
#116	20	18	9,4	247	84	71%	11%			-0,3	-0,2					0,0					-0,2	0,0	-0,1	++	-0,1		
#117	20	18	12,9	238	92	36%	30%	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0	++	0,0		
#118	18	16	n.d.	191	n.d.	n.d.													-0,1					++	-0,1		
#119	18	16	n.d.	171	n.d.	n.d.													-0,2					++	-0,2		
#120	20	18	n.d.	200	n.d.	n.d.													-0,3					++	-0,3		
#121	20	18	n.d.	253	n.d.	n.d.													-0,2					++	-0,2		
#122	20	18	n.d.	115	n.d.	n.d.													-0,3					++	-0,3		
#123	20	18	n.d.	153	n.d.	n.d.													-0,1					++	-0,1		
#124	20	18	41,0	n.d.	n.d.	77%	23%																		y		
#125	20	18	18,0	320	99	84%	16%			-0,8	-0,1														++	-0,5	
#126	20	18	17,0	203	90	80%	2%																		y		
#127	20	18	35,0	119	92	95%	2%			0,5		-0,7									-0,5	-0,5	-0,5	++	-0,3		
#128	20	18	64,0	291	96	93%	9%																		y		

#129	20	19	28,0	n.d.	n.d.	78%	12%																					y	
#130	21	19	33,0	n.d.	n.d.	89%	5%																					y	
#132	22	20	7,5	n.d.	n.d.	68%	20%																					y	
#133	22	20	20,0	n.d.	n.d.	75%	14%																					y	
#134	22	20	9,7	n.d.	n.d.	75%	3%																					y	
#135	22	20	30,0	158	88	67%	9%			0,1	3,5																	?	1,8
#136	24	22	15,0	n.d.	n.d.	65%	13%																					y	
#137	24	22	61,0	n.d.	n.d.	81%	23%																					y	
#139	19	13	n.e	n.d.	n.d.	n.a.																						n.e	
#145	23	14	35,0	n.d.	n.d.	73%	11%																					y	
#146	1	6	29,0	n.d.	n.d.	n.a.																						-	
#147	5	10	6,7	n.d.	n.d.	n.a.		0,8																				+	
#151	14	14	13,0	n.d.	n.d.	64%	23%	-1,3	-0,4																			++	-0,4
#153	16	15	1,5	n.d.	n.d.	40%	24%																					y	
#154	16	15	n.e	n.d.	n.d.	22%	21%																					y	
#155	16	16	7,8	n.d.	n.d.	57%	17%	-1,3	-0,7																			++	-0,7
#156	17	16	2,0	64	98	57%	33%	-1,3																				++	
#157	17	16	2,4	n.d.	n.d.	23%	11%																					y	
#158	17	16	10,0	n.d.	n.d.	n.a.		-0,6																				++	
#159	17	16	4,9	n.d.	n.d.	55%	22%	-1,3																				++	
#160	17	16	2,8	n.d.	n.d.	34%	22%																					y	
#161	17	16	4,9	n.d.	n.d.	34%	9%	-0,7																				++	
#162	17	16	n.e	n.d.	n.d.	n.a.																						n.e	
#163	17	17	n.d.	84	85	n.d.										0,6												++	0,6
#164	18	16	3,0	n.d.	n.d.	n.a.		-0,8	-0,1																			++	-0,1
#165	18	17	3,5	n.d.	n.d.	53%	28%																					y	
#166	18	17	4,1	n.d.	n.d.	20%	34%																					y	
#167	18	17	n.e	48	n.d.	44%	13%																					y	
#168	18	17	n.e	n.d.	n.d.	n.a.																						n.e	
#169	19	17	2,8	78	99	20%	16%	-0,1								-0,1												++	-0,1
#170	19	18	n.e	n.d.	n.d.	n.a.																						n.e	
#171	19	18	n.e	n.d.	n.d.	n.a.																						n.e	

#172	19	18	n.e	n.d.	n.d.	n.a.																					n.e	
#173	19	18	n.e	n.d.	n.d.	n.a.																					n.e	
#174	19	19	n.d.	73	n.d.	n.d.								1,3													+	1,3
#175	19	19	n.d.	105	82	n.d.								0,3	0,1												++	0,2
#176	20	19	n.e	n.d.	n.d.	n.a.																					n.e	
#177	2	2	41,0	262	100	n.a.					n.a.	n.a.															-	n.a.
#178	14	9	16,0	n.d.	n.d.	67%	33%																				y	
#179	16	10	51,0	n.d.	n.d.	n.a.																					-	
#180	16	11	18,0	n.d.	n.d.	37%	6%																				y	
#181	16	13	21,0	n.d.	n.d.	79%	7%																				y	
#182	17	11	2,5	n.d.	n.d.	73%	19%																				y	
#183	18	12	36,0	n.d.	n.d.	21%	16%																				y	
#184	18	13	10,0	100	100	50%	3%																				y	
#185	18	13	17,0	81	100	72%	1%																				y	
#186	18	14	20,0	77	96	45%	22%																				y	
#187	19	13	35,0	217	95	85%	10%		-1,1																		+++	-1,1
#188	19	14	15,0	n.d.	n.d.	77%	8%																				y	
#189	19	14	16,0	102	99	59%	4%																				y	
#190	19	14	41,0	n.d.	n.d.	64%	13%																				y	
#191	19	14	29,0	248	99	94%	8%	0,1				-0,6	0,2	-0,3													++	-0,2
#192	19	15	70,0	n.d.	n.d.	90%	14%	-1,0	-1,0																		+++	-1,0
#193	20	14	2,7	n.d.	n.d.	33%	37%																				y	
#194	20	14	32,0	98	97	75%	3%																				y	
#195	20	14	20,0	43	97	34%	12%																				y	
#196	20	15	n.e	n.d.	n.d.	n.a.																					n.e	
#197	20	15	5,5	18	n.d.	54%	20%																				y	
#198	20	15	14,0	57	100	52%	21%																				y	
#199	21	15	7,3	n.d.	n.d.	29%	12%																				y	
#200	21	15	33,0	97	n.d.	78%	7%																				y	
#201	21	15	51,0	134	97	87%	6%	-0,3				0,1	-0,3														++	-0,1
#202	21	15	16,0	29	n.d.	58%	3%																				y	
#203	21	16	3,1	17	n.d.	33%	2%																				y	

#204	22	17	5,7	20	n.d.	45%	17%															y	
#205	23	17	34,0	n.d.	n.d.	84%	19%															y	
#206	24	18	11,0	n.d.	n.d.	47%	33%															y	
#207	24	20	12,0	115	95	59%	17%				n.a.	n.a.										-	n.a.
#208	24	20	9,5	182	92	74%	11%				0,6	0,3										++	0,5
#209	na	na	18,3	402	100	n.a.																-	

[1] The number of amino acid residues present between the respective N-terminal reference amino acid residue and the first amino acid of the inserted natriuretic peptide;

[2] The number of amino acid residues present between the last amino acid of the inserted natriuretic peptide and the respective C-terminal reference amino acid residue

No conclusive data for compounds #104 and #135 were obtained. 12 compounds (#54, #61, #89, #139, #162, #168, #170, #171, #172, #173, #176,#196) showed very low expression levels (≤ 1µg/ml in rcs) and consequently no activity; activity of #61 was shown after compound preparation (pcs). 7 compounds (#7, #24, #70, #83, #90, #154, #167) showed in most cases low activity as rcs, although their expression level was very low; the activity of #24 and #90 was confirmed by compound preparation (pcs). No activity was observed in rcs of compounds #18, #26, #29, #92, #96, #101, #104, #158, #164, #179; however, the activity of compounds #18, #92, #158, #164 was shown using higher concentrations (rel. activity rcs); the lack of activity of #26 was thereby confirmed.

Table 8: Expression levels and activities of brain natriuretic peptide engrafted antibody constructs

not applicable (na)

Compound	TPP	# aa N-term[1]	# aa C-term[2]	µg/ml pcs	% purity pcs	qualit. activity on hNPRA	qualit. activity of corresp. ANP cpd.[3]
B1	TPP-9902	20	18	304	96	++	++
B2	TPP-11153	22	19	202	99	+	
B3	TPP-11154	20	18	205	100	-	++
B4	TPP-11155	17	17	226	97	-	
B5	TPP-11156	18	13	115	75	++	+++
B6	TPP-11157	18	13	125	93	-	+++
B7	TPP-18029	23	14	265	99	+	++
B8	TPP-18031	3	3	260	99	-	-
B9	TPP-18032	7	7	262	99	-	-
B10	TPP-18033	19	14	310	98	+	++
B11	TPP-18028	20	15	74	99	+	+++
B12	TPP-18034	20	18	315	97	++	++
B13	TPP-18030	19	14	304	100	+	++
#209	TPP-5657	na	na	402	100	-	-

[1] The number of amino acid residues present between the respective N-terminal reference amino acid residue and the first amino acid of the inserted natriuretic peptide;

[2] The number of amino acid residues present between the last amino acid of the inserted natriuretic peptide and the respective C-terminal reference amino acid residue

[3]Corresponding ANP Cpd. refers to an ANP engrafted antibody construct with the same integration locus and comprising the same N-terminal and C-terminal sequence

Purified compound samples were tested as described in Example 3 in quadruplets in dilution series on stable hNPRA-CHO k1 cells. The activities of BNP engrafted antibody constructs are graphically depicted in Figure 11.

TPP-11156, TPP-9902 and TPP-11153 showed significant activity on hNPRA cells in contrast to TPP-1154, TPP-11155, and TPP-11157. Opposed results were observed on rNPRA with EC50 < 20nM for TPP-1154, TPP-11155, and TPP-11157, and EC50 >1µM for TPP-9902, TPP-11153, and TPP-11156 (see Example 3). This can be explained by the presence of a human BNP sequence in TPP-11156, TPP-9902 and TPP-11153, whereas TPP-1154, TPP-11155, and TPP-11157 comprise a rat BNP sequence (see Table 5). In contrast to all other human BNP engrafted antibody constructs, TPP-18031 and TPP-18032 with low numbers of additional amino acids N- and C-terminal to BNP showed no activity on hNPRA.

Example 6: Specific linker sequences are particularly advantageous for achieving good homogeneity and expression levels

The purity of purified compound samples (Example 5, Table 7, column "% purity pcs") was determined by capillary Gel Electrophoresis according to manufacturer's instructions (LabChip GX, Caliper Life Sciences) under reduced conditions. The purity in % was calculated as sum of peak areas corresponding to the intact light and heavy chain relative to the sum of all peaks observed.

Ntls sequences comprising a GS linker sequence, a PN linker sequence or the sequence of SEQ ID NOs 2, 4, 9, 11, 13 or 15 and Ctls sequences comprising a GS linker sequence, a PN linker sequence or the sequence of SEQ ID NOs 3, 5, 12, 14, 15 or 20 have proven particularly useful as they not only achieve high natriuretic peptide activities (provided that at least 12 amino acid residues are present between the respective N-terminal reference amino acid residue and the first amino acid of the inserted natriuretic peptide) but also good expression levels (in contrast to e.g., sequences used in compounds #186, #195 and #202) and (in contrast to e.g., sequences used in compounds 6 and 7) a low degree of inhomogeneity (see Table 9). With linker sequences comprising a GS linker sequence as well as linker sequences comprising a PN linker sequence very good purities of 98% in average were observed. Similarly good values were observed for compounds with linkers comprising sequences of SEQ ID NOs 2, 3, 4, 5, 9, 11, 12, 13, 14, 15 and 20. Notably, the Ntls having the sequence of SEQ ID NO 9 resulted only in combination with the Ctls having the sequence of SEQ ID NO 20 in compounds with very good purity; compounds with a combination of the Ntls having the sequence of SEQ ID NO 11 and the Ctls having the sequence of SEQ ID NO 12 showed only very good purity when SEQ ID NO 11 was flanked by Asp (D) on the N-terminal side and not by Thr (T) or Val (V) and when the SEQ ID NO 12 VNHLRSEKLT was flanked by Gly (G) on the C-terminal side but not by Tyr (Y) or Phe (F) as in compounds #126 and #135.

Table 9: Ntls and Ctls effects on antibody purity (excerpt of Table 7)

Cpd	TPP	Insertion Site	SEQ ID NO comprised in Ntls	SEQ ID NO comprised in Ctls	# aa N-term[1]	# aa C-term[2]	N-terminal sequence[3]	C-terminal sequence[4]	µg/ml pcs	% purity pcs	qualit. activity
2	TPP-13056	CDRH1	GS	GS	9	5	SGFTFGSGSG	GSGSGM	179	96	-
3	TPP-13055	CDRH1	GS	GS	12	8	SGFTFGSGSGSGS	SGSGSGSGM	196	97	++
4	TPP-13054	CDRH1	GS	GS	15	10	SGFTFGSGSGSGGSGG	GGSGGSGSGSG	214	96	++
5	TPP-12545	CDRH1	GS	GS	18	10	SGFTFGSGSGSGSGGGSGG	GSGSGGSGSGM	229	93	++
9	TPP-10294	CDRH1	GS	GS	23	14	SGFTFGSGSGSGSGSGSPDGGSGG	GSYGSGSGSGSGSGM	226	97	++
10	TPP-12547	CDRH1	GS	GS	23	14	SGFTFGSGSGSGSGSGSPDGGSGG	GSYGSGSGSGSGSGM	265	96	++
91	TPP-10282	CDRH2	GS	GS	20	15	ISGSGSGSGSGSGSPDGGSGG	GSYGSGSGSGSGSGST	275	99	++
99	TPP-10281	CDRH3	GS	GS	10	3	CAKSPDGGSGG	GSYG	257	100	-
100	TPP-10280	CDRH3	GS	GS	10	8	CAKSPDGGSGG	GSYQHWGQG	188	99	-
169	TPP-10361	CDRL2	GS	GS	19	17	YGSGSGSGSGSGSPDGGSGG	GSYGSGGSGSGSGNRPSG	78	99	++
184	TPP-10776	CDRL3	GS	GS	18	13	CGSGSGSGSGSGPDGGSGG	GSGSGSGSGSGSGF	100	100	y
185	TPP-	CDRL3	GS	GS	18	13	CGSGSGSGSGSGSDGGSGG	GSGSGSGSGSGSGF	81	100	y

	10777										
189	TPP-10356	CDRL3	GS	GS	19	14	CGSGSGSGSGSGSPDGGSGG	GSYGSGSGSGSGSGF	102	99	y
198	TPP-10358	CDRL3	GS	GS	20	15	CGGSGSGSGSGSGSPDGGSGG	GSYGSGSGSGSGSGGF	57	100	y
18	TPP-10767	CDRH2	PN	PN	13	12	ISGPNPNKNPNPGG	GSNENPNPNPGST	290	98	+
55	TPP-10765	CDRH2	PN	PN	17	14	ISGPNPNKNPNPNPGSGG	GSNPNENPNPNPGST	271	95	++
93	TPP-10286	CDRH2	PN	PN	20	15	ISGPNPNKNPNPNSPDGGSGG	GSYNPNENPNPNPGST	286	98	+++
94	TPP-10283	CDRH2	PN	PN	20	15	ISGPNPNPNPNPNSPDGGSGG	GSYNPNPNPNPNPGST	318	98	+++
111	TPP-10289	CDRH3	PN	PN	19	17	CAKVHPNPNPNPNPDGGSGG	GSNPNPNPNPHVDVWGQG	296	98	++
125	TPP-10290	CDRH3	PN	PN	20	18	CAKVHPNPNPNPNSPDGGSGG	GSYNPNPNPNPHVDVWGQG	320	99	++
191	TPP-10355	CDRL3	PN	PN	19	14	CAAWNPNPNPNPNPNGGSGG	GSNPNPNPNPNPNVF	248	99	++
63	TPP-10844	CDRH2	2	3	18	13	ISGTYISNVNHKPDGGSGG	GSNTKVDKKVEGST	239	96	++
80	TPP-10845	CDRH2	2	3	19	14	ISGSTYISNVNHKPDGGSGG	GSNTKVDKKVEGGST	214	95	++
128	TPP-10288	CDRH3	2	3	20	18	CAKTQTYISNVNHKPDGGSGG	GSNTKVDKKAEYFQHWGQG	291	96	y
61	TPP-10847	CDRH2	4	5	18	13	ISGTSASLAITGPDGGSGG	GSDRFSGSKSGGST	334	97	++
76	TPP-10848	CDRH2	4	5	19	14	ISGSTSASLAITGPDGGSGG	GSDRFSGSKSGGGST	299	97	++
156	TPP-10571	CDRL2	15	15	17	16	YGVPKEKEKEKVSTAVGG	GSAPLEVPKEKEKEKVG	64	98	++
42	TPP-	CDRH2	9	20	17	11	ISVVVTSHQSPTPGGSGG	GGSTPLKSLAST	112	97	++

	13060										
43	TPP-13061	CDRH2	9	20	17	11	ISVVVTSHQAPGEGGSGG	GGSTPLKSLAST	141	96	++
44	TPP-13062	CDRH2	9	20	17	11	ISVVVTSHQAPGEGGSGG	GSTPKLKSLAST	166	93	+++
46	TPP-13064	CDRH2	9	10	17	11	ISVVVTSHPTPGEGGSGG	GEKKKLKSLAST	166	92	++
45	TPP-13063	CDRH2	9	10	17	11	ISVVVTSHQSPTPGGSGG	GEKKKLKSLAST	135	90	++
40	TPP-13058	CDRH2	9	10	17	11	ISVVVTSHQAPGSGGSGG	GEKKKLKSLAST	154	85	++
47	TPP-13065	CDRH2	9	10	17	11	ISVVVTSHQAPSPGSTGG	GEKKKLKSLAST	123	83	++
41	TPP-13059	CDRH2	9	10	17	11	ISVVVTSHQAPTSGGSGG	GEKKKLKSLAST	106	79	n.d.
201	TPP-10439	CDRL3	11	12	21	15	CQSYDQVKLELGHRAPDGGSGG	GSVNHLRSEKLTGVVF	134	97	++
194	TPP-10440	CDRL3	11	12	20	14	CQSYDQVKLELGHRPDGGSGG	GSNHLRSEKLTGVVF	98	97	y
187	TPP-10782	CDRL3	11	12	19	13	CQSYDKLELGHRAPDGGSGG	GSVNHLRSEKGVVF	217	95	+++
126	TPP-10445	CDRH3	11	12	20	18	CAKLTQVKLELGHRPDGGSGG	GSNHLRSEKLTYFQHWGQG	203	90	y
135	TPP-10444	CDRH3	11	12	22	20	CAKLTAVQVKLELGHRPDGGSGG	GSNHLRSEKLTFNYFQHWGQG	158	88	?
50	TPP-10452	CDRH2	13	14	17	12	ISGSAVVNVRAPDGGSGG	GSKGDKIAIGGST	87	97	++
74	TPP-10451	CDRH2	13	14	19	14	ISGSSGAVVNVRAPDGGSGG	GSKGDKIAIWTTGST	142	97	++
26	TPP-10772	CDRH2	13	14	16	11	ISGSAVVNVRADGGSGG	GSGDKIAIGGST	181	98	-
6	TPP-	CDRH1			19	17	SPAVVYIEILDRHPDGGSGG	GSGREVPISNGSGFVVAM	150	76	y

	10454										
7	TPP-10453	CDRH1			19	17	SGAVVYIEILDRHPDGGSGG	GSGREVPISNGSGFVVAM	117	70	y
186	TPP-10784	CDRL3			18	14	CQSYDGFILPIEVYGGSGG	GSKVRFDYDLFGVVF	77	96	y
195	TPP-10442	CDRL3			20	14	CQSYDGFILPIEVYPDGGSGG	GSKVRFDYDLFGVVF	43	97	y
202	TPP-10441	CDRL3			21	15	CQSYDGFILPIEVYFPDGGSGG	GSRKVRFDYDLFGVVF	29	n.d.	y

[1] The number of amino acid residues present between the respective N-terminal reference amino acid residue and the first amino acid of the inserted natriuretic peptide;

[2] The number of amino acid residues present between the last amino acid of the inserted natriuretic peptide and the respective C-terminal reference amino acid residue

[3] The N-terminal sequence corresponds to the nearest neighboring reference aa N-terminal from the inserted natriuretic peptide plus the amino acid stretch present between said reference aa and the first amino acid residue of the inserted natriuretic peptide

[4] The C-terminal sequence corresponds the amino acid stretch present between the last amino acid residue of the inserted natriuretic peptide and the nearest neighboring reference aa C-terminal from the inserted natriuretic peptide plus and said reference aa

Example 7: IgG1, IgG2 and IgG4 isotypes provide equally suitable antibody scaffolds

Compounds 9, 33, 65, 91, 127 and 191 (human IgG1 TPP-10294, TPP-10277, TPP-10279, TPP-10282, TPP-10269 and TPP-10355, respectively) were generated as different IgG isotypes. Purified compound samples were tested as described in Example 3 in quadruplets in dilution series on stable hNPRA-CHO k1 cells. The activities of ANP engrafted human IgG2 and IgG4 isotype constructs (e.g. compound 9 IgG4 TPP-10992) are similar to their corresponding IgG1 isotype as graphically depicted in Figure 12.

Example 8: Human and non-human IgGs provide equally suitable antibody scaffolds

Compound 9 (human IgG1 TPP-10294 and IgG4 TPP-10992) and compound 117 (human IgG1 TPP-5665) were generated as non-human IgG isotypes. Purified compound samples were tested as described in Example 3 in quadruplets in dilution series on stable hNPRA-CHO k1 cells. ANP engrafted rat and mouse isotype constructs, e.g. compound 9 rat IgG1 TPP-13992, showed activities similar to their corresponding human IgG isotype (Figure 13).

Example 9: Human IgGs comprising varying germline sequences provide equally suitable antibody scaffolds

22 additional ANP engrafted IgG4 antibodies (compounds A to S) were constructed. In each case ANP was incorporated within CDRH1. The heavy chains of these constructs comprise varying HV and CDRH3 sequences and were paired with varying lambda or kappa light chains. The structure of compounds A to S is summarized in Tables 10 and 11.

Table 10: Design of ANP engrafted antibody constructs A to S

Cmpd.	Insertion Site	# aa N-term[1]	# aa C-term[2]	N-terminal sequence[3]	C-terminal sequence[4]
A – P	CDRH1	23	14	SGFTFGSGSGSGSGSPDGGSGG	GSYGSGSGSGSGSM
Q - S	CDRH1	23	14	SGYSFGSGSGSGSGSPDGGSGG	GSYGSGSGSGSGSI

[1] The number of amino acid residues present between the respective N-terminal reference amino acid residue and the first amino acid of the inserted natriuretic peptide;

[2] The number of amino acid residues present between the last amino acid of the inserted natriuretic peptide and the respective C-terminal reference amino acid residue

[3] The N-terminal sequence corresponds to the nearest neighboring reference aa N-terminal from the inserted natriuretic peptide plus the amino acid stretch present between said reference aa and the first amino acid residue of the inserted natriuretic peptide

[4] The C-terminal sequence corresponds the amino acid stretch present between the last amino acid residue of the inserted natriuretic peptide and the nearest neighboring reference aa C-terminal from the inserted natriuretic peptide plus and said reference aa

Table 11: Design of ANP engrafted antibody constructs A to S

Cmpd	TPP	HV	CDRH3	LV / KV	Purity
9	TPP-10992	HV3-23	K**LTG**AEYFQHW	LV1-40	99
A	TPP-13944	HV3-23	KLTGAEYFQHW	LV2-14	98
B	TPP-13945	HV3-23	KLTGAEYFQHW	LV3-21	93
C	TPP-13941	HV3-23	KDYGDYAEYFQHW	LV1-40	100
D	TPP-13956	HV3-23	KLTGAEYFQHW	KV1-5	99
E	TPP-13955	HV3-23	KLTGAEYFQHW	KV3-20	99
F	TPP-13940	HV3-23	KVLRFLEWLLYAEYFQHW	LV1-40	98
G	TPP-13939	HV3-23	KVQLERAEYFQHW	LV1-40	100
H	TPP-13943	HV3-23	KYNRNHAEYFQHW	LV1-40	54
I	TPP-13942	HV3-23	KYNWNDAEYFQHW	LV1-40	99
J	TPP-14684	HV3-23	RGATFALDW	KV3-20	97
K	TPP-13958	HV3-23	RGRLPDVW	KV1-5	99
L	TPP-13957	HV3-23	RGRLPDVW	KV3-20	97
M	TPP-13948	HV3-23	RGRLPDVW	LV1-40	98
N	TPP-14289	HV3-23	RGRLPDVW	LV1-47	
O	TPP-13946	HV3-23	RGRLPDVW	LV2-14	97
P	TPP-13947	HV3-23	RGRLPDVW	LV3-21	96
Q	TPP-13952	HV5-51	RGRLPDVW	LV2-14	99
R	TPP-13953	HV5-51	RGRLPDVW	LV3-21	98
S	TPP-13962	HV5-51	RGRLPDVW	KV1-5	99

Purified compound samples of IgG scaffold constructs A to S comprising varying germline sequences were tested as described in Example 3 in quadruplets in dilution series on stable hNPRA-CHO k1 cells. Exemplary activity data are graphically depicted in Figure 14.

Example 10: CNP engrafted IgG protects against induced endothelial barrier permeability

Endothelial monolayer permeability was assayed by real-time impedance measurement with an xCELLigence RTCA system utilizing microtiter well plates covered with microelectrodes (E-Plates). Relative impedance changes are expressed as unitless Cell Index (CI) values.

Primary Human Pulmonary Artery Endothelial Cells (HPAECs) were seeded at low passages in collagen pre-coated E-Plates. After tight monolayer and cell barrier formation with constant CI values, HPAECs were pre-treated with the indicated concentrations of compound TPP-12899 or the respective negative control antibody construct TPP-5657, followed by compromising the EC barrier with the disruptive agonists LPS (200 ng/ml), IL-1β (0.5 ng/ml), or thrombin (2 U/ml). CI were recorded every 10 min to monitor effects on cell growth and monolayer permeability. All cell indices were normalized at the last recording point before test substance application (=normalized CI).

The experiments were performed with n=4 with 3 technical triplicates each. Results were expressed as mean ± SEM. Data were statistically analyzed using one-way ANOVA followed by Sidak's multiple post-test; p-values < 0.05 were considered as significant.

Figure 15 graphically depicts the effects on endothelial monolayer permeability expressed as Cell Index values. As shown in Figure 15, pre-treatment of human endothelial monolayer cultures with TPP-12899 protected against induced endothelial barrier permeability in a dose-dependent manner. This was independent of the applied barrier disruptive agent; both, with fast and strong acting thrombin as well as with long-lasting pro-inflammatory stimuli LPS and IL-1β significant effects were observed. The respective negative control showed no effect.

Example 11: Long term effects of ANP engrafted IgG in a chronic heart failure rat model (TGR(mRenR2)27

The TGR(mRenR2)27 rat model shows hypertension and endothelial dysfunction, as well as end-organ damage. Male renin-transgenic rats (Ganten D., Nature. 1990; 344(6266):541-4) at the age of 8 weeks were used. The nonselective inhibitor of nitric oxide synthetases L-NAME (Nω-Nitro-L-arginine methyl ester) was chronically administered via the drinking water (20 mg/l) in all study groups to induce endothelial dysfunction. TPP-13992, the rat IgG1 counterpart of TPP-10294 used in Example 8 and TPP-10155, a rat IgG1 isotype control antibody were administered once weekly intraperitoneally. Body weight and survival were assessed. The placebo group was treated with vehicle (PBS) and the healthy control group was treated with captopril-food from weaning on. Food and water were given ad libitum. Daily observation of the behavior and general health status of the animals was performed. At the end of the experiment (week 14), the rats were anaesthetized. The rats were then exsanguinated and the heart was removed from the thoracic cavity for analysis. Urine was collected at the end of the study to determine different urine parameters, e.g. urinary protein creatinine ratio. Figure 16 graphically depicts the therapeutic effects of TPP-13992 on survival, body weight gain, urinary protein/creatinine ratio and left atrial weight.

Example 12: Hemodynamic effects of ANP engrafted IgG in healthy beagle dogs

The effects of TPP-10992 on cardiovascular and ECG parameters after single subcutaneous administration were assessed in a primary pharmacodynamic study in conscious telemetered beagle dogs.

Telemetry devices (DSI™, USA) were surgically implanted to measure blood pressure as well as heart rate, followed by a recovery period to allow wound closure. On the day of the study, telemetry sensors were activated for continuous hemodynamic measurements. The transmitted signals were collected by telemetry receivers located in the animal facility. All collected data were processed by a data acquisition program and averaged over a predefined period of 12h. As vehicle for TPP-10992 NaCl (0.9%) was

used and doses of 0.1 mg/kg, 0.3 mg/kg and 1.0 mg/kg bodyweight were applied via subcutaneous injection.

The results are graphically depicted in Figure 17. In healthy dogs, TPP-10992 showed a dose-dependent and long-lasting (>5d) reduction in blood pressure which was significant at 1.0 mg/kg s.c. (compared to placebo). No effects on heart rate were observable.

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Ala Ala Trp Asn Pro Asn Pro Asn Pro Asn Pro Asn Pro Asn Gly Gly
1               5                   10                  15

Ser Gly Gly Ser Leu Arg Arg Ser Ser Cys Phe Gly Gly Arg Met Asp
            20                  25                  30

Arg Ile Gly Ala Gln Ser Gly Leu Gly Cys Asn Ser Phe Arg Tyr Gly
        35                  40                  45

Ser Asn Pro Asn Pro Asn Pro Asn Pro Asn Pro Asn Val
    50                  55                  60
```

<210> 60
<211> 66
<212> PRT
<213> artificial

<220>
<223> N-terminal Sequence-NP-C-terminal Sequence (without ref aas)

<400> 60

```
Ala Lys Gly Ile Thr Gly Thr Lys Lys Tyr Gln Ser Ser Pro Asp Gly
1               5                   10                  15
```

Gly Ser Gly Gly Ser Leu Arg Arg Ser Ser Cys Phe Gly Gly Arg Met
20 25 30

Asp Arg Ile Gly Ala Gln Ser Gly Leu Gly Cys Asn Ser Phe Arg Tyr
35 40 45

Gly Ser Tyr Ser Tyr Thr Tyr Asn Tyr Ala Glu Tyr Phe Gln His Trp
50 55 60

Gly Gln
65

<210> 61
<211> 61
<212> PRT
<213> artificial

<220>
<223> N-terminal Sequence-NP-C-terminal Sequence (without ref aas)

<400> 61

Ser Gly Ser Thr Tyr Ile Ser Asn Val Asn His Lys Pro Asp Gly Gly
1 5 10 15

Ser Gly Gly Ser Leu Arg Arg Ser Ser Cys Phe Gly Gly Arg Met Asp
20 25 30

Arg Ile Gly Ala Gln Ser Gly Leu Gly Cys Asn Ser Phe Arg Tyr Gly
35 40 45

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Gly Gly Ser
50 55 60

<210> 62
<211> 59
<212> PRT
<213> artificial

<220>
<223> N-terminal Sequence-NP-C-terminal Sequence (without ref aas)

<400> 62

Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Pro Asp Gly Gly Ser

1 5 10 15

Gly Gly Ser Leu Arg Arg Ser Ser Cys Phe Gly Gly Arg Met Asp Arg
20 25 30

Ile Gly Ala Gln Ser Gly Leu Gly Cys Asn Ser Phe Arg Tyr Gly Ser
35 40 45

Asp Arg Phe Ser Gly Ser Lys Ser Gly Gly Ser
50 55

<210> 63
<211> 61
<212> PRT
<213> artificial

<220>
<223> N-terminal Sequence-NP-C-terminal Sequence (without ref aas)

<400> 63

Gly Val Pro Lys Glu Lys Glu Lys Glu Lys Val Ser Thr Ala Val Gly
1 5 10 15

Gly Ser Leu Arg Arg Ser Ser Cys Phe Gly Gly Arg Met Asp Arg Ile
20 25 30

Gly Ala Gln Ser Gly Leu Gly Cys Asn Ser Phe Arg Tyr Gly Ser Ala
35 40 45

Pro Leu Glu Val Pro Lys Glu Lys Glu Lys Glu Lys Val
50 55 60

<210> 64
<211> 56
<212> PRT
<213> artificial

<220>
<223> N-terminal Sequence-NP-C-terminal Sequence (without ref aas)

<400> 64

Ser Val Val Val Thr Ser His Gln Ala Pro Gly Glu Gly Gly Ser Gly
1 5 10 15

```
Gly Ser Leu Arg Arg Ser Ser Cys Phe Gly Gly Arg Met Asp Arg Ile
            20                  25                  30

Gly Ala Gln Ser Gly Leu Gly Cys Asn Ser Phe Arg Tyr Gly Gly Ser
        35                  40                  45

Thr Pro Leu Lys Ser Leu Ala Ser
    50                  55
```

<210> 65
<211> 447
<212> PRT
<213> human

<400> 65

```
Glu Val Gln Leu Leu 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 Ser Ser Tyr
            20                  25                  30

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

Ser Ala Ile Ser Gly Ser Gly 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 Leu Tyr
65                  70                  75                  80

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

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

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

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    130                 135                 140
```

```
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160

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

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

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        195                 200                 205

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    210                 215                 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225                 230                 235                 240

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

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            260                 265                 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    290                 295                 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305                 310                 315                 320

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

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            340                 345                 350
```

```
Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
        355                 360                 365


Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380


Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385                 390                 395                 400


Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                405                 410                 415


Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            420                 425                 430


Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445


<210>  66
<211>  217
<212>  PRT
<213>  human

<400>  66

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


Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
            20                  25                  30


Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45


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


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


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

```
Leu Ser Gly Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110


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


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


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


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


Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190


His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195                 200                 205


Lys Thr Val Ala Pro Thr Glu Cys Ser
    210                 215


<210>  67
<211>  499
<212>  PRT
<213>  artificial

<220>
<223>  NP engrafted HC

<400>  67

Glu Val Gln Leu Leu 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 Ser Ser Tyr
            20                  25                  30


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

```
Ser Ala Ile Ser Gly Ser Gly 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 Leu Tyr
65                  70                  75                  80

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

Thr Ser Val His Gln Glu Thr Lys Lys Tyr Gln Ser Ser Pro Asp Gly
            100                 105                 110

Gly Ser Gly Gly Ser Leu Arg Arg Ser Ser Cys Phe Gly Gly Arg Ile
        115                 120                 125

Asp Arg Ile Gly Ala Gln Ser Gly Leu Gly Cys Asn Ser Phe Arg Tyr
    130                 135                 140

Gly Ser Tyr Ser Tyr Thr Tyr Asn Tyr Glu Trp His Val Asp Val Trp
145                 150                 155                 160

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
                165                 170                 175

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
            180                 185                 190

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
        195                 200                 205

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
    210                 215                 220

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
225                 230                 235                 240

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
                245                 250                 255

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
```

```
            260                 265                 270

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
        275                 280                 285

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
    290                 295                 300

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
305                 310                 315                 320

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
                325                 330                 335

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
            340                 345                 350

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
        355                 360                 365

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
    370                 375                 380

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
385                 390                 395                 400

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
                405                 410                 415

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
            420                 425                 430

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
        435                 440                 445

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
    450                 455                 460

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
465                 470                 475                 480
```

```
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
                485                 490                 495


Ser Pro Gly



<210>  68
<211>  499
<212>  PRT
<213>  artificial

<220>
<223>  NP engrafted HC

<400>  68

Glu Val Gln Leu Leu 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 Ser Ser Tyr
            20                  25                  30


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


Ser Ala Ile Ser Gly Ser Gly 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 Leu Tyr
65                  70                  75                  80


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


Thr Ser Val His Gln Glu Thr Lys Lys Tyr Gln Ser Ser Pro Asp Gly
            100                 105                 110


Gly Ser Gly Gly Ser Leu Arg Arg Ser Ser Cys Phe Gly Gly Arg Met
        115                 120                 125


Asp Arg Ile Gly Ala Gln Ser Gly Leu Gly Cys Asn Ser Phe Arg Tyr
    130                 135                 140
```

```
Gly Ser Tyr Ser Tyr Thr Tyr Asn Tyr Glu Trp His Val Asp Val Trp
145                 150                 155                 160

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
                165                 170                 175

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
            180                 185                 190

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
        195                 200                 205

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
    210                 215                 220

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
225                 230                 235                 240

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
                245                 250                 255

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
            260                 265                 270

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
        275                 280                 285

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
    290                 295                 300

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
305                 310                 315                 320

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
                325                 330                 335

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
            340                 345                 350

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
```

```
        355                 360                 365

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
    370                 375                 380

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
385                 390                 395                 400

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
                405                 410                 415

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
            420                 425                 430

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
        435                 440                 445

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
    450                 455                 460

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
465                 470                 475                 480

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
                485                 490                 495

Ser Pro Gly
```

<210> 69
<211> 504
<212> PRT
<213> artificial

<220>
<223> NP engrafted HC

<400> 69

```
Glu Val Gln Leu Leu 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 Ser Ser Tyr
```

```
            20                  25                  30

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

Ser Ala Ile Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
    50                  55                  60

Pro Asp Gly Gly Ser Gly Gly Ser Leu Arg Arg Ser Ser Cys Phe Gly
65                  70                  75                  80

Gly Arg Met Asp Arg Ile Gly Ala Gln Ser Gly Leu Gly Cys Asn Ser
                85                  90                  95

Phe Arg Tyr Gly Ser Tyr Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
            100                 105                 110

Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser
        115                 120                 125

Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg
    130                 135                 140

Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys Leu Thr Gly Ala Glu
145                 150                 155                 160

Tyr Phe Gln His Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
                165                 170                 175

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
            180                 185                 190

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
        195                 200                 205

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
    210                 215                 220

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
225                 230                 235                 240
```

```
Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
                245                 250                 255

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
            260                 265                 270

Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
        275                 280                 285

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
    290                 295                 300

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
305                 310                 315                 320

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
                325                 330                 335

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
            340                 345                 350

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
        355                 360                 365

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
    370                 375                 380

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
385                 390                 395                 400

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

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
            420                 425                 430

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
        435                 440                 445

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
```

```
    450                 455                 460

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
465                 470                 475                 480

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
                485                 490                 495

Lys Ser Leu Ser Leu Ser Pro Gly
            500
```

<210> 70
<211> 504
<212> PRT
<213> artificial

<220>
<223> NP engrafted HC

<400> 70

```
Glu Val Gln Leu Leu 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 Ser Ser Tyr
            20                  25                  30

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

Ser Ala Ile Ser Gly Pro Asn Pro Asn Pro Asn Pro Asn Pro Asn Ser
    50                  55                  60

Pro Asp Gly Gly Ser Gly Gly Ser Leu Arg Arg Ser Ser Cys Phe Gly
65                  70                  75                  80

Gly Arg Met Asp Arg Ile Gly Ala Gln Ser Gly Leu Gly Cys Asn Ser
                85                  90                  95

Phe Arg Tyr Gly Ser Tyr Asn Pro Asn Pro Asn Pro Asn Pro Asn Pro
            100                 105                 110

Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser
```

```
        115                 120                 125

Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg
    130                 135                 140

Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys Leu Thr Gly Ala Glu
145                 150                 155                 160

Tyr Phe Gln His Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
                165                 170                 175

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
            180                 185                 190

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
        195                 200                 205

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
    210                 215                 220

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
225                 230                 235                 240

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
                245                 250                 255

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
            260                 265                 270

Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
        275                 280                 285

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
    290                 295                 300

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
305                 310                 315                 320

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
                325                 330                 335
```

```
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
            340                 345                 350

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
        355                 360                 365

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
    370                 375                 380

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
385                 390                 395                 400

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

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
            420                 425                 430

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
        435                 440                 445

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
    450                 455                 460

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
465                 470                 475                 480

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
                485                 490                 495

Lys Ser Leu Ser Leu Ser Pro Gly
            500
```

<210> 71
<211> 499
<212> PRT
<213> artificial

<220>
<223> NP engrafted HC

<400> 71

```
Glu Val Gln Leu Leu 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 Ser Ser Tyr
            20                  25                  30

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

Ser Ala Ile Ser Gly Ser Gly 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 Leu Tyr
65                  70                  75                  80

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

Ala Lys Val His Pro Asn Pro Asn Pro Asn Pro Asn Ser Pro Asp Gly
            100                 105                 110

Gly Ser Gly Gly Ser Leu Arg Arg Ser Ser Cys Phe Gly Gly Arg Met
        115                 120                 125

Asp Arg Ile Gly Ala Gln Ser Gly Leu Gly Cys Asn Ser Phe Arg Tyr
    130                 135                 140

Gly Ser Tyr Asn Pro Asn Pro Asn Pro Asn Pro His Val Asp Val Trp
145                 150                 155                 160

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
                165                 170                 175

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
            180                 185                 190

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
        195                 200                 205

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
```

```
    210                 215                 220

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
225                 230                 235                 240

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
                245                 250                 255

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
            260                 265                 270

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
        275                 280                 285

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
    290                 295                 300

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
305                 310                 315                 320

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
                325                 330                 335

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
            340                 345                 350

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
        355                 360                 365

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
    370                 375                 380

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
385                 390                 395                 400

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
                405                 410                 415

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
            420                 425                 430
```

```
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
        435                 440                 445


Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
    450                 455                 460


Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
465                 470                 475                 480


Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
                485                 490                 495


Ser Pro Gly
```

<210> 72
<211> 504
<212> PRT
<213> artificial

<220>
<223> NP engrafted HC

<400> 72

```
Glu Val Gln Leu Leu 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 Gly Ser Gly
            20                  25                  30


Ser Gly Ser Gly Ser Gly Ser Gly Ser Pro Asp Gly Gly Ser Gly Gly
        35                  40                  45


Ser Leu Arg Arg Ser Ser Cys Phe Gly Gly Arg Met Asp Arg Ile Gly
    50                  55                  60


Ala Gln Ser Gly Leu Gly Cys Asn Ser Phe Arg Tyr Gly Ser Tyr Gly
65                  70                  75                  80


Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Met Ser Trp Val Arg Gln
                85                  90                  95
```

```
Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Ser Gly
            100                 105                 110

Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser
        115                 120                 125

Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg
    130                 135                 140

Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys Leu Thr Gly Ala Glu
145                 150                 155                 160

Tyr Phe Gln His Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
                165                 170                 175

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
            180                 185                 190

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
        195                 200                 205

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
    210                 215                 220

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
225                 230                 235                 240

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
                245                 250                 255

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys
            260                 265                 270

Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
        275                 280                 285

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
    290                 295                 300

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
```

```
305                 310                 315                 320

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
                325                 330                 335

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
            340                 345                 350

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
        355                 360                 365

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
    370                 375                 380

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
385                 390                 395                 400

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

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
            420                 425                 430

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
        435                 440                 445

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
    450                 455                 460

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
465                 470                 475                 480

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
                485                 490                 495

Lys Ser Leu Ser Leu Ser Pro Gly
            500
```

<210> 73
<211> 500
<212> PRT

<213> artificial

<220>
<223> NP engrafted HC

<400> 73

```
Glu Val Gln Leu Leu 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 Ser Ser Tyr
            20                  25                  30


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


Ser Ala Ile Ser Gly Pro Asn Pro Asn Lys Asn Pro Asn Pro Asn Pro
    50                  55                  60


Gly Ser Gly Gly Ser Leu Arg Arg Ser Ser Cys Phe Gly Gly Arg Met
65                  70                  75                  80


Asp Arg Ile Gly Ala Gln Ser Gly Leu Gly Cys Asn Ser Phe Arg Tyr
                85                  90                  95


Gly Ser Asn Pro Asn Glu Asn Pro Asn Pro Asn Pro Gly Ser Thr Tyr
            100                 105                 110


Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
        115                 120                 125


Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
    130                 135                 140


Ala Val Tyr Tyr Cys Ala Lys Leu Thr Gly Ala Glu Tyr Phe Gln His
145                 150                 155                 160


Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
                165                 170                 175


Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
            180                 185                 190
```

```
Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
        195                 200                 205

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
    210                 215                 220

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
225                 230                 235                 240

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
                245                 250                 255

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
            260                 265                 270

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
        275                 280                 285

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
    290                 295                 300

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
305                 310                 315                 320

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
                325                 330                 335

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
            340                 345                 350

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
        355                 360                 365

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
    370                 375                 380

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
385                 390                 395                 400

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
```

405 410 415

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
420 425 430

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
435 440 445

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
450 455 460

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
465 470 475 480

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
485 490 495

Leu Ser Pro Gly
500

<210> 74
<211> 502
<212> PRT
<213> artificial

<220>
<223> NP engrafted HC

<400> 74

Glu Val Gln Leu Leu 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 Ser Ser Tyr
20 25 30

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

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

Asp Gly Gly Ser Gly Gly Ser Leu Arg Arg Ser Ser Cys Phe Gly Gly

```
65                  70                  75                  80

Arg Met Asp Arg Ile Gly Ala Gln Ser Gly Leu Gly Cys Asn Ser Phe
                85                  90                  95

Arg Tyr Gly Ser Asn Thr Lys Val Asp Lys Lys Val Glu Gly Gly Ser
            100                 105                 110

Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
        115                 120                 125

Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
    130                 135                 140

Asp Thr Ala Val Tyr Tyr Cys Ala Lys Leu Thr Gly Ala Glu Tyr Phe
145                 150                 155                 160

Gln His Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr
                165                 170                 175

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
            180                 185                 190

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
        195                 200                 205

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
    210                 215                 220

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
225                 230                 235                 240

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
                245                 250                 255

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
            260                 265                 270

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
        275                 280                 285
```

```
Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
    290                 295                 300

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
305                 310                 315                 320

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
                325                 330                 335

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
            340                 345                 350

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
        355                 360                 365

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
    370                 375                 380

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
385                 390                 395                 400

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
                405                 410                 415

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
            420                 425                 430

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
        435                 440                 445

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
    450                 455                 460

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
465                 470                 475                 480

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
                485                 490                 495

Leu Ser Leu Ser Pro Gly
```

500

<210> 75
<211> 500
<212> PRT
<213> artificial

<220>
<223> NP engrafted HC

<400> 75

Glu Val Gln Leu Leu 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 Ser Ser Tyr
20 25 30

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

Ser Ala Ile Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Pro Asp
50 55 60

Gly Gly Ser Gly Gly Ser Leu Arg Arg Ser Ser Cys Phe Gly Gly Arg
65 70 75 80

Met Asp Arg Ile Gly Ala Gln Ser Gly Leu Gly Cys Asn Ser Phe Arg
85 90 95

Tyr Gly Ser Asp Arg Phe Ser Gly Ser Lys Ser Gly Gly Ser Thr Tyr
100 105 110

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
115 120 125

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
130 135 140

Ala Val Tyr Tyr Cys Ala Lys Leu Thr Gly Ala Glu Tyr Phe Gln His
145 150 155 160

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly

```
                165                 170                 175

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
            180                 185                 190

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
        195                 200                 205

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
    210                 215                 220

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
225                 230                 235                 240

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
                245                 250                 255

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
            260                 265                 270

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
        275                 280                 285

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
    290                 295                 300

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
305                 310                 315                 320

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
                325                 330                 335

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
            340                 345                 350

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
        355                 360                 365

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
    370                 375                 380
```

```
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
385                 390                 395                 400


Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
                405                 410                 415


Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
            420                 425                 430


Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
        435                 440                 445


Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
    450                 455                 460


Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
465                 470                 475                 480


Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
                485                 490                 495


Leu Ser Pro Gly
            500


<210>  76
<211>  501
<212>  PRT
<213>  artificial

<220>
<223>  NP engrafted HC

<400>  76

Glu Val Gln Leu Leu 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 Gly Ser Gly
            20                  25                  30


Ser Gly Ser Gly Ser Gly Ser Gly Ser Pro Asp Gly Gly Ser Gly Gly
        35                  40                  45
```

```
Ser Leu Arg Arg Ser Ser Cys Phe Gly Gly Arg Met Asp Arg Ile Gly
    50                  55                  60

Ala Gln Ser Gly Leu Gly Cys Asn Ser Phe Arg Tyr Gly Ser Tyr Gly
65                  70                  75                  80

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Met Ser Trp Val Arg Gln
                85                  90                  95

Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Ser Gly
            100                 105                 110

Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser
        115                 120                 125

Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg
    130                 135                 140

Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys Leu Thr Gly Ala Glu
145                 150                 155                 160

Tyr Phe Gln His Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala
                165                 170                 175

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser
            180                 185                 190

Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
        195                 200                 205

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
    210                 215                 220

Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu
225                 230                 235                 240

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr
                245                 250                 255

Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg
```

```
            260                 265                 270

Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu
        275                 280                 285

Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
    290                 295                 300

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
305                 310                 315                 320

Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
                325                 330                 335

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
            340                 345                 350

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
        355                 360                 365

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
    370                 375                 380

Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
385                 390                 395                 400

Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn
                405                 410                 415

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
            420                 425                 430

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
        435                 440                 445

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg
    450                 455                 460

Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys
465                 470                 475                 480
```

```
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
                485                 490                 495


Ser Leu Ser Leu Gly
            500


<210>  77
<211>  493
<212>  PRT
<213>  artificial

<220>
<223>  NP engrafted HC

<400>  77

Glu Val Gln Leu Leu 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 Gly Ser Gly
            20                  25                  30


Ser Gly Ser Gly Gly Ser Gly Gly Ser Leu Arg Arg Ser Ser Cys Phe
        35                  40                  45


Gly Gly Arg Met Asp Arg Ile Gly Ala Gln Ser Gly Leu Gly Cys Asn
    50                  55                  60


Ser Phe Arg Tyr Gly Gly Ser Gly Gly Ser Gly Ser Gly Ser Gly Met
65                  70                  75                  80


Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala
                85                  90                  95


Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys Gly
            100                 105                 110


Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln
        115                 120                 125


Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys
    130                 135                 140
```

```
Leu Thr Gly Ala Glu Tyr Phe Gln His Trp Gly Gln Gly Thr Leu Val
145                 150                 155                 160

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
                165                 170                 175

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
            180                 185                 190

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
        195                 200                 205

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
    210                 215                 220

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
225                 230                 235                 240

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
                245                 250                 255

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
            260                 265                 270

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
        275                 280                 285

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
    290                 295                 300

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
305                 310                 315                 320

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
                325                 330                 335

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
            340                 345                 350

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
```

```
        355                 360                 365

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
    370                 375                 380

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
385                 390                 395                 400

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
                405                 410                 415

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
            420                 425                 430

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
        435                 440                 445

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
    450                 455                 460

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
465                 470                 475                 480

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
                485                 490
```

<210> 78
<211> 497
<212> PRT
<213> artificial

<220>
<223> NP engrafted HC

<400> 78

```
Glu Val Gln Leu Leu 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 Ser Ser Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
```

```
        35                  40                  45

Ser Ala Ile Ser Val Val Val Thr Ser His Gln Ala Pro Gly Glu Gly
    50                  55                  60

Gly Ser Gly Gly Ser Leu Arg Arg Ser Ser Cys Phe Gly Gly Arg Met
65                  70                  75                  80

Asp Arg Ile Gly Ala Gln Ser Gly Leu Gly Cys Asn Ser Phe Arg Tyr
                85                  90                  95

Gly Gly Ser Thr Pro Leu Lys Ser Leu Ala Ser Thr Tyr Tyr Ala Asp
            100                 105                 110

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr
        115                 120                 125

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
    130                 135                 140

Tyr Cys Ala Lys Leu Thr Gly Ala Glu Tyr Phe Gln His Trp Gly Gln
145                 150                 155                 160

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
                165                 170                 175

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
            180                 185                 190

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
        195                 200                 205

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
    210                 215                 220

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
225                 230                 235                 240

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
                245                 250                 255
```

```
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
            260                 265                 270

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
        275                 280                 285

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
    290                 295                 300

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
305                 310                 315                 320

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
                325                 330                 335

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
            340                 345                 350

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
        355                 360                 365

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
    370                 375                 380

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

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
                405                 410                 415

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
            420                 425                 430

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
        435                 440                 445

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
    450                 455                 460

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
```

465 470 475 480

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
485 490 495

Gly

<210> 79
<211> 499
<212> PRT
<213> artificial

<220>
<223> NP engrafted HC

<400> 79

Glu Val Gln Leu Leu 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 Ser Ser Tyr
20 25 30

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

Ser Ala Ile Ser Gly Ser Gly 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 Leu Tyr
65 70 75 80

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

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

Gly Ser Gly Gly Ser Leu Arg Arg Ser Ser Cys Phe Gly Gly Arg Met
115 120 125

Asp Arg Ile Gly Ala Gln Ser Gly Leu Gly Cys Asn Ser Phe Arg Tyr

```
    130                 135                 140

Gly Ser Tyr Ser Tyr Thr Tyr Asn Tyr Ala Glu Tyr Phe Gln His Trp
145                 150                 155                 160

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
                165                 170                 175

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
            180                 185                 190

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
        195                 200                 205

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
    210                 215                 220

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
225                 230                 235                 240

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
                245                 250                 255

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
            260                 265                 270

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
        275                 280                 285

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
    290                 295                 300

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
305                 310                 315                 320

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
                325                 330                 335

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
            340                 345                 350
```

```
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
        355                 360                 365


Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
    370                 375                 380


Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
385                 390                 395                 400


Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
                405                 410                 415


Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
            420                 425                 430


Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
        435                 440                 445


Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
    450                 455                 460


Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
465                 470                 475                 480


Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
                485                 490                 495


Ser Pro Gly
```

<210> 80
<211> 267
<212> PRT
<213> artificial

<220>
<223> NP engrafted LC

<400> 80

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

```
Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
            20                  25                  30

Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45

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

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

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asn Pro Asn
                85                  90                  95

Pro Asn Pro Asn Pro Asn Pro Asn Gly Gly Ser Gly Gly Ser Leu Arg
            100                 105                 110

Arg Ser Ser Cys Phe Gly Gly Arg Met Asp Arg Ile Gly Ala Gln Ser
        115                 120                 125

Gly Leu Gly Cys Asn Ser Phe Arg Tyr Gly Ser Asn Pro Asn Pro Asn
    130                 135                 140

Pro Asn Pro Asn Pro Asn Val Phe Gly Ser Gly Thr Lys Val Thr Val
145                 150                 155                 160

Leu Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser
                165                 170                 175

Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser
            180                 185                 190

Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser
        195                 200                 205

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

Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp
```

225 230 235 240

Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr
245 250 255

Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
260 265

<210> 81
<211> 274
<212> PRT
<213> artificial

<220>
<223> NP engrafted LC

<400> 81

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

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Pro
50 55 60

Asp Gly Gly Ser Gly Gly Ser Leu Arg Arg Ser Ser Cys Phe Gly Gly
65 70 75 80

Arg Met Asp Arg Ile Gly Ala Gln Ser Gly Leu Gly Cys Asn Ser Phe
85 90 95

Arg Tyr Gly Ser Tyr Gly Ser Gly Gly Ser Gly Ser Gly Ser Gly Asn
100 105 110

Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr
115 120 125

Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp

```
    130                 135                 140

Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser Leu Ser Gly Val Val Phe Gly
145                 150                 155                 160

Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala Pro Ser
                165                 170                 175

Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn Lys Ala
            180                 185                 190

Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val Thr Val
        195                 200                 205

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

Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu
225                 230                 235                 240

Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser Cys Gln
                245                 250                 255

Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro Thr Glu
            260                 265                 270

Cys Ser
```

<210> 82
<211> 366
<212> DNA
<213> artificial

<220>
<223> NP engrafted HC encoding construct

<400> 82

```
gaagtgcagc tgctggaaag cggcggaggc ctggtgcagc ctggcggatc tctgagactg       60

agctgtgccg ccagcggctt caccttcagc agctacgcca tgagctgggt gcgccaggcc      120

cctggaaaag gcctggaatg ggtgtccgcc atctctggca gcggcggcag cacctactac      180
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gccgattctg tgaagggccg gttcaccatc agccgggaca acagcaagaa caccctgtac 240

ctgcagatga acagcctgcg ggccgaggac accgccgtgt actactgtac aagcgtgcac 300

caggaaacaa agaagtacca gagcagcccc gacggcggca gtggcggaag tctgagaaga 360

agctcc 366

<210> 83
<211> 525
<212> DNA
<213> artificial

<220>
<223> NP engrafted HC encoding construct

<400> 83
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agctgtgccg ccagcggctt tacatttggc agcggctctg gatctggctc cggaagcgga 120

tctcctgatg gtggaagcgg aggcagcctg agaagaagca gctgtttcgg cggcagaatg 180

gacagaatcg gcgcccaatc tggcctgggc tgcaacagct ttagatacgg cagctacggc 240

tccggcagtg gttccggtag tggctctgga atgagctggg ttcgacaggc ccctggcaaa 300

ggccttgaat gggtgtccgc catttctggc agcggaggct ctacctacta cgccgatagc 360

gtgaagggca gattcaccat cagccgggac aacagcaaga acaccctgta cctgcagatg 420

aactccctga gagccgagga caccgccgtg tactattgcg ccaaactgac aggcgccgag 480

tacttccagc attggggaca gggaaccctg gtcacagtct cttca 525

<210> 84
<211> 333
<212> DNA
<213> human

<400> 84
cagtctgtgc tgacacagcc tcctagtgtg tctggcgccc ctggccagag agtgaccatc 60

agctgtaccg gcagcagctc caacatcgga gccggctatg acgtgcactg gtatcagcag 120

ctgcctggca ccgcccccaa actgctgatc tacggcaaca gcaaccggcc cagcggcgtg 180

cccgatagat tttccggcag caagagcggc accagcgcca gcctggctat tactggactg 240

caggccgagg acgaggccga ctactactgc cagagctacg acagcagcct gagcggcgtg 300

gtgtttggcg gcggaacaaa gctgaccgtg cta 333

<210> 85
<211> 98
<212> PRT
<213> human

<400> 85

Glu Val Gln Leu Leu 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 Ser Ser Tyr
20 25 30

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

Ser Ala Ile Ser Gly Ser Gly 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 Leu Tyr
65 70 75 80

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

Ala Lys

<210> 86
<211> 17
<212> PRT
<213> human

<400> 86

Ala Glu Tyr Phe Gln His Trp Gly Gln Gly Thr Leu Val Thr Val Ser
1 5 10 15

Ser

<210> 87
<211> 329

<212> PRT
<213> human

<400> 87

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


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


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60


Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80


Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95


Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110


Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125


Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140


Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160


Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175


Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190


His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
```

```
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly
                325
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<210> 88
<211> 99
<212> PRT
<213> human

<400> 88

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

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
            20                  25                  30

Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45
```

```
Leu Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60


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


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


Leu Ser Gly



<210>  89
<211>  12
<212>  PRT
<213>  human

<400>  89

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
1               5                   10


<210>  90
<211>  106
<212>  PRT
<213>  human

<400>  90

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


Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
            20                  25                  30


Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
        35                  40                  45


Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
    50                  55                  60


Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65                  70                  75                  80
```

Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
85 90 95

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
100 105

<210> 91
<211> 18
<212> PRT
<213> artificial

<220>
<223> NP variant

<220>
<221> misc_feature
<222> (1)..(1)
<223> Xaa can be any naturally occurring amino acid

<220>
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<222> (5)..(7)
<223> Xaa can be any naturally occurring amino acid

<220>
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<223> Xaa can be any naturally occurring amino acid

<220>
<221> misc_feature
<222> (15)..(15)
<223> Xaa can be any naturally occurring amino acid

<400> 91

Xaa Cys Phe Gly Xaa Xaa Xaa Asp Arg Ile Xaa Xaa Xaa Ser Xaa Leu
1 5 10 15

Gly Cys

<210> 92
<211> 7
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 92

Ser Gly Phe Thr Phe Ser Ser
1 5

<210> 93
<211> 10
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 93

Ser Gly Phe Thr Phe Gly Ser Gly Ser Gly
1 5 10

<210> 94
<211> 6
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 94

Gly Ser Gly Ser Gly Met
1 5

<210> 95
<211> 13
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 95

Ser Gly Phe Thr Phe Gly Ser Gly Ser Gly Ser Gly Ser
1 5 10

<210> 96
<211> 9
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 96

Ser Gly Ser Gly Ser Gly Ser Gly Met
1   5

<210> 97
<211> 16
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 97

Ser Gly Phe Thr Phe Gly Ser Gly Ser Gly Ser Gly Gly Ser Gly Gly
1   5   10   15

<210> 98
<211> 12
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 98

Gly Gly Ser Gly Gly Ser Gly Ser Gly Ser Gly Met
1   5   10

<210> 99
<211> 19
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 99

Ser Gly Phe Thr Phe Gly Ser Gly Ser Gly Ser Gly Ser Gly Gly Gly
1   5   10   15

Ser Gly Gly

<210> 100
<211> 11
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 100

Gly Ser Gly Ser Gly Gly Ser Gly Ser Gly Met
1 5 10

<210> 101
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 101

Ser Pro Ala Val Val Tyr Ile Glu Ile Leu Asp Arg His Pro Asp Gly
1 5 10 15

Gly Ser Gly Gly
20

<210> 102
<211> 18
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 102

Gly Ser Gly Arg Glu Val Pro Ile Ser Asn Gly Ser Gly Phe Val Val
1 5 10 15

Ala Met

<210> 103
<211> 20
<212> PRT

<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 103

Ser Gly Ala Val Val Tyr Ile Glu Ile Leu Asp Arg His Pro Asp Gly
1 5 10 15

Gly Ser Gly Gly
20

<210> 104
<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 104

Ser Ser Ser Asp Arg Ser Ala Leu Leu Lys Ser Lys Leu Arg Ala Leu
1 5 10 15

Leu Thr Ala Pro Arg
20

<210> 105
<211> 24
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 105

Ser Gly Phe Thr Phe Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly
1 5 10 15

Ser Pro Asp Gly Gly Ser Gly Gly
20

<210> 106
<211> 15
<212> PRT

<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 106

Gly Ser Tyr Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Met
1 5 10 15

<210> 107
<211> 25
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 107

Ser Gly Phe Thr Phe Ser Ser Asp Arg Ser Ala Leu Leu Lys Ser Lys
1 5 10 15

Leu Arg Ala Leu Leu Thr Ala Pro Arg
20 25

<210> 108
<211> 14
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 108

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Met
1 5 10

<210> 109
<211> 4
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 109

Ile Ser Gly Ser

1

<210> 110
<211> 4
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 110

Gly Gly Ser Thr
1

<210> 111
<211> 8
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 111

Ile Ser Gly Ser Gly Ser Gly Ser
1 5

<210> 112
<211> 8
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 112

Gly Ser Gly Ser Gly Gly Ser Thr
1 5

<210> 113
<211> 9
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 113

Ile Ser Gly Ser Gly Ser Gly Ser Gly
1 5

<210> 114
<211> 10
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 114

Gly Ser Ser Gly Ser Gly Ser Gly Ser Thr
1 5 10

<210> 115
<211> 11
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 115

Ile Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly
1 5 10

<210> 116
<211> 12
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 116

Gly Ser Ser Gly Ser Gly Ser Gly Ser Gly Ser Thr
1 5 10

<210> 117
<211> 12
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 117

Ile Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Gly
1 5 10

<210> 118
<211> 15
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 118

Gly Glu Lys Glu Lys Glu Lys Val Ser Thr Ala Val Gly Ser Thr
1 5 10 15

<210> 119
<211> 13
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 119

Ile Ser Gly Ser Ala Val Val Asn Gly Gly Ser Gly Gly
1 5 10

<210> 120
<211> 9
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 120

Gly Lys Ile Ala Ile Gly Gly Ser Thr
1 5

<210> 121
<211> 14
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 121

Ile Ser Gly Pro Asn Pro Asn Lys Asn Pro Asn Pro Gly Gly
1   5   10

<210> 122
<211> 13
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 122

Gly Ser Asn Glu Asn Pro Asn Pro Asn Pro Gly Ser Thr
1   5   10

<210> 123
<211> 15
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 123

Ile Ser Gly Ser Val Val Val Thr Ser His Gly Gly Ser Gly Gly
1   5   10   15

<210> 124
<211> 10
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 124

Gly Gly Ser Gly Ser Gly Ser Gly Ser Thr
1   5   10

<210> 125
<211> 15
<212> PRT

<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 125

Ile Ser Gly Ser Ala Val Val Asn Val Arg Gly Gly Ser Gly Gly
1 5 10 15

<210> 126
<211> 11
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 126

Gly Gly Asp Lys Ile Ala Ile Gly Gly Ser Thr
1 5 10

<210> 127
<211> 15
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 127

Ile Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Ser Gly Gly
1 5 10 15

<210> 128
<211> 15
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 128

Ile Ser Gly Leu Ala Val Gln Ile Arg Arg Gly Gly Ser Gly Gly
1 5 10 15

<210> 129

<211> 15
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 129

Gly Gly Ser Gly Arg Glu Thr Leu Thr Leu Tyr Val Gly Ser Thr
1 5 10 15

<210> 130
<211> 16
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 130

Ile Ser Gly Ser Ala Val Val Asn Val Arg Ala Gly Gly Ser Gly Gly
1 5 10 15

<210> 131
<211> 16
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 131

Ile Ser Gly Ser Tyr Ala Met Ser Trp Val Arg Gly Gly Ser Gly Gly
1 5 10 15

<210> 132
<211> 13
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 132

Gly Ser Tyr Ala Met Ser Trp Val Arg Gln Gly Ser Thr
1 5 10

<210> 133
<211> 16
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 133

Ile Ser Gly Pro Asn Pro Asn Lys Asn Pro Asn Pro Asn Pro Gly Gly
1 5 10 15

<210> 134
<211> 15
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 134

Gly Ser Asn Pro Asn Glu Asn Pro Asn Pro Asn Pro Gly Ser Thr
1 5 10 15

<210> 135
<211> 17
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 135

Ile Ser Gly Ser Ala Val Val Asn Val Arg Ala Asp Gly Gly Ser Gly
1 5 10 15

Gly

<210> 136
<211> 12
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 136

Gly Ser Gly Asp Lys Ile Ala Ile Gly Gly Ser Thr
1 5 10

<210> 137
<211> 17
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 137

Ile Ser Gly Ser Gly Ser Gly Ser Gly Ser Pro Asp Gly Gly Ser Gly
1 5 10 15

Gly

<210> 138
<211> 17
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 138

Ile Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Gly Ser Gly
1 5 10 15

Gly

<210> 139
<211> 17
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 139

Ile Ser Gly Ser Val Val Val Thr Ser His Gln Ala Pro Gly Ser Gly

1 5 10 15

Gly

<210> 140
<211> 16
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 140

Gly Ser Gly Glu Lys Lys Lys Leu Lys Ser Leu Ala Tyr Gly Ser Thr
1 5 10 15

<210> 141
<211> 17
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 141

Ile Ser Gly Arg Tyr Asn Ile Leu Lys Ile Gln Lys Val Gly Ser Gly
1 5 10 15

Gly

<210> 142
<211> 16
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 142

Gly Gly Ser Gly Glu Tyr Leu Ile Thr Tyr Gln Ile Met Gly Ser Thr
1 5 10 15

<210> 143

<211> 17
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 143

Ile Ser Gly Arg Gln Leu Leu Phe Cys Arg Val Thr Leu Gly Ser Gly
1 5 10 15

Gly

<210> 144
<211> 18
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 144

Gly Gly Ser Gly Glu Gln Ala Tyr Pro Glu Tyr Leu Ile Thr Tyr Gly
1 5 10 15

Ser Thr

<210> 145
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 145

Ile Ser Val Val Val Thr Ser His Gln Ala Pro Gly Glu Gly Gly Ser
1 5 10 15

Gly Gly

<210> 146

<211> 12
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 146

Gly Glu Lys Lys Lys Leu Lys Ser Leu Ala Ser Thr
1 5 10

<210> 147
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 147

Ile Ser Gly Val Val Thr Ser His Gln Ala Pro Gly Glu Gly Gly Ser
1 5 10 15

Gly Gly

<210> 148
<211> 12
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 148

Gly Glu Lys Lys Lys Leu Lys Ser Leu Gly Ser Thr
1 5 10

<210> 149
<211> 12
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 149

Gly Glu Lys Lys Lys Leu Lys Ser Gly Gly Ser Thr
1 5 10

<210> 150
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 150

Ile Ser Gly Ser Val Thr Ser His Gln Ala Pro Gly Glu Gly Gly Ser
1 5 10 15

Gly Gly

<210> 151
<211> 12
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 151

Gly Glu Lys Lys Lys Gly Lys Ser Gly Gly Ser Thr
1 5 10

<210> 152
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 152

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

Gly Gly

<210> 153
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 153

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

Gly Gly

<210> 154
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 154

Ile Ser Val Val Val Thr Ser His Gln Ser Pro Thr Pro Gly Gly Ser
1 5 10 15

Gly Gly

<210> 155
<211> 12
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 155

Gly Gly Ser Thr Pro Leu Lys Ser Leu Ala Ser Thr
1 5 10

<210> 156
<211> 12
<212> PRT

<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 156

Gly Ser Thr Pro Lys Leu Lys Ser Leu Ala Ser Thr
1 5 10

<210> 157
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 157

Ile Ser Val Val Val Thr Ser His Pro Thr Pro Gly Glu Gly Gly Ser
1 5 10 15

Gly Gly

<210> 158
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 158

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

Gly Gly

<210> 159
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 159

Ile Ser Val Val Val Thr Ser His Gln Ala Asn Gly Ser Gly Gly Ser
1 5 10 15

Gly Gly

<210> 160
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 160

Ile Ser Gly Ser Ala Val Val Asn Val Arg Ala Pro Asp Gly Gly Ser
1 5 10 15

Gly Gly

<210> 161
<211> 13
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 161

Gly Ser Lys Gly Asp Lys Ile Ala Ile Gly Gly Ser Thr
1 5 10

<210> 162
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 162

Ile Ser Thr Ser Ala Ser Leu Ala Ile Thr Gly Pro Asp Gly Gly Ser

1 5 10 15

Gly Gly

<210> 163
<211> 13
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 163

Gly Ser Asp Arg Phe Ser Gly Ser Lys Ser Gly Ser Thr
1 5 10

<210> 164
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 164

Ile Ser Gly Phe Ile Leu Pro Ile Glu Val Tyr Pro Asp Gly Gly Ser
1 5 10 15

Gly Gly

<210> 165
<211> 13
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 165

Gly Ser Lys Val Arg Phe Asp Tyr Asp Leu Phe Ser Thr
1 5 10

<210> 166

<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 166

Ile Ser Ser Ala Leu Leu Lys Ser Lys Leu Arg Ala Leu Leu Thr Ala
1 5 10 15

Pro Gly

<210> 167
<211> 14
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 167

Gly Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Thr
1 5 10

<210> 168
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 168

Ile Ser Gly Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Gly Gly Ser
1 5 10 15

Gly Gly

<210> 169
<211> 15
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 169

Gly Ser Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Gly Ser Thr
1   5   10   15

<210> 170
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 170

Ile Ser Gly Pro Asn Pro Asn Lys Asn Pro Asn Pro Asn Pro Gly Ser
1   5   10   15

Gly Gly

<210> 171
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 171

Ile His Pro Leu Gln Asn Arg Trp Ala Leu Trp Phe Phe Lys Gly Ser
1   5   10   15

Gly Gly

<210> 172
<211> 16
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 172

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

<210> 173
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 173

Ile Ser Gly Ser Val Thr Ile Phe Ser Leu Ala Thr Asn Glu Gly Ser
1 5 10 15

Gly Gly

<210> 174
<211> 18
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 174

Gly Gly Ser Gly Lys Thr Thr Trp His Arg Ile Ser Val Phe Gly Gly
1 5 10 15

Ser Thr

<210> 175
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 175

Ile Tyr Leu Glu Gly Lys Ile Asp Tyr Gly Glu Tyr Met Asp Gly Ser
1 5 10 15

Gly Gly

<210> 176
<211> 18
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 176

Gly Gly Ser Asn Val Arg Arg Gln Ala Thr Thr Ile Ile Ala Asp Asn
1 5 10 15

Ile Thr

<210> 177
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 177

Ile Ser Gly Ser Val Gln Gly Ile Ile Asn Phe Glu Gln Lys Gly Ser
1 5 10 15

Gly Gly

<210> 178
<211> 18
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 178

Gly Gly Ser Gly Pro Val Lys Val Trp Gly Ser Ile Lys Gly Gly Gly
1 5 10 15

Ser Thr

<210> 179
<211> 19
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 179

Ile Ser Gly Val Val Val Thr Ser His Gln Ala Pro Gly Glu Gly Gly
1 5 10 15

Ser Gly Gly

<210> 180
<211> 13
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 180

Gly Glu Lys Lys Lys Leu Lys Ser Leu Ala Gly Ser Thr
1 5 10

<210> 181
<211> 19
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 181

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

Ser Gly Gly

<210> 182
<211> 14
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 182

Gly Ser Asp Arg Phe Ser Gly Ser Lys Ser Gly Gly Ser Thr
1 5 10

<210> 183
<211> 19
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 183

Ile Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Pro Asp Gly Gly
1 5 10 15

Ser Gly Gly

<210> 184
<211> 14
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 184

Gly Ser Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Thr
1 5 10

<210> 185
<211> 19
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 185

Ile Ser Gly Thr Tyr Ile Ser Asn Val Asn His Lys Pro Asp Gly Gly
1 5 10 15

Ser Gly Gly

<210> 186
<211> 14
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 186

Gly Ser Asn Thr Lys Val Asp Lys Lys Val Glu Gly Ser Thr
1 5 10

<210> 187
<211> 19
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 187

Ile Ser Gly Gly Phe Ile Leu Pro Ile Glu Val Tyr Pro Asp Gly Gly
1 5 10 15

Ser Gly Gly

<210> 188
<211> 14
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 188

Gly Ser Lys Val Arg Phe Asp Tyr Asp Leu Phe Gly Ser Thr

1 5 10

<210> 189
<211> 19
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 189

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

Ser Gly Gly

<210> 190
<211> 14
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 190

Gly Glu Lys Lys Lys Leu Lys Ser Leu Ala Tyr Gly Ser Thr
1 5 10

<210> 191
<211> 14
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 191

Gly Glu Lys Pro Lys Pro Lys Pro Leu Ala Tyr Gly Ser Thr
1 5 10

<210> 192
<211> 14
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 192

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Gly Ser Thr
1   5   10

<210> 193
<211> 19
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 193

Ile Ser Gly Pro Asn Pro Asn Lys Asn Pro Asn Pro Asn Pro Gly Gly
1   5   10   15

Ser Gly Gly

<210> 194
<211> 19
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 194

Ile Ser Gly Asp Ile Tyr Leu Ala Ile Asn Ile Thr Asn Gly Glu Gly
1   5   10   15

Ser Gly Gly

<210> 195
<211> 18
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 195

Gly Gly Ser Gly Asp Ile Tyr Leu Ala Ile Asn Ile Thr Asn Gly Glu
1 5 10 15

Ser Thr

<210> 196
<211> 19
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 196

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

Ser Gly Gly

<210> 197
<211> 18
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 197

Gly Gly Ser Gly Val Gln Gly Ile Ile Asn Phe Glu Gln Lys Gly Gly
1 5 10 15

Ser Thr

<210> 198
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 198

Ile Ser Gly Ser Val Pro Lys Glu Lys Glu Lys Glu Lys Val Ser Thr
1 5 10 15

Ala Val Gly Gly
20

<210> 199
<211> 13
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 199

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Thr
1 5 10

<210> 200
<211> 15
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 200

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Thr
1 5 10 15

<210> 201
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 201

Ile Ser Gly Ser Ser Gly Ala Val Val Asn Val Arg Ala Pro Asp Gly
1 5 10 15

Gly Ser Gly Gly
20

<210> 202
<211> 15
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 202

Gly Ser Lys Gly Asp Lys Ile Ala Ile Trp Thr Thr Gly Ser Thr
1 5 10 15

<210> 203
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 203

Ile Ser Gly Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Asp Gly
1 5 10 15

Gly Ser Gly Gly
20

<210> 204
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 204

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

Gly Ser Gly Gly
20

<210> 205
<211> 15
<212> PRT

<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 205

Gly Ser Asp Arg Phe Ser Gly Ser Lys Ser Gly Gly Gly Ser Thr
1 5 10 15

<210> 206
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 206

Ile Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Pro Asp Gly
1 5 10 15

Gly Ser Gly Gly
20

<210> 207
<211> 19
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 207

Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Ser Pro Asp Gly Gly
1 5 10 15

Ser Gly Gly

<210> 208
<211> 15
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 208

Gly Ser Tyr Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Thr
1 5 10 15

<210> 209
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 209

Ile Ser Thr Gln Thr Tyr Ile Ser Asn Val Asn His Lys Pro Asp Gly
1 5 10 15

Gly Ser Gly Gly
20

<210> 210
<211> 15
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 210

Gly Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Thr
1 5 10 15

<210> 211
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 211

Ile Ser Gly Ser Thr Tyr Ile Ser Asn Val Asn His Lys Pro Asp Gly
1 5 10 15

Gly Ser Gly Gly

20

<210> 212
<211> 15
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 212

Gly Ser Asn Thr Lys Val Asp Lys Lys Val Glu Gly Gly Ser Thr
1 5 10 15

<210> 213
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 213

Ile Ser Gly Pro Asn Pro Asn Pro Asn Pro Asn Pro Asn Pro Asp Gly
1 5 10 15

Gly Ser Gly Gly
20

<210> 214
<211> 15
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 214

Gly Ser Asn Pro Asn Pro Asn Pro Asn Pro Asn Pro Gly Ser Thr
1 5 10 15

<210> 215
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 215

Ile Ser Ala Val Gln Val Lys Leu Glu Leu Gly His Arg Pro Asp Gly
1   5   10   15

Gly Ser Gly Gly
            20

<210> 216
<211> 15
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 216

Gly Ser Asn His Leu Arg Ser Glu Lys Leu Thr Phe Asn Ser Thr
1   5   10   15

<210> 217
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 217

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

Gly Ser Gly Gly
            20

<210> 218
<211> 15
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 218

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

<210> 219
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 219

Ile Ser Gly Ser Gly Phe Ile Leu Pro Ile Glu Val Tyr Pro Asp Gly
1 5 10 15

Gly Ser Gly Gly
20

<210> 220
<211> 15
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 220

Gly Ser Lys Val Arg Phe Asp Tyr Asp Leu Phe Gly Gly Ser Thr
1 5 10 15

<210> 221
<211> 16
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 221

Gly Ser Tyr Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Thr
1 5 10 15

<210> 222
<211> 20
<212> PRT

<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 222

Ile Ser Asp Arg Ser Ala Leu Leu Lys Ser Lys Leu Arg Ala Leu Leu
1 5 10 15

Thr Ala Pro Arg
20

<210> 223
<211> 16
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 223

Gly Ser Asp Arg Ser Ala Leu Leu Lys Ser Lys Leu Arg Ala Ser Thr
1 5 10 15

<210> 224
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 224

Ile Ser Asp Arg Ser Ala Leu Leu Lys Ser Lys Leu Arg Ala Leu Leu
1 5 10 15

Thr Ala Pro Gly
20

<210> 225
<211> 16
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 225

Gly Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Thr
1 5 10 15

<210> 226
<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 226

Ile Ser Gly Ser Ser Asp Lys Thr His Thr Ser Pro Pro Ser Pro Asp
1 5 10 15

Gly Gly Ser Gly Gly
20

<210> 227
<211> 15
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 227

Gly Ser Lys Thr His Thr Ser Pro Pro Ser Pro Gly Gly Ser Thr
1 5 10 15

<210> 228
<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 228

Ile Ser Gly Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Ser Pro Asp
1 5 10 15

Gly Gly Ser Gly Gly

20

<210> 229
<211> 16
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 229

Gly Ser Tyr Ser Ser Tyr Ala Met Ser Trp Val Arg Gly Gly Ser Thr
1 5 10 15

<210> 230
<211> 16
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 230

Gly Ser Tyr Ser Ser Tyr Ala Met Ser Trp Val Arg Gln Gly Ser Thr
1 5 10 15

<210> 231
<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 231

Ile Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Pro Asp
1 5 10 15

Gly Gly Ser Gly Gly
20

<210> 232
<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 232

Ile Ser Gly Ser Pro Asn Pro Asn Pro Asn Pro Asn Pro Ser Pro Asp
1   5   10   15

Gly Gly Ser Gly Gly
            20

<210> 233
<211> 16
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 233

Gly Ser Tyr Pro Asn Pro Asn Pro Asn Pro Asn Pro Ser Gly Ser Thr
1   5   10   15

<210> 234
<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 234

Ile Ser Gly Pro Asn Pro Asn Lys Asn Pro Asn Pro Asn Ser Pro Asp
1   5   10   15

Gly Gly Ser Gly Gly
            20

<210> 235
<211> 16
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 235

Gly Ser Tyr Asn Pro Asn Glu Asn Pro Asn Pro Asn Pro Gly Ser Thr
1 5 10 15

<210> 236
<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 236

Ile Ser Gly Pro Asn Pro Asn Pro Asn Pro Asn Pro Asn Ser Pro Asp
1 5 10 15

Gly Gly Ser Gly Gly
20

<210> 237
<211> 16
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 237

Gly Ser Tyr Asn Pro Asn Pro Asn Pro Asn Pro Asn Pro Gly Ser Thr
1 5 10 15

<210> 238
<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 238

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

Gly Gly Ser Gly Gly
20

<210> 239
<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 239

Ile Ser Gly Ser Val Val Tyr Ile Glu Ile Leu Asp Arg His Pro Asp
1 5 10 15

Gly Gly Ser Gly Gly
20

<210> 240
<211> 16
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 240

Gly Ser Gly Arg Glu Val Pro Ile Ser Asn Gly Ser Gly Gly Ser Thr
1 5 10 15

<210> 241
<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 241

Ile Ser Gly Ala Val Val Tyr Ile Glu Ile Leu Asp Arg His Pro Asp
1 5 10 15

Gly Gly Ser Gly Gly
20

<210> 242
<211> 21
<212> PRT

<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 242

Ile Ser Pro Ala Val Val Tyr Ile Glu Ile Leu Asp Arg His Pro Asp
1 5 10 15

Gly Gly Ser Gly Gly
20

<210> 243
<211> 16
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 243

Gly Ser Gly Arg Glu Val Pro Ile Ser Asn Gly Ser Gly Phe Ser Thr
1 5 10 15

<210> 244
<211> 11
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 244

Cys Ala Lys Ser Pro Asp Gly Gly Ser Gly Gly
1 5 10

<210> 245
<211> 4
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 245

Gly Ser Tyr Gly

1

<210> 246
<211> 9
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 246

Gly Ser Tyr Gln His Trp Gly Gln Gly
1 5

<210> 247
<211> 13
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 247

Cys Ala Lys Val His Gln Glu Thr Gly Gly Ser Gly Gly
1 5 10

<210> 248
<211> 11
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 248

Gly Ser Trp His Val Gln His Trp Gly Gln Gly
1 5 10

<210> 249
<211> 15
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 249

Cys Ala Lys Val His Gln Glu Thr Pro Asp Gly Gly Ser Gly Gly
1 5 10 15

<210> 250
<211> 13
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 250

Gly Ser Tyr Glu Trp His Val Gln His Trp Gly Gln Gly
1 5 10

<210> 251
<211> 16
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 251

Cys Thr Ser Val His Gln Glu Thr Lys Lys Tyr Gln Ser Ser Gly Gly
1 5 10 15

<210> 252
<211> 19
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 252

Gly Ser Tyr Ser Tyr Thr Tyr Asn Tyr Glu Trp His Val Asp Val Trp
1 5 10 15

Gly Gln Gly

<210> 253
<211> 17
<212> PRT

<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 253

Cys Thr Ser Val His Gln Glu Thr Ser Ser Pro Asp Gly Gly Ser Gly
1 5 10 15

Gly

<210> 254
<211> 15
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 254

Gly Ser Tyr Ser Tyr Glu Trp His Val Asp Val Trp Gly Gln Gly
1 5 10 15

<210> 255
<211> 17
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 255

Cys Ala Lys Thr His Thr Ser Pro Pro Ser Pro Asp Gly Gly Ser Gly
1 5 10 15

Gly

<210> 256
<211> 15
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 256

Gly Ser Ser Pro Pro Ser Pro Tyr Phe Gln His Trp Gly Gln Gly
1 5 10 15

<210> 257
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 257

Cys Thr Ser Val His Gln Glu Thr Lys Ser Ser Pro Asp Gly Gly Ser
1 5 10 15

Gly Gly

<210> 258
<211> 16
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 258

Gly Ser Tyr Ser Asn Tyr Glu Trp His Val Asp Val Trp Gly Gln Gly
1 5 10 15

<210> 259
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 259

Cys Thr Ser Val His Gln Glu Thr Lys Lys Tyr Gln Ser Ser Pro Asp
1 5 10 15

Gly Gly

<210> 260
<211> 19
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 260

Cys Thr Ser Val His Gln Glu Thr Lys Lys Ser Ser Pro Asp Gly Gly
1 5 10 15

Ser Gly Gly

<210> 261
<211> 17
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 261

Gly Ser Tyr Ser Tyr Asn Tyr Glu Trp His Val Asp Val Trp Gly Gln
1 5 10 15

Gly

<210> 262
<211> 19
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 262

Cys Thr Ser Val His Gln Glu Thr Lys Lys Tyr Gln Ser Ser Gly Gly
1 5 10 15

Ser Gly Gly

<210> 263
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 263

Cys Thr Ser Val His Gln Glu Thr Lys Lys Gln Ser Ser Pro Asp Gly
1 5 10 15

Gly Ser Gly Gly
20

<210> 264
<211> 18
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 264

Gly Ser Tyr Ser Tyr Tyr Asn Tyr Glu Trp His Val Asp Val Trp Gly
1 5 10 15

Gln Gly

<210> 265
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 265

Cys Ala Lys Val His Pro Asn Pro Asn Pro Asn Pro Asn Pro Asp Gly
1 5 10 15

Gly Ser Gly Gly

20

<210> 266
<211> 18
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 266

Gly Ser Asn Pro Asn Pro Asn Pro Asn Pro His Val Asp Val Trp Gly
1 5 10 15

Gln Gly

<210> 267
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 267

Cys Thr Ser Val His Gln Glu Thr Lys Lys Tyr Gln Ser Ser Pro Asp
1 5 10 15

Gly Gly Ser Gly
20

<210> 268
<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 268

Cys Thr Ser Val His Gln Glu Thr Lys Lys Tyr Gln Ser Ser Pro Asp
1 5 10 15

Gly Gly Ser Gly Gly

20

<210> 269
<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 269

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

Gly Gly Ser Gly Gly
20

<210> 270
<211> 18
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 270

Gly Glu Lys Lys Lys Leu Lys Ser Leu Ala Tyr Phe Gln His Trp Gly
1 5 10 15

Gln Gly

<210> 271
<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 271

Cys Ala Lys Ser Ser Asp Lys Thr His Thr Ser Pro Pro Ser Pro Asp
1 5 10 15

Gly Gly Ser Gly Gly

20

<210> 272
<211> 19
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 272

Gly Ser Lys Thr His Thr Ser Pro Pro Ser Pro Tyr Phe Gln His Trp
1 5 10 15

Gly Gln Gly

<210> 273
<211> 19
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 273

Cys Ala Lys Val Glu Thr Lys Lys Tyr Gln Ser Ser Pro Asp Gly Gly
1 5 10 15

Ser Gly Gly

<210> 274
<211> 17
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 274

Gly Ser Tyr Ser Tyr Thr Tyr Asn Tyr Glu Val Gln His Trp Gly Gln
1 5 10 15

Gly

<210> 275
<211> 19
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 275

Cys Ala Lys Val His Thr Lys Lys Tyr Gln Ser Ser Pro Asp Gly Gly
1 5 10 15

Ser Gly Gly

<210> 276
<211> 17
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 276

Gly Ser Tyr Ser Tyr Thr Tyr Asn Tyr His Val Gln His Trp Gly Gln
1 5 10 15

Gly

<210> 277
<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 277

Cys Ala Lys Leu Thr Val Glu Thr Lys Lys Tyr Gln Ser Ser Pro Asp
1 5 10 15

Gly Gly Ser Gly Gly

20

<210> 278
<211> 19
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 278

Gly Ser Tyr Ser Tyr Thr Tyr Asn Tyr Glu Trp His Val Gln His Trp
1 5 10 15

Gly Gln Gly

<210> 279
<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 279

Cys Ala Lys Leu Thr Ala Glu Thr Lys Lys Tyr Gln Ser Ser Pro Asp
1 5 10 15

Gly Gly Ser Gly Gly
20

<210> 280
<211> 19
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 280

Gly Ser Tyr Ser Tyr Thr Tyr Asn Tyr Glu Asn Tyr Phe Gln His Trp
1 5 10 15

Gly Gln Gly

<210> 281
<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 281

Cys Ala Lys Gly Ile Thr Gly Thr Lys Lys Tyr Gln Ser Ser Pro Asp
1 5 10 15

Gly Gly Ser Gly Gly
20

<210> 282
<211> 19
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 282

Gly Ser Tyr Ser Tyr Thr Tyr Asn Tyr Ala Glu Tyr Phe Gln His Trp
1 5 10 15

Gly Gln Gly

<210> 283
<211> 19
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 283

Gly Ser Tyr Asp Tyr Val Trp Gly Ser Tyr Ala Tyr Phe Gln His Trp
1 5 10 15

Gly Gln Gly

<210> 284
<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 284

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

Gly Gly Ser Gly Gly
20

<210> 285
<211> 19
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 285

Gly Glu Lys Lys Lys Leu Lys Ser Leu Ala Tyr Tyr Phe Gln His Trp
1 5 10 15

Gly Gln Gly

<210> 286
<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 286

Cys Ala Lys Val His Pro Asn Pro Asn Pro Asn Pro Asn Ser Pro Asp
1 5 10 15

Gly Gly Ser Gly Gly

20

<210> 287
<211> 19
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 287

Gly Ser Tyr Asn Pro Asn Pro Asn Pro Asn Pro His Val Asp Val Trp
1 5 10 15

Gly Gln Gly

<210> 288
<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 288

Cys Ala Lys Leu Thr Gln Val Lys Leu Glu Leu Gly His Arg Pro Asp
1 5 10 15

Gly Gly Ser Gly Gly
20

<210> 289
<211> 19
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 289

Gly Ser Asn His Leu Arg Ser Glu Lys Leu Thr Tyr Phe Gln His Trp
1 5 10 15

Gly Gln Gly

<210> 290
<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 290

Cys Ala Lys Val His Gln Glu Thr Lys Lys Tyr Gln Ser Ser Pro Asp
1 5 10 15

Gly Gly Ser Gly Gly
20

<210> 291
<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 291

Cys Ala Lys Thr Gln Thr Tyr Ile Ser Asn Val Asn His Lys Pro Asp
1 5 10 15

Gly Gly Ser Gly Gly
20

<210> 292
<211> 19
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 292

Gly Ser Asn Thr Lys Val Asp Lys Lys Ala Glu Tyr Phe Gln His Trp
1 5 10 15

Gly Gln Gly

<210> 293
<211> 20
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 293

Gly Ser Tyr Ser Tyr Thr Thr Tyr Asn Tyr Glu Trp His Val Asp Val
1 5 10 15

Trp Gly Gln Gly
20

<210> 294
<211> 22
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 294

Cys Ala Thr Ser Val His Gln Glu Thr Lys Lys Tyr Gln Ser Ser Pro
1 5 10 15

Asp Gly Gly Ser Gly Gly
20

<210> 295
<211> 20
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 295

Gly Ser Tyr Ser Tyr Thr Tyr Asn Tyr Glu Trp His Val Asp Val His
1 5 10 15

Trp Gly Gln Gly

20

<210> 296
<211> 23
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 296

Cys Ala Lys Leu Thr Ala Glu Glu Trp Lys Lys Lys Tyr Glu Lys Glu
1 5 10 15

Lys Glu Lys Asn Lys Gly Ser
20

<210> 297
<211> 21
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 297

Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ala Glu Tyr Phe Gln
1 5 10 15

His Trp Gly Gln Gly
20

<210> 298
<211> 23
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 298

Cys Ala Asp Ser Ser Asp Arg Ser Ala Leu Leu Lys Ser Lys Leu Arg
1 5 10 15

Ala Leu Leu Thr Ala Pro Arg

20

<210> 299
<211> 21
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 299

Gly Ser Asn His Leu Arg Ser Glu Lys Leu Thr Phe Asn Tyr Phe Gln
1 5 10 15

His Trp Gly Gln Gly
20

<210> 300
<211> 23
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 300

Cys Thr Ser Val His Gln Glu Thr Lys Lys Tyr Gln Tyr Gln Ser Ser
1 5 10 15

Pro Asp Gly Gly Ser Gly Gly
20

<210> 301
<211> 21
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 301

Gly Ser Tyr Ser Tyr Thr Tyr Thr Tyr Asn Tyr Glu Trp His Val Asp
1 5 10 15

Val Trp Gly Gln Gly

20

<210> 302
<211> 23
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 302

Cys Ala Lys Leu Thr Asp Arg Ser Ala Leu Leu Lys Ser Lys Leu Arg
1 5 10 15

Ala Leu Leu Thr Ala Pro Arg
20

<210> 303
<211> 23
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 303

Cys Ala Lys Leu Thr Ala Val Gln Val Lys Leu Glu Leu Gly His Arg
1 5 10 15

Pro Asp Gly Gly Ser Gly Gly
20

<210> 304
<211> 25
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 304

Cys Thr Ser Val His Gln Glu Thr Lys Lys Tyr Gln Ser Ser Tyr Gln
1 5 10 15

Ser Ser Pro Asp Gly Gly Ser Gly Gly

20 25

<210> 305
<211> 23
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 305

Gly Ser Tyr Ser Tyr Thr Tyr Ser Tyr Thr Tyr Asn Tyr Glu Trp His
1 5 10 15

Val Asp Val Trp Gly Gln Gly
20

<210> 306
<211> 25
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 306

Cys Ala Lys Leu Thr Ala Val Gln Val Lys Leu Glu Leu Gly His Arg
1 5 10 15

Ala Gln Pro Asp Gly Gly Ser Gly Gly
20 25

<210> 307
<211> 23
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 307

Gly Ser Pro Val Asn His Leu Arg Ser Glu Lys Leu Thr Phe Asn Tyr
1 5 10 15

Phe Gln His Trp Gly Gln Gly

20

<210> 308
<211> 17
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 308

Ser Ser Ser Asn Ile Gly Ser Lys Leu Arg Ala Leu Leu Thr Ala Pro
1 5 10 15

Arg

<210> 309
<211> 15
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 309

Gly Ser Gly Ser Gly Gly Ser Gly Gly Ser Gly Ser Gly Tyr Asp
1 5 10 15

<210> 310
<211> 14
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 310

Gly Ser Tyr Gly Ser Gly Gly Ser Gly Ser Gly Ser Gly Asp
1 5 10

<210> 311
<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 311

Ser Ser Leu Gly Gln Ile Gln Leu Thr Ile Arg His Ser Ser Pro Asp
1   5   10   15

Gly Gly Ser Gly Gly
            20

<210> 312
<211> 19
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 312

Gly Ser Asn Lys Leu Ile Val Val Val His Ala Ser Arg Asn Leu Ile
1   5   10   15

Gly Tyr Asp

<210> 313
<211> 22
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 313

Ser Pro Leu Gly Gln Ile Gln Leu Thr Ile Arg His Ser Ser Gln Pro
1   5   10   15

Asp Gly Gly Ser Gly Gly
            20

<210> 314
<211> 20
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 314

Gly Ser Arg Asn Lys Leu Ile Val Val Val His Ala Ser Arg Asn Leu
1   5   10   15

Ile Ala Tyr Asp
            20

<210> 315
<211> 22
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 315

Ser Ser Leu Gly Gln Ile Gln Leu Thr Ile Arg His Ser Ser Gln Pro
1   5   10   15

Asp Gly Gly Ser Gly Gly
            20

<210> 316
<211> 20
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 316

Gly Ser Arg Asn Lys Leu Ile Val Val Val His Ala Ser Arg Asn Leu
1   5   10   15

Ile Gly Tyr Asp
            20

<210> 317
<211> 22
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 317

Ser Ser Ser Asn Ile Gly Ser Ala Leu Leu Lys Ser Lys Leu Arg Ala
1   5   10   15

Leu Leu Thr Ala Pro Arg
            20

<210> 318
<211> 20
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 318

Gly Ser Ser Asp Arg Ser Ala Leu Leu Lys Ser Lys Leu Arg Ala Leu
1   5   10   15

Leu Thr Ala Asp
            20

<210> 319
<211> 20
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 319

Gly Ser Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Ser Gly
1   5   10   15

Ser Gly Tyr Asp
            20

<210> 320
<211> 24
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 320

Ser Ser Ser Asn Ile Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly
1   5   10   15

Ser Pro Asp Gly Gly Ser Gly Gly
            20

<210> 321
<211> 15
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 321

Gly Ser Tyr Gly Ser Gly Gly Ser Gly Ser Gly Ser Gly Tyr Asp
1   5   10   15

<210> 322
<211> 7
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 322

Asn Ser Asn Arg Pro Ser Gly
1   5

<210> 323
<211> 6
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 323

Tyr Gly Gly Ser Gly Ser
1   5

<210> 324
<211> 11
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 324

Gly Ser Gly Ser Asn Ser Asn Arg Pro Ser Gly
1 5 10

<210> 325
<211> 13
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 325

Tyr Gly Lys Thr His Thr Ser Pro Pro Ser Pro Gly Gly
1 5 10

<210> 326
<211> 17
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 326

Gly Gly Lys Thr His Thr Ser Pro Pro Ser Pro Gly Asn Arg Pro Ser
1 5 10 15

Gly

<210> 327
<211> 14
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 327

Tyr Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Gly Gly
1 5 10

<210> 328
<211> 18
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 328

Gly Gly Lys Thr His Thr Ser Pro Pro Ser Pro Ser Gly Asn Arg Pro
1 5 10 15

Ser Gly

<210> 329
<211> 14
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 329

Tyr Gly Ser Lys Thr His Thr Ser Pro Pro Ser Pro Gly Gly
1 5 10

<210> 330
<211> 15
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 330

Tyr Gly Ser Gly Ser Gly Ser Gly Ser Gly Gly Gly Ser Gly Gly
1 5 10 15

<210> 331

<211> 15
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 331

Gly Ser Gly Gly Ser Gly Ser Gly Ser Gly Asn Arg Pro Ser Gly
1 5 10 15

<210> 332
<211> 16
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 332

Tyr Gly Ser Ser Asp Lys Thr His Thr Ser Pro Pro Ser Pro Gly Gly
1 5 10 15

<210> 333
<211> 20
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 333

Gly Gly Ser Gly Ser Gly Ser Gly Gly Ser Gly Ser Gly Ser Gly Asn
1 5 10 15

Arg Pro Ser Gly
20

<210> 334
<211> 17
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 334

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

Gly

<210> 335
<211> 16
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 335

Gly Ser Asp Arg Phe Ser Gly Ser Lys Ser Gly Asn Arg Pro Ser Gly
1 5 10 15

<210> 336
<211> 17
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 336

Tyr Gly Phe Ile Leu Pro Ile Glu Val Tyr Pro Asp Gly Gly Ser Gly
1 5 10 15

Gly

<210> 337
<211> 16
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 337

Gly Ser Lys Val Arg Phe Asp Tyr Asp Leu Phe Asn Arg Pro Ser Gly
1 5 10 15

<210> 338
<211> 17
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 338

Tyr Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Gly Gly Ser Gly
1 5 10 15

Gly

<210> 339
<211> 17
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 339

Gly Ser Gly Ser Gly Gly Ser Gly Ser Gly Ser Gly Asn Arg Pro Ser
1 5 10 15

Gly

<210> 340
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 340

Tyr Gly Val Pro Lys Glu Lys Glu Lys Glu Lys Val Ser Thr Ala Val
1 5 10 15

Gly Gly

<210> 341
<211> 17
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 341

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

Gly

<210> 342
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 342

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

Gly Gly

<210> 343
<211> 17
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 343

Gly Ser Asp Arg Phe Ser Gly Ser Lys Ser Gly Gly Asn Arg Pro Ser
1 5 10 15

Gly

<210> 344
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 344

Tyr Gly Gly Ser Gly Ser Gly Ser Gly Ser Gly Pro Asp Gly Gly Ser
1 5 10 15

Gly Gly

<210> 345
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 345

Tyr Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly
1 5 10 15

Gly Gly

<210> 346
<211> 17
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 346

Gly Ser Tyr Glu Lys Glu Lys Glu Lys Asn Lys Thr Leu Lys Asn Val
1 5 10 15

Gly

<210> 347
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 347

Tyr Gly Thr Tyr Ile Ser Asn Val Asn His Lys Pro Asp Gly Gly Ser
1 5 10 15

Gly Gly

<210> 348
<211> 17
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 348

Gly Ser Asn Thr Lys Val Asp Lys Lys Val Glu Gly Asn Arg Pro Ser
1 5 10 15

Gly

<210> 349
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 349

Tyr Gly Ala Glu Glu Trp Lys Lys Lys Tyr Glu Lys Glu Lys Glu Lys
1 5 10 15

Gly Gly

<210> 350
<211> 17
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 350

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser
1 5 10 15

Gly

<210> 351
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 351

Tyr Gly Gly Phe Ile Leu Pro Ile Glu Val Tyr Pro Asp Gly Gly Ser
1 5 10 15

Gly Gly

<210> 352
<211> 17
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 352

Gly Ser Lys Val Arg Phe Asp Tyr Asp Leu Phe Gly Asn Arg Pro Ser
1 5 10 15

Gly

<210> 353
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 353

Tyr Gly Ser Ala Leu Leu Lys Ser Lys Leu Arg Ala Leu Leu Thr Ala
1 5 10 15

Pro Gly

<210> 354
<211> 18
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 354

Gly Ser Asp Gly Ser Gly Gly Ser Gly Ser Gly Ser Gly Asn Arg Pro
1 5 10 15

Ser Gly

<210> 355
<211> 19
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 355

Tyr Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Pro Asp Gly Gly
1 5 10 15

Ser Gly Gly

<210> 356
<211> 19
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 356

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

Ser Gly Gly

<210> 357
<211> 18
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 357

Gly Ser Asp Arg Phe Ser Gly Ser Lys Ser Gly Gly Gly Asn Arg Pro
1 5 10 15

Ser Gly

<210> 358
<211> 19
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 358

Tyr Gly Gly Thr Tyr Ile Ser Asn Val Asn His Lys Pro Asp Gly Gly
1 5 10 15

Ser Gly Gly

<210> 359
<211> 18
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 359

Gly Ser Asn Thr Lys Val Asp Lys Lys Val Glu Gly Gly Asn Arg Pro
1 5 10 15

Ser Gly

<210> 360
<211> 19
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 360

Tyr Thr Gln Thr Tyr Ile Ser Asn Val Asn His Lys Pro Asp Gly Gly
1 5 10 15

Ser Gly Gly

<210> 361
<211> 18
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 361

Gly Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Asn Arg Pro
1 5 10 15

Ser Gly

<210> 362
<211> 19
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 362

Tyr Gly Gly Gly Phe Ile Leu Pro Ile Glu Val Tyr Pro Asp Gly Gly
1 5 10 15

Ser Gly Gly

<210> 363
<211> 18
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 363

Gly Ser Lys Val Arg Phe Asp Tyr Asp Leu Phe Gly Gly Asn Arg Pro
1 5 10 15

Ser Gly

<210> 364
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 364

Tyr Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Pro Asp Gly
1 5 10 15

Gly Ser Gly Gly
20

<210> 365
<211> 18
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 365

Gly Ser Tyr Gly Ser Gly Gly Ser Gly Ser Gly Ser Gly Asn Arg Pro
1 5 10 15

Ser Gly

<210> 366
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 366

Tyr Gly Ser Gln Val Lys Leu Glu Leu Gly His Arg Ala Pro Asp Gly
1 5 10 15

Gly Ser Gly Gly
20

<210> 367
<211> 19
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 367

Gly Ser Val Asn His Leu Arg Ser Glu Lys Leu Thr Ser Gly Asn Arg
1 5 10 15

Pro Ser Gly

<210> 368
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 368

Tyr Pro Ala Val Val Tyr Ile Glu Ile Leu Asp Arg His Pro Asp Gly
1 5 10 15

Gly Ser Gly Gly
20

<210> 369
<211> 19
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 369

Gly Ser Gly Arg Glu Val Pro Ile Ser Asn Gly Ser Gly Phe Asn Arg
1 5 10 15

Pro Ser Gly

<210> 370
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 370

Tyr Gly Gly Val Val Tyr Ile Glu Ile Leu Asp Arg His Pro Asp Gly
1 5 10 15

Gly Ser Gly Gly
20

<210> 371
<211> 19
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 371

Gly Ser Gly Arg Glu Val Pro Ile Ser Asn Gly Ser Gly Gly Asn Arg
1 5 10 15

Pro Ser Gly

<210> 372
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 372

Tyr Gly Ala Val Val Tyr Ile Glu Ile Leu Asp Arg His Pro Asp Gly
1 5 10 15

Gly Ser Gly Gly
20

<210> 373
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 373

Tyr Gly Ser Arg Ser Ala Leu Leu Lys Ser Lys Leu Arg Ala Leu Leu
1 5 10 15

Thr Ala Pro Arg
20

<210> 374
<211> 20
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 374

Gly Ser Asp Gly Ser Gly Ser Gly Gly Ser Gly Ser Gly Ser Gly Asn
1 5 10 15

Arg Pro Ser Gly
20

<210> 375
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 375

Tyr Gly Ser Arg Ser Ala Leu Leu Lys Ser Lys Leu Arg Ala Leu Leu
1 5 10 15

Thr Ala Pro Gly
20

<210> 376
<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 376

Tyr Gly Ser Ala Val Gln Val Lys Leu Glu Leu Gly His Arg Pro Asp
1 5 10 15

Gly Gly Ser Gly Gly
20

<210> 377
<211> 20
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 377

Gly Ser Asn His Leu Arg Ser Glu Lys Leu Thr Phe Asn Ser Gly Asn
1 5 10 15

Arg Pro Ser Gly
20

<210> 378
<211> 15
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 378

Cys Gly Ser Gly Ser Gly Ser Gly Pro Asp Gly Gly Ser Gly Gly
1 5 10 15

<210> 379
<211> 10
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 379

Gly Ser Gly Ser Gly Ser Gly Ser Gly Phe
1 5 10

<210> 380
<211> 17
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 380

Cys Gln Ser Tyr Asp Ile Leu Pro Ile Glu Pro Asp Gly Gly Ser Gly
1 5 10 15

Gly

<210> 381
<211> 11
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 381

Gly Ser Arg Phe Asp Tyr Asp Gly Val Val Phe
1 5 10

<210> 382
<211> 17
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 382

Cys Gly Ser Gly Ser Gly Ser Gly Ser Gly Pro Asp Gly Gly Ser Gly
1 5 10 15

Gly

<210> 383
<211> 12
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 383

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Phe

1 5 10

<210> 384
<211> 17
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 384

Cys Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Gly Gly Ser Gly
1 5 10 15

Gly

<210> 385
<211> 14
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 385

Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Phe
1 5 10

<210> 386
<211> 18
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 386

Cys Gln Ser Tyr Asp Lys Leu Glu Leu Gly His Pro Asp Gly Gly Ser
1 5 10 15

Gly Gly

<210> 387

<211> 12
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 387

Gly Ser His Leu Arg Ser Glu Lys Gly Val Val Phe
1 5 10

<210> 388
<211> 19
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 388

Cys Gln Ser Tyr Asp Ile Leu Pro Ile Glu Val Tyr Pro Asp Gly Gly
1 5 10 15

Ser Gly Gly

<210> 389
<211> 13
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 389

Gly Ser Lys Val Arg Phe Asp Tyr Asp Gly Val Val Phe
1 5 10

<210> 390
<211> 19
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 390

Cys Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Pro Asp Gly Gly
1 5 10 15

Ser Gly Gly

<210> 391
<211> 19
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 391

Cys Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Asp Gly Gly
1 5 10 15

Ser Gly Gly

<210> 392
<211> 19
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 392

Cys Gln Ser Tyr Asp Gly Phe Ile Leu Pro Ile Glu Val Tyr Gly Gly
1 5 10 15

Ser Gly Gly

<210> 393
<211> 15
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 393

Gly Ser Lys Val Arg Phe Asp Tyr Asp Leu Phe Gly Val Val Phe
1 5 10 15

<210> 394
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 394

Cys Gln Ser Tyr Asp Lys Leu Glu Leu Gly His Arg Ala Pro Asp Gly
1 5 10 15

Gly Ser Gly Gly
20

<210> 395
<211> 14
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 395

Gly Ser Val Asn His Leu Arg Ser Glu Lys Gly Val Val Phe
1 5 10

<210> 396
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 396

Cys Gln Val His Gln Glu Thr Lys Lys Tyr Gln Ser Ser Pro Asp Gly
1 5 10 15

Gly Ser Gly Gly
20

<210> 397
<211> 15
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 397

Gly Ser Tyr Ser Tyr Thr Tyr Asn Tyr Glu Trp His Val Val Phe
1 5 10 15

<210> 398
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 398

Cys Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Pro Asp Gly
1 5 10 15

Gly Ser Gly Gly
20

<210> 399
<211> 15
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 399

Gly Ser Tyr Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Phe
1 5 10 15

<210> 400
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 400

Cys Gln Ser Tyr Asp Pro Asn Pro Asn Pro Asn Pro Asn Pro Asp Gly
1 5 10 15

Gly Ser Gly Gly
20

<210> 401
<211> 15
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 401

Gly Ser Asn Pro Asn Pro Asn Pro Asn Pro Ser Gly Val Val Phe
1 5 10 15

<210> 402
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 402

Cys Ala Ala Trp Asn Pro Asn Pro Asn Pro Asn Pro Asn Pro Asn Gly
1 5 10 15

Gly Ser Gly Gly
20

<210> 403
<211> 15
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 403

Gly Ser Asn Pro Asn Pro Asn Pro Asn Pro Asn Pro Asn Val Phe

1 5 10 15

<210> 404
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 404

Cys Gln Ser Tyr Asp Gln Val Lys Leu Glu Leu Gly His Arg Ala Gly
1 5 10 15

Gly Ser Gly Gly
20

<210> 405
<211> 16
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 405

Gly Ser Val Asn His Leu Arg Ser Glu Lys Leu Thr Gly Val Val Phe
1 5 10 15

<210> 406
<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 406

Cys Gln Ser Val His Gln Glu Thr Lys Lys Tyr Gln Ser Ser Pro Asp
1 5 10 15

Gly Gly Ser Gly Gly
20

<210> 407

<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 407

Cys Gln Ser Tyr Asp Gln Val Lys Leu Glu Leu Gly His Arg Pro Asp
1 5 10 15

Gly Gly Ser Gly Gly
20

<210> 408
<211> 15
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 408

Gly Ser Asn His Leu Arg Ser Glu Lys Leu Thr Gly Val Val Phe
1 5 10 15

<210> 409
<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 409

Cys Gln Ser Tyr Asp Gly Phe Ile Leu Pro Ile Glu Val Tyr Pro Asp
1 5 10 15

Gly Gly Ser Gly Gly
20

<210> 410
<211> 16
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 410

Gly Ser Tyr Ser Tyr Thr Tyr Asn Tyr Glu Trp His Val Asp Val Phe
1   5   10   15

<210> 411
<211> 16
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 411

Gly Ser Tyr Ser Tyr Thr Tyr Asn Tyr Glu Trp His Val Val Val Phe
1   5   10   15

<210> 412
<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 412

Cys Gly Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Pro Asp
1   5   10   15

Gly Gly Ser Gly Gly
            20

<210> 413
<211> 16
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 413

Gly Ser Tyr Gly Ser Gly Ser Gly Ser Gly Ser Gly Ser Gly Gly Phe
1   5   10   15

<210> 414
<211> 22
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 414

Cys Gln Ser Tyr Asp Ser Ser Ala Leu Leu Lys Ser Lys Leu Arg Ala
1 5 10 15

Leu Leu Thr Ala Pro Arg
20

<210> 415
<211> 22
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 415

Cys Gln Ser Ala Val Gln Val Lys Leu Glu Leu Gly His Arg Ala Pro
1 5 10 15

Asp Gly Gly Ser Gly Gly
20

<210> 416
<211> 16
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 416

Gly Ser Val Asn His Leu Arg Ser Glu Lys Leu Thr Phe Asn Val Phe
1 5 10 15

<210> 417
<211> 22
<212> PRT

<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 417

Cys Gln Ser Tyr Asp Gln Val Lys Leu Glu Leu Gly His Arg Ala Pro
1 5 10 15

Asp Gly Gly Ser Gly Gly
20

<210> 418
<211> 22
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 418

Cys Gln Ser Tyr Asp Gly Phe Ile Leu Pro Ile Glu Val Tyr Phe Pro
1 5 10 15

Asp Gly Gly Ser Gly Gly
20

<210> 419
<211> 16
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 419

Gly Ser Arg Lys Val Arg Phe Asp Tyr Asp Leu Phe Gly Val Val Phe
1 5 10 15

<210> 420
<211> 22
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 420

Cys Gln Ser Tyr Val His Gln Glu Thr Lys Lys Tyr Gln Ser Ser Pro
1 5 10 15

Asp Gly Gly Ser Gly Gly
20

<210> 421
<211> 17
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 421

Gly Ser Tyr Ser Tyr Thr Tyr Asn Tyr Glu Trp His Val Gly Val Val
1 5 10 15

Phe

<210> 422
<211> 23
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 422

Cys Gln Ser Tyr Asp Val His Gln Glu Thr Lys Lys Tyr Gln Ser Ser
1 5 10 15

Pro Asp Gly Gly Ser Gly Gly
20

<210> 423
<211> 18
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 423

Gly Ser Tyr Ser Tyr Thr Tyr Asn Tyr Glu Trp His Val Ser Gly Val
1 5 10 15

Val Phe

<210> 424
<211> 24
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 424

Cys Gln Ser Tyr Asp Ala Val Gln Val Lys Leu Glu Leu Gly His Arg
1 5 10 15

Ala Pro Asp Gly Gly Ser Gly Gly
20

<210> 425
<211> 18
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 425

Gly Ser Val Asn His Leu Arg Ser Glu Lys Leu Thr Phe Asn Gly Val
1 5 10 15

Val Phe

<210> 426
<211> 25
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 426

Cys Gln Ser Tyr Asp Ser Ser Asp Arg Ser Ala Leu Leu Lys Ser Lys
1 5 10 15

Leu Arg Ala Leu Leu Thr Ala Pro Arg
20 25

<210> 427
<211> 19
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 427

Gly Ser Gly Gly Ser Val Asn His Leu Arg Ser Glu Lys Leu Thr Gly
1 5 10 15

Val Val Phe

<210> 428
<211> 21
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 428

Gly Ser Asp Arg Ser Ala Leu Leu Lys Ser Lys Leu Arg Ala Leu Leu
1 5 10 15

Thr Ala Val Val Phe
20

<210> 429
<211> 25
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 429

Cys Gln Ser Tyr Asp Ser Ser Asp Arg Ser Ala Leu Leu Lys Ser Lys
1 5 10 15

Leu Arg Ala Leu Leu Thr Ala Pro Glu
20 25

<210> 430
<211> 23
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 430

Cys Thr Ser Val His Gln Glu Thr Lys Lys Tyr Gln Ser Ser Pro Asp
1 5 10 15

Gly Gly Ser Gly Gly Ser Gly
20

<210> 431
<211> 20
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 431

Gly Gly Ser Tyr Ser Tyr Thr Tyr Asn Tyr Glu Trp His Val Asp Val
1 5 10 15

Trp Gly Gln Gly
20

<210> 432
<211> 18
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 432

Ser Tyr Ser Tyr Thr Tyr Asn Tyr Glu Trp His Val Asp Val Trp Gly
1 5 10 15

Gln Gly

<210> 433
<211> 22
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 433

Cys Thr Ser Val His Gln Glu Thr Lys Lys Tyr Gln Ser Ser Pro Asp
1 5 10 15

Gly Gly Ser Gly Gly Ser
20

<210> 434
<211> 24
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 434

Gly Ser Gly Gly Tyr Gly Ser Tyr Ser Tyr Thr Tyr Asn Tyr Glu Trp
1 5 10 15

His Val Asp Val Trp Gly Gln Gly
20

<210> 435
<211> 21
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 435

Cys Gln Ser Tyr Asp Gln Val Lys Leu Glu Leu Gly His Arg Ala Gly
1 5 10 15

Gly Ser Gly Gly Ser
20

<210> 436
<211> 21
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 436

Gly Ser Gly Gly Ser Gly Ser Val Asn His Leu Arg Ser Glu Lys Leu
1 5 10 15

Thr Gly Val Val Phe
20

<210> 437
<211> 24
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 437

Gly Ser Gly Gly Ser Gly Ser Tyr Ser Tyr Thr Tyr Asn Tyr Glu Trp
1 5 10 15

His Val Asp Val Trp Gly Gln Gly
20

<210> 438
<211> 23
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 438

Gly Gly Gly Ser Gly Ser Tyr Ser Tyr Thr Tyr Asn Tyr Glu Trp His
1 5 10 15

Val Asp Val Trp Gly Gln Gly
20

<210> 439
<211> 22
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 439

Cys Thr Ser Val His Gln Glu Thr Lys Lys Tyr Gln Ser Ser Pro Tyr
1 5 10 15

Lys Gly Ala Asn Lys Lys
20

<210> 440
<211> 20
<212> PRT
<213> artificial

<220>
<223> N-terminal sequence (with ref aa)

<400> 440

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

Ser Gly Gly Ser
20

<210> 441
<211> 19
<212> PRT
<213> artificial

<220>
<223> C-terminal sequence (with ref aa)

<400> 441

Gly Ser Gly Gly Ser Gly Glu Lys Lys Lys Leu Lys Ser Leu Ala Tyr
1 5 10 15

Gly Ser Thr

<210> 442
<211> 499
<212> PRT
<213> artificial

<220>
<223> NP engrafted HC

<400> 442

Glu Val Gln Leu Leu 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 Ser Ser Tyr
20 25 30

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

Ser Ala Ile Ser Gly Ser Gly 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 Leu Tyr
65 70 75 80

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

Thr Ser Val His Gln Glu Thr Lys Lys Tyr Gln Ser Ser Pro Asp Gly
100 105 110

Gly Ser Gly Gly Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met
115 120 125

Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg

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    130                 135                 140

Gly Ser Tyr Ser Tyr Thr Tyr Asn Tyr Glu Trp His Val Asp Val Trp
145                 150                 155                 160

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
                165                 170                 175

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
            180                 185                 190

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
        195                 200                 205

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
    210                 215                 220

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
225                 230                 235                 240

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
                245                 250                 255

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
            260                 265                 270

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
        275                 280                 285

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
    290                 295                 300

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
305                 310                 315                 320

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
                325                 330                 335

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
            340                 345                 350
```

```
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
        355                 360                 365


Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
    370                 375                 380


Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
385                 390                 395                 400


Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
                405                 410                 415


Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
            420                 425                 430


Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
        435                 440                 445


Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
    450                 455                 460


Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
465                 470                 475                 480


Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
                485                 490                 495


Ser Pro Gly
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<210> 443
<211> 500
<212> PRT
<213> artificial

<220>
<223> NP engrafted HC

<400> 443

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Glu Val Gln Leu Leu 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 Ser Ser Tyr
            20                  25                  30

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

Ser Ala Ile Ser Gly Ser Val Val Val Thr Ser His Gln Ala Pro Gly
    50                  55                  60

Gly Gly Ser Gly Gly Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys
65                  70                  75                  80

Met Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg
                85                  90                  95

Arg Gly Glu Lys Lys Lys Leu Lys Ser Leu Ala Tyr Gly Ser Thr Tyr
            100                 105                 110

Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
        115                 120                 125

Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr
    130                 135                 140

Ala Val Tyr Tyr Cys Ala Lys Leu Thr Gly Ala Glu Tyr Phe Gln His
145                 150                 155                 160

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
                165                 170                 175

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
            180                 185                 190

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
        195                 200                 205

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
    210                 215                 220

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
```

```
225                 230                 235                 240

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
                245                 250                 255

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
            260                 265                 270

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
        275                 280                 285

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
    290                 295                 300

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
305                 310                 315                 320

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
                325                 330                 335

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
            340                 345                 350

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
        355                 360                 365

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
    370                 375                 380

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
385                 390                 395                 400

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
                405                 410                 415

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
            420                 425                 430

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
        435                 440                 445
```

```
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
    450                 455                 460


Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
465                 470                 475                 480


Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
                485                 490                 495


Leu Ser Pro Gly
            500


<210>  444
<211>  499
<212>  PRT
<213>  artificial

<220>
<223>  NP engrafted HC

<400>  444

Glu Val Gln Leu Leu 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 Ser Ser Tyr
            20                  25                  30


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


Ser Ala Ile Ser Gly Ser Gly 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 Leu Tyr
65                  70                  75                  80


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


Ala Lys Gly Ile Thr Gly Thr Lys Lys Tyr Gln Ser Ser Pro Asp Gly
            100                 105                 110
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Gly Ser Gly Gly Met Val Gln Gly Ser Gly Cys Phe Gly Arg Lys Met
        115                 120                 125

Asp Arg Ile Ser Ser Ser Ser Gly Leu Gly Cys Lys Val Leu Arg Arg
    130                 135                 140

Gly Ser Tyr Ser Tyr Thr Tyr Asn Tyr Ala Glu Tyr Phe Gln His Trp
145                 150                 155                 160

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
                165                 170                 175

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
            180                 185                 190

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
        195                 200                 205

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
    210                 215                 220

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
225                 230                 235                 240

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
                245                 250                 255

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
            260                 265                 270

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
        275                 280                 285

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
    290                 295                 300

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
305                 310                 315                 320

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
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                325                 330                 335

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
            340                 345                 350

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
        355                 360                 365

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
    370                 375                 380

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
385                 390                 395                 400

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
                405                 410                 415

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
            420                 425                 430

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
        435                 440                 445

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
    450                 455                 460

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
465                 470                 475                 480

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
                485                 490                 495

Ser Pro Gly
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<210> 445
<211> 499
<212> PRT
<213> artificial

<220>
<223> NP engrafted HC

<400> 445

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Glu Val Gln Leu Leu 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 Ser Ser Tyr
            20                  25                  30

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

Ser Ala Ile Ser Gly Ser Gly 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 Leu Tyr
65                  70                  75                  80

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

Thr Ser Val His Gln Glu Thr Lys Lys Tyr Gln Ser Ser Pro Tyr Lys
            100                 105                 110

Gly Ala Asn Lys Lys Gly Leu Ser Lys Gly Cys Phe Gly Leu Lys Leu
        115                 120                 125

Asp Arg Ile Gly Ser Met Ser Gly Leu Gly Cys Gly Ser Gly Gly Ser
    130                 135                 140

Gly Ser Tyr Ser Tyr Thr Tyr Asn Tyr Glu Trp His Val Asp Val Trp
145                 150                 155                 160

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
                165                 170                 175

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
            180                 185                 190

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
        195                 200                 205
```

```
Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
    210                 215                 220

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
225                 230                 235                 240

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
                245                 250                 255

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
            260                 265                 270

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
        275                 280                 285

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
    290                 295                 300

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
305                 310                 315                 320

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
                325                 330                 335

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
            340                 345                 350

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
        355                 360                 365

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
    370                 375                 380

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
385                 390                 395                 400

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
                405                 410                 415

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
```

```
            420                 425                 430

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
        435                 440                 445

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
    450                 455                 460

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
465                 470                 475                 480

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
                485                 490                 495

Ser Pro Gly
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<210> 446
<211> 499
<212> PRT
<213> artificial

<220>
<223> NP engrafted HC

<400> 446

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Glu Val Gln Leu Leu 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 Ser Ser Tyr
            20                  25                  30

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

Ser Ala Ile Ser Gly Ser Gly 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 Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
```

```
                85                  90                  95

Thr Ser Val His Gln Glu Thr Lys Lys Tyr Gln Ser Ser Pro Asp Gly
            100                 105                 110

Gly Ser Gly Gly Ser Gly Leu Ser Lys Gly Cys Phe Gly Leu Lys Leu
        115                 120                 125

Asp Arg Ile Gly Ser Met Ser Gly Leu Gly Cys Gly Ser Gly Gly Tyr
    130                 135                 140

Gly Ser Tyr Ser Tyr Thr Tyr Asn Tyr Glu Trp His Val Asp Val Trp
145                 150                 155                 160

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
                165                 170                 175

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
            180                 185                 190

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
        195                 200                 205

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
    210                 215                 220

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
225                 230                 235                 240

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
                245                 250                 255

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
            260                 265                 270

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
        275                 280                 285

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
    290                 295                 300
```

```
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
305                 310                 315                 320

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
                325                 330                 335

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
            340                 345                 350

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
        355                 360                 365

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
    370                 375                 380

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
385                 390                 395                 400

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
                405                 410                 415

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
            420                 425                 430

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
        435                 440                 445

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
    450                 455                 460

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
465                 470                 475                 480

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
                485                 490                 495

Ser Pro Gly
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<210> 447

<211> 217
<212> PRT
<213> human

<400> 447

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Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
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Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
            20                  25                  30


Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45


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


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


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


Leu Asp Gly Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110


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


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


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


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


Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190
```

```
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195                 200                 205


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

Claims

1. An antibody or a fragment thereof comprising at least one heterologous amino acid sequence incorporated within at least one CDR region of said antibody or fragment thereof, wherein said at least one heterologous amino acid sequence comprises an N-terminal linker sequence (Ntls), a Brain Natriuretic Peptide (BNP) and a C-terminal linker sequence (Ctls), wherein optionally at least a portion of said at least one CDR region is replaced by said at least one heterologous amino acid sequence incorporated therein, and wherein

   a) at least 12 amino acid residues are present between

      i) amino acid residue HC res25 according to Kabat and the first amino acid residue of said BNP in case of an incorporation of said heterologous amino acid sequence within CDRH1;

      ii) amino acid residue HC res51 according to Kabat and the first amino acid residue of said BNP in case of an incorporation of said heterologous amino acid sequence within CDRH2;

      iii) amino acid residue HC res92 according to Kabat and the first amino acid residue of said BNP in case of an incorporation of said heterologous amino acid sequence within CDRH3;

      iv) amino acid residue LC res26 according to Kabat and the first amino acid residue of said BNP in case of an incorporation of said heterologous amino acid sequence within CDRL1;

      v) amino acid residue LC res49 according to Kabat and the first amino acid residue of said BNP in case of an incorporation of said heterologous amino acid sequence within CDRL2; and/or

      vi) amino acid residue LC res88 according to Kabat and the first amino acid residue of said BNP in case of an incorporation of said heterologous amino acid sequence within CDRL3; and wherein

   b) at least 9 amino acid residues are present between the last amino acid residue of said BNP and

      i) amino acid residue HC res35a according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRH1;

      ii) amino acid residue HC res57 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRH2;

      iii) amino acid residue HC res106 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRH3;

      iv) amino acid residue LC res 32 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRL1;

v) amino acid residue LC res57 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRL2; and/or

vi) amino acid residue LC res98 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRL3.

2. The antibody or fragment thereof according to claim 1, wherein said BNP is selected from the group consisting of human BNP having the sequence of SEQ ID NO 24 and a peptide having at least 80% sequence identity therewith.

3. The antibody or fragment thereof according to claim 1 or 2, wherein

a) said Ntls comprises

i) a GS linker sequence;

ii) a PN linker sequence;

iii) an amino acid sequence which is part of a human IgG antibody scaffold or a sequence that shares at least 80% sequence identity therewith, particularly an amino acid sequence which is part of the fab domain scaffold of a human IgG antibody or a sequence that shares at least 80% sequence identity therewith, more particularly the sequence of any one of SEQ ID NOs 1, 2 or 4 or a sequence that shares at least 80% sequence identity with any one of SEQ ID NOs 1, 2 or 4

iv) the sequence of SEQ ID NO 6 or a sequence that shares at least 60% sequence identity therewith;

v) the sequence of SEQ ID NO 7 or a sequence that shares at least 60% sequence identity therewith;

vi) the sequence of SEQ ID NO 9 or a sequence that shares at least 60% sequence identity therewith;

vii) the sequence of SEQ ID NO 11 or a sequence that shares at least 60% sequence identity therewith;

viii) the sequence of SEQ ID NO 13 or a sequence that shares at least 60% sequence identity therewith;

ix) the sequence of SEQ ID NO 15 or a sequence that shares at least 60% sequence identity therewith;

x) the sequence of SEQ ID NO 21 or a sequence that shares at least 60% sequence identity therewith; or

xi) any combination thereof, and wherein

b) said Ctls comprises

i) a GS linker sequence;

ii) a PN linker sequence;

iii) an amino acid sequence which is part of a human IgG antibody scaffold or a sequence that shares at least 80% sequence identity therewith, particularly an amino acid sequence which is part of the fab domain scaffold of a human IgG antibody or a sequence that shares at least 80% sequence identity therewith, more particularly the sequence of any one of SEQ ID NOs 1, 3 or 5 or a sequence that shares at least 80% sequence identity with any one of SEQ ID NOs 1, 3 or 5;

iv) the sequence of SEQ ID NO 6 or a sequence that shares at least 60% sequence identity therewith;

v) the sequence of SEQ ID NO 8 or a sequence that shares at least 60% sequence identity therewith;

vi) the sequence of SEQ ID NO 10 or a sequence that shares at least 60% sequence identity therewith;

vii) the sequence of SEQ ID NO 12 or a sequence that shares at least 60% sequence identity therewith;

viii) the sequence of SEQ ID NO 14 or a sequence that shares at least 60% sequence identity therewith;

ix) the sequence of SEQ ID NO 15 or a sequence that shares at least 60% sequence identity therewith;

x) the sequence of SEQ ID NO 20 or a sequence that shares at least 60% sequence identity therewith;

xi) the sequence of SEQ ID NO 22 or a sequence that shares at least 60% sequence identity therewith; or

xii) any combination thereof.

4. The antibody or fragment thereof according to claim 3, wherein

i) said Ntls and said Ctls each comprise a GS linker sequence;

ii) said Ntls and said Ctls each comprise a PN linker sequence;

iii) said Ntls and said Ctls each comprise an amino acid sequence which is part of a human IgG antibody scaffold or a sequence that shares at least 80% sequence identity therewith, particularly an amino acid sequence which is part of the fab domain scaffold of a human IgG antibody or a sequence that shares at least 80% sequence identity therewith, more particularly said Ntls comprises the sequence of any one of SEQ ID NOs 1, 2 or 4 or a sequence that shares at least 80% sequence identity with any one of SEQ ID NOs 1, 2 or 4 and said Ctls comprises the sequence of any one of SEQ ID NOs 1, 3 or 5 or a sequence that shares at least 80% sequence identity with any one of SEQ ID NOs 1, 3 or 5;

iv) said Ntls and said Ctls each comprise the sequence of SEQ ID NO 6 or a sequence that shares at least 60% sequence identity therewith;

v) said Ntls comprises the sequence of SEQ ID NO 7 or a sequence that shares at least 60% sequence identity therewith and said Ctls comprises the sequence of SEQ ID NO 8 or a sequence that shares at least 60% sequence identity therewith;

vi) said Ntls comprises the sequence of SEQ ID NO 9 or a sequence that shares at least 60% sequence identity therewith and said Ctls comprises the sequence of SEQ ID NO 10 or a sequence that shares at least 60% sequence identity therewith;

vii) said Ntls comprises the sequence of SEQ ID NO 11 or a sequence that shares at least 60% sequence identity therewith and said Ctls comprises the sequence of SEQ ID NO 12 or a sequence that shares at least 60% sequence identity therewith;

viii) said Ntls comprises the sequence of SEQ ID NO 13 or a sequence that shares at least 60% sequence identity therewith and said Ctls comprises the sequence of SEQ ID NO 14 or a sequence that shares at least 60% sequence identity therewith;

ix) said Ntls and said Ctls each comprise the sequence of SEQ ID NO 15 or a sequence that shares at least 60% sequence identity therewith;

x) said Ntls comprises the sequence of SEQ ID NO 9 or a sequence that shares at least 60% sequence identity therewith and said Ctls comprises the sequence of SEQ ID NO 20 or a sequence that shares at least 60% sequence identity therewith; or

xi) said Ntls comprises the sequence of SEQ ID NO 21 or a sequence that shares at least 60% sequence identity therewith and said Ctls comprises the sequence of SEQ ID NO 22 or a sequence that shares at least 60% sequence identity therewith.

5. The antibody or fragment thereof according to any one of the preceding claims, wherein said Ntls further comprises an anchoring element A1 at its C terminal end and/or wherein said Ctls further comprises an anchoring element A2 at its N terminal end, wherein A1 and/or A2 predominantly comprise glycine and serine residues, particularly wherein at least 60% of the amino acid residues of A1 and/or A2 are selected from glycine and serine residues.

6. The antibody or fragment thereof according to any one of the preceding claims, wherein the amino acid stretch present between

i) amino acid residue HC res25 according to Kabat and the first amino acid residue of the BNP in case of an incorporation of said heterologous amino acid sequence within CDRH1;

ii) amino acid residue HC res51 according to Kabat and the first amino acid residue of the BNP in case of an incorporation of said heterologous amino acid sequence within CDRH2;

iii) amino acid residue HC res92 according to Kabat and the first amino acid residue of the BNP in case of an incorporation of said heterologous amino acid sequence within CDRH3;

iv) amino acid residue LC res26 according to Kabat and the first amino acid residue of the BNP in case of an incorporation of said heterologous amino acid sequence within CDRL1;

v) amino acid residue LC res49 according to Kabat and the first amino acid residue of the BNP in case of an incorporation of said heterologous amino acid sequence within CDRL2; and/or

vi) amino acid residue LC res88 according to Kabat and the first amino acid residue of the BNP in case of an incorporation of said heterologous amino acid sequence within CDRL3

comprises the sequence of any one of SEQ ID NOs 26 to 38 or a sequence having at least 80% sequence identity with any one of SEQ ID NOs 26 to 38;

and wherein the amino acid stretch present between the last amino acid residue of said BNP and

i) amino acid residue HC res35a according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRH1;

ii) amino acid residue HC res57 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRH2;

iii) amino acid residue HC res106 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRH3;

iv) amino acid residue LC res 32 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRL1;

v) amino acid residue LC res57 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRL2; and/or

vi) amino acid residue LC res98 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRL3

comprises the sequence of any one of SEQ ID NOs 39 to 51 or a sequence having at least 80% sequence identity with any one of SEQ ID NOs 39 to 51.

7. The antibody or fragment thereof according to any one of the preceding claims, wherein said Ntls and/or said Ctls comprise(s) at least 3, 4, 5, 6, 7, 8, 9 or 10 and up to 30, 28, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11 or 10 amino acid residues in total.

8. The antibody or fragment thereof according to any one of the preceding claims, wherein the amino acid stretch present between

i) amino acid residue HC res25 according to Kabat and amino acid residue HC res35a according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRH1;

ii) amino acid residue HC res51 according to Kabat and amino acid residue HC res57 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRH2;

iii) amino acid residue HC res92 according to Kabat and amino acid residue HC res106 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRH3;

iv) amino acid residue LC res26 according to Kabat and amino acid residue LC res 32 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRL1;

v) amino acid residue LC res49 according to Kabat and amino acid residue LC res57 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRL2; and/or

vi) amino acid residue LC res88 according to Kabat and amino acid residue LC res98 according to Kabat in case of an incorporation of said heterologous amino acid sequence within CDRL3

comprises the sequence of any one of SEQ ID NOs 52 to 64 or a sequence having at least 80% sequence identity with any one of SEQ ID NOs 52 to 64.

9. The antibody or fragment thereof according to any one of the preceding claims, comprising at least one further natriuretic peptide, particularly wherein said BNP and said at least one further natriuretic peptide are incorporated within at least two separate CDR regions, more particularly wherein said at least one further natriuretic peptide is selected from ANP, BNP and CNP, most particularly from ANP and CNP.

10. The antibody or fragment thereof according to any one of the preceding claims, wherein said antibody or fragment thereof is a human or humanized antibody or fragment thereof, particularly wherein said antibody or fragment thereof is of the class IgG.

11. The antibody or fragment thereof according to any one of the preceding claims, wherein the light chain comprises or consists of the amino acid sequence of SEQ ID NO 66 and the heavy chain comprises or consists of the amino acid sequence of any one of SEQ ID NOs 442 to 444.

12. The antibody fragment according to any one of the preceding claims, wherein said antibody fragment is selected from the group consisting of Fab, Fab', Fab'-SH, F(ab')2, and Fv fragments;

diabodies; single domain antibodies (Dabs); linear antibodies; single-chain antibody molecules (scFv); and disulfide-stabilized Fv antibody fragments (dsFv).

13. A composition comprising the antibody or fragment thereof according to any one of claims 1 to 12 and optionally a pharmaceutically acceptable carrier.

14. A nucleic acid or a mixture of nucleic acids encoding the antibody or fragment thereof according to any one of claims 1 to 12.

15. A host cell comprising the nucleic acid or the mixture of nucleic acids according to claim 14.

16. A process for producing an antibody or fragment thereof, comprising culturing the host cell according to claim 15 under conditions suitable for expression of the antibody or fragment thereof.

17. The antibody or fragment thereof according to any one of claims 1 to 12 for use in a method for treatment.

18. The antibody or fragment thereof according to any one of claims 1 to 12 for use in the treatment of cardiovascular, renal, pulmonary, skeletal, ocular, thromboembolic or fibrotic diseases or disorders, dwarfism, achondroplasia or other cGMP-related and/or natriuretic peptide responsive disorders.