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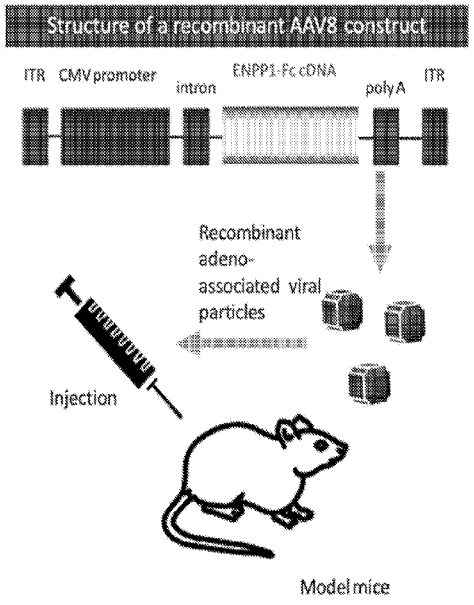
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(54) Title: TREATMENT OF DISEASES INVOLVING DEFICIENCY OF ENPP1 OR ENPP3

FIG. 4 – SCHEMATIC VIEW OF ADMINSTRATION



(57) Abstract: The present disclosure provides, among other things, vectors for expression of ENPP1 or ENPP3 *in vivo* and methods for the treatment of diseases of calcification and ossification in a subject.

[Continued on next page]

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TREATMENT OF DISEASES INVOLVING DEFICIENCY OF ENPP1 OR ENPP3

Cross Reference

This application claims priority to U.S. Application No. 62/794,450 filed on January 18, 2019 (01/18/2019), U.S. Application No. 62/821,692 filed on March 21, 2019 (03/21/2019), and U.S. Application No. 62/877,044 filed on July 22, 2019 (07/22/2019), the contents of each of which are herein incorporated by reference in their entirety.

Field

The invention generally relates to the treatment of diseases involving a deficiency of ENPP1 or ENPP3 by providing nucleic acid encoding ENPP1 or ENPP3 to a mammal.

Background

ENPP1 (also known as PC-1) is a type 2 extracellular membrane-bound glycoprotein located on the mineral-depositing matrix vesicles of osteoblasts and chondrocytes and hydrolyzes extracellular nucleotides (principally ATP) into adenosine monophosphate (AMP) and inorganic pyrophosphate (PPi). PPi functions as a potent inhibitor of ectopic tissue mineralization by binding to nascent hydroxyapatite (HA) crystals, thereby preventing the future growth of these crystals. ENPP1 generates PPi via hydrolysis of nucleotide triphosphates (NTPs), Progressive Ankylosis Protein (ANK) transports intracellular PPi into the extracellular space, and Tissue Non-specific Alkaline Phosphatase (TNAP) removes PPi via direct hydrolysis of PPi into Pi. *WO 2011/113027-Quinn et al., WO 2012/125182 –Quinn et al, WO 2016/100803 –Quinn et al and WO 2017/218786 –Yan et al.* describe NPP1.

ENPP3 like ENPP1 also belongs to the phosphodiesterase I /nucleotide pyrophosphatase enzyme family. These enzymes are type II transmembrane proteins that catalyze the cleavage of phosphodiester and phosphosulfate bonds of a variety of molecules, including deoxynucleotides, NAD, and nucleotide sugars. ENPP1 been shown to be effective in treating certain diseases of ectopic tissue calcification, such as reducing generalized arterial calcifications in a mouse model for GACI (generalized arterial calcification of infants), which is a severe disease occurring in

infants and involving extensive arterial calcification (*Albright, et al., 2015, Nature Comm. 10006*).

Summary of The Invention

In one aspect, the disclosure provides a recombinant polynucleotide encoding a recombinant polypeptide comprising ectonucleotide pyrophosphatase/phosphodiesterase-1 (ENPP1) or ectonucleotide pyrophosphatase/phosphodiesterase-3 (ENPP3).

In another aspect, the disclosure provides a viral vector comprising any of the recombinant polynucleotides described herein

In some embodiments, the recombinant polynucleotide encodes a human ENPP1 or a human ENPP3 polypeptide. Thus, the disclosure also provides a viral vector comprising a recombinant polynucleotide encoding a recombinant polypeptide comprising ectonucleotide pyrophosphatase/phosphodiesterase-1 (ENPP1) or ectonucleotide pyrophosphatase/phosphodiesterase-3 (ENPP3).

In some embodiments of any of the polynucleotides or viral vectors described herein, the recombinant polypeptide is an ENPP1 fusion polypeptide.

In some embodiments of any of the polynucleotides or viral vectors described herein, the recombinant polypeptide is an ENPP3 fusion polypeptide.

In some embodiments of any of the polynucleotides or viral vectors described herein, the ENPP1 fusion polypeptide is an ENPP1-Fc fusion polypeptide or ENPP1-Albumin fusion polypeptide.

In some embodiments of any of the polynucleotides or viral vectors described herein, the ENPP3 fusion polypeptide is an ENPP3-Fc fusion polypeptide or ENPP3-Albumin fusion polypeptide.

In some embodiments of any of the polynucleotides or viral vectors described herein, the recombinant polypeptide comprises a signal peptide fused to ENPP1 or ENPP3.

In some embodiments of any of the polynucleotides or viral vectors described herein, the signal peptide is Azurocidin signal peptide or NPP2 signal peptide or NPP7 signal peptide.

In some embodiments of any of the polynucleotides or viral vectors described herein, the viral vector is Adeno-Associated Viral Vector, or Herpes Simplex Vector, or Alphaviral Vector, or Lentiviral Vectors. In one aspect of the invention, the serotype of Adeno-Associated viral vector

(AAV) is AAV1, or AAV2, or AAV3, or AAV4, or AAV5, or AAV6, or AAV7, or AAV8, or AAV9, or AAV-rh74.

In yet another aspect, the disclosure provides an Adeno-Associated viral vector comprising a recombinant polypeptide encoding an ENPP1-Fc fusion polypeptide.

In yet another aspect, the disclosure provides an Adeno-Associated viral vector comprising a recombinant polypeptide encoding a recombinant polypeptide comprising an Azurocidin signal peptide fused to ENPP1-Fc fusion polypeptide.

In some embodiments, the viral vector is not an insect viral vector, such as a baculoviral vector.

In some embodiments, the viral vector is capable of infecting mammalian cells such as human cells (e.g human liver cells or HEK cells, HeLa or A549 or Hepatocytes). In some embodiments the viral vector is capable of infecting, entering, and/or fusing with mammalian cells, such as human cells. In some embodiments, all or a functional part (e.g., that capable of expressing a polypeptide described herein) of the polynucleotide of the viral vector integrates or is integrated into the genome of the cell contacted by a viral vector described herein. In some embodiments, all or a functional part of the polynucleotide of the viral vector is capable of persisting in an extrachromosomal state without integrating into the genome of the mammaliancell contacted with a viral vector described herein.

In some embodiments, the recombinant polynucleotide comprises a vector or a plasmid that encodes viral proteins and/or a human ENPP1. In some embodiments, the recombinant polynucleotide comprises a vector or a plasmid that encodes viral proteins and/or a human ENPP3. In some embodiments, the vector or said plasmid is capable of expressing the encoded polypeptide comprising an Azurocidin signal peptide fused to ectonucleotide pyrophosphatase/phosphodiesterase-1 (ENPP1) or to ectonucleotide pyrophosphatase/phosphodiesterase-3 (ENPP3).

In some embodiments, the encoded polypeptide comprises an Azurocidin signal peptide fused to ectonucleotide pyrophosphatase/phosphodiesterase-1 (ENPP1) comprises a transmembrane domain, a somatomedin domain, catalytic domain and a nuclease domain.

In some embodiments, the encoded polypeptide comprises an Azurocidin signal peptide fused to ectonucleotide pyrophosphatase/phosphodiesterase-1 (ENPP1) is secreted into the cytosol.

In some embodiments, the recombinant polynucleotide encoding polypeptide comprises a transmembrane domain fused to ectonucleotide pyrophosphatase/phosphodiesterase-1 (ENPP1) is not secreted and is membrane bound.

In some embodiments, the disclosure provides a recombinant polynucleotide encoding a polypeptide comprising ectonucleotide pyrophosphatase/phosphodiesterase-1 (ENPP1) In some embodiments the polypeptide comprising ectonucleotide pyrophosphatase/phosphodiesterase-1 (ENPP1) comprises amino acid residues of SEQ ID NO: 1.

In some embodiments, the encoded polypeptide comprises an Azurocidin signal peptide fused to ectonucleotide pyrophosphatase/phosphodiesterase-1 (ENPP1)

In some embodiments, the encoded polypeptide comprising an Azurocidin signal peptide fused to ectonucleotide pyrophosphatase/phosphodiesterase-1 (ENPP1) lacks polyaspartic domain or negatively charged bone targeting domain.

In some embodiments, the vector is a viral vector. In some embodiments the viral vector is an Adeno-associated viral (AAV) vector. In some embodiments, any of the polynucleotidesdescribed herein encodes the Azurocidin signal peptide fused to the ENPP1 or Azurocidin signal peptide fused to the ENPP3 and the ENPP1 or the ENPP3 fused to an Fc polypeptide to form in amino to carboxy terminal order Azurocidin signal peptide-ENPP1-Fc or Azurocidin signal peptide-ENPP3-Fc, respectively.

In some embodiments, the recombinant polynucleotide encodes the Azurocidin signal peptide fused to ENPP1 or the Azurocidin signal peptide fused to ENPP3 and the ENPP1 or the ENPP3 fused to human serum albumin to form in amino to carboxy terminal order Azurocidin signal peptide-ENPP1-albumin or Azurocidin signal peptide-ENPP3-albumin, respectively.

In some embodiments, the Fc or albumin sequence is fused directly to the C terminus of the ENPP1 or ENPP3 protein. In some embodiments, the Fc or albumin sequence is fused through a linker, such as a flexible linker to the C terminus of the ENPP1 or ENPP3 protein. In some embodiments, the linker is selected from SEQ ID No: 57-88.

In some embodiments, the viral vector comprising and capable of expressing a nucleic acid sequence encoding a signal peptide fused to the N-terminus of ENPP1 or ENPP3. In some embodiments of the viral vector, the vector comprises a promoter. In some embodiments of the viral vector, the promoter is a liver specific promoter.

In some embodiments of the viral vector, the liver specific promoter is selected from the group consisting of: albumin promoter, phosphoenol pyruvate carboxykinase (PEPCK) promoter and alpha-1-antitrypsin promoter. In some embodiments of the viral vector, the vector comprises a sequence encoding a polyadenylation signal.

In some embodiments of the viral vector, the signal peptide is an Azurocidin signal peptide. In some embodiments of the viral vector, the viral vector is an Adeno-associated viral (AAV) vector. In some embodiments of the viral vector, the AAV vector having a serotype is selected from the group consisting of: AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, and AAV-rh74.

In some embodiments of the viral vector, the polynucleotide of the invention encodes Azurocidin signal peptide fused to ENPP1 or Azurocidin signal peptide fused to ENPP3, and the ENPP1 or the ENPP3 fused to an Fc polypeptide to form in amino to carboxy terminal order Azurocidin signal peptide-ENPP1-Fc or Azurocidin signal peptide-ENPP3-Fc, respectively.

In some embodiments of the viral vector, the polynucleotide encodes Azurocidin signal peptide fused to ENPP1 or Azurocidin signal peptide fused to ENPP3, and the ENPP1 or the ENPP3 fused to human serum albumin to form in amino to carboxy terminal order Azurocidin signal peptide-ENPP1-albumin or Azurocidin signal peptide-ENPP3-albumin, respectively.

In yet another aspect, the disclosure provides a cell (e.g., a mammalian cell, such as a rodent cell, a non-human primate cell, or a human cell) comprising any of the polynucleotides described herein.

In some embodiments, the invention also provides a method of obtaining a recombinant viral vector comprising the steps of:

i. providing a cell comprising a polynucleotide of the invention,

ii. maintaining the cell under conditions adequate for assembly of the virus, and

iii. purifying the viral vector produced by the cell.

In another aspect, the disclosure provides a method of producing a recombinant viral vector. The method comprises:

i. providing a cell or population of cells comprising a polynucleotide described herein, wherein the cell expresses viral proteins essential for packaging or assembly of the polynucleotide into a recombinant viral vector; and

ii. maintaining the cell or population of cells under conditions adequate for the assembly of packaging of said recombinant viral vector.

In some embodiments, the method comprises purifying the viral vector from the cell or population of cells, or from the media in which the cell or population of cells were maintained.

In some embodiments, the cell is a mammalian cell, such as a rodent cell (e.g., rat cell, mouse cell, hamster cell), non-human primate cell, or a human cell (e.g., HEK293, HeLa or A549).

In some embodiments, the method further comprises introducing into the cell or population of cells a recombinant nucleic acid encoding one or more viral proteins (such as those that are essential for packaging or assembly of a viral vector), e.g., infecting the cell or population of cells with a helper virus containing such recombinant nucleic acid, transfection or the cell or population of cells with a helper plasmids comprising such recombinant nucleic acid, and the like.

In some embodiments, the viral vector is capable of expressing one or more polypeptides described herein upon infection in a target cell.

In some embodiments, the disclosure provides a pharmaceutical composition comprising the purified viral vector as described herein. In some embodiments, the disclosure provides a sterile pharmaceutical composition comprising the strerile/endotoxin free purified viral vector as described herein.

In another aspect, the disclosure provides a viral vector obtained and purified by the any of the methods described herein.

In another aspect, the disclosure provides a pharmaceutical composition comprising any of the viral vectors obtained and purified by any of the methods described herein.

In certain embodiments, the invention provides a method of providing ENPP1 or ENPP3 to a mammal, the method comprising administering to the mammal a viral vector of the invention.

In certain embodiments, the disclosure provides a method of expressing ENPP1 or ENPP3 in a mammal (e.g., a human, such as a human in need of such expression), the method

comprising administering to the mammal any of the viral vectors described herein. Prior to, at the same time as, and/or following administration of the viral vector to the mammal, the method can further include detecting and/or measuring in a biological sample obtained from the mammal one or more of the following parameters: expression of ENPP1 and/or ENPP3, levels of activity of ENPP1 and/or ENPP3, and/or pyrophosphate levels or concentration. In some embodiments, the one or more parameters are detected or measured within a week, 1-2 weeks, and/or within a month, following administration of the viral vector to the mammal. In some embodiments, the mammal (e.g., a human) is one with an ENPP1 or ABCC6 deficiency.

In another aspect, the disclosure provides a pharmaceutical composition comprising any of the viral vectors as described herein and a physiologically compatible carrier.

In some embodiments, the disclosure provides a method of preventing or reducing the progression of a condition or disease in a mammal in need thereof, the method comprising administering to said mammal a therapeutically effective amount of a composition according to the invention, wherein the condition or disease includes, without limitation, one or more of the following: a deficiency of NPP1, a low level of PPi, a progressive disorder characterized by accumulation of deposits of calcium and other minerals in arterial and/or connective tissues, ectopic calcification of soft tissue, arterial or venous calcification, calcification of heart tissue, such as aorta tissue and coronary tissue, Pseudoxanthoma elasticum (PXE), X-linked hypophosphatemia (XLH), Chronic kidney disease (CKD), Mineral bone disorders (MBD), vascular calcification, pathological calcification of soft tissue, pathological ossification of soft tissue, Generalized arterial calcification of infants (GACI), and Ossification of posterior longitudinal ligament (OPLL), whereby said disease in said mammal is prevented or its progress reduced.

In another aspect, the disclosure provides a method of treating, preventing, and/or ameliorating a disease or disorder of pathological calcification or pathological ossification in a subject in need thereof, the method comprising administering a therapeutically effective amount of any of the viral vectors described herein, thereby treating, preventing, or ameliorating said disease or disorder. In some embodiments, the viral vector comprises a polynucleotide encoding a human ENPP1 or a human ENPP3 polypeptide.

In another aspect, the disclosure provides a method of treating a subject having an ENPP1 protein deficiency, the method comprising administering a therapeutically effective amount of a viral vector which encodes a recombinant ENPP1 or ENPP3 polypeptide to a subject, thereby treating the subject. In one aspect of the invention, the viral vector encodes a human ENPP1 or a human ENPP3 polypeptide.

In another aspect, the subject has a disease or disorder or an ENPP1 protein deficiency that is associated with a loss of function mutation in an NPP1 gene of the subject or a loss of function mutation in an ABCC6 gene of the subject.

In some embodiments of any of the methods described herein, the viral vector is an AAV vector encoding ENPP1-Fc fusion polypeptide, and the vector is administered to a subject at a dosage of 1×10^{12} to 1×10^{15} vg/kg , preferably 1×10^{13} to 1×10^{14} vg/kg.

In some embodiments of any of the methods described herein, the viral vector is an AAV vector encoding ENPP1-Fc fusion polypeptide, and the vector is administered to a subject at a dosage of 5×10^{11} -$5x10^{15}$ vg/kg.

In some embodiments of any of the methods described herein, the viral vector is an AAV vector encoding ENPP1-Fc fusion polypeptide, and approximately $1x10^{12}$-$1X10^{15}$ vg/kg per subject is administered for delivering and expressing an ENPP1-Fc polypeptide.

In some embodiments of any of the methods described herein, the viral vector is an AAV vector encoding ENPP3-Fc fusion polypeptide, and the vector is administered to a subject at a dosage of 1×10^{12} to 1×10^{15} vg/kg , preferably 1×10^{13} to 1×10^{14} vg/kg.

In some embodiments of any of the methods described herein, the viral vector is an AAV vector encoding ENPP3-Fc fusion polypeptide, and the vector is administered to a subject at a dosage of 5×10^{11} -$5x10^{15}$ vg/kg.

In some embodiments of any of the methods described herein, the viral vector is an AAV vector encoding ENPP3-Fc fusion polypeptide, and approximately $1x10^{12}$-$1X10^{15}$ vg/kg per subject is administered for delivering and expressing an ENPP3-Fc polypeptide.

In some embodiments of any of the methods described herein, administration of AAV vectors encoding an ENPP1-Fc polypeptide to a subject produces a dose dependent increase in plasma pyrophosphate (PPi) and a dose dependent increase in plasma ENPP1 concentration in said subject.

Prior to, at the same time as, and/or following administration of the viral vector to the mammal, any of the methods described herein can further include detecting and/or measuring in a biological sample obtained from the mammal one or more of the following parameters: expression of ENPP1 and/or ENPP3, levels of activity of ENPP1 and/or ENPP3, and/or pyrophosphate levels or concentration. In some embodiments, the one or more parameters are detected or measured within a week, 1-2 weeks, and/or within a month, following administration of the viral vector to the mammal.

In yet another aspect, , the disclosure provides a method of treating or preventing a disease or disorder of pathological calcification or pathological ossification in a subject in need

thereof, comprising administering a therapeutically effective amount of a viral vector which encodes a recombinant ENPP1 or ENPP3 polypeptide to said subject, thereby treating or preventing said disease or disorder.

In another aspect, the disclosure provides a method of of treating a subject having an ENPP1 protein deficiency, comprising administering a therapeutically effective amount of a viral vector which encodes a recombinant ENPP1 or ENPP3 polypeptide to said subject, thereby treating said subject.

In some embodiments of any of the methods described herein, said disease or disorder or said ENPP1 protein deficiency is associated with a loss of function mutation in an NPP1 gene or a loss of function mutation in an ABCC6 gene in said subject.

In some embodiments of any of the methods described herein, said viral vector encodes recombinant ENPP1 polypeptide.

In some embodiments of any of the methods described herein, said viral vector encodes recombinant ENPP3 polypeptide.

In some embodiments of any of the methods described herein, said viral vector encodes a recombinant ENPP1-Fc fusion polypeptide or a recombinant ENPP1-albumin fusion polypeptide.

In some embodiments of any of the methods described herein, said viral vector encodes a recombinant ENPP3-Fc fusion polypeptide or a recombinant ENPP3-albumin fusion polypeptide.

In some embodiments of any of the methods described herein, said viral vector encodes a recombinant polypeptide comprising a signal peptide fused to ENPP1 or ENPP3.

In some embodiments of any of the methods described herein, said vector encodes ENPP1-Fc or ENPP1-albumin.

In some embodiments of any of the methods described herein, said signal peptide is an azurocidin signal peptide, an NPP2 signal peptide, or an NPP7 signal peptide.

In some embodiments of any of the methods described herein, the viral vector is Adeno-Associated Viral Vector, or Herpes Simplex Vector, or Alphaviral Vector, or Lentiviral Vectors.

In some embodiments of any of the methods described herein, the serotype of Adeno-Associated viral vector (AAV) is AAV1, or AAV2, or AAV3, or AAV4, or AAV5, or AAV6, or AAV7, or AAV8, or AAV9, or AAV-rh74.

In some embodiments of any of the methods described herein, the viral vector is an Adeno-Associated viral (AAV) vector encoding a recombinant polypeptide comprising an Azurocidin signal peptide fused to ENPP1-Fc fusion polypeptide.

In some embodiments of any of the methods described herein, said AAV vector encoding said ENPP1-Fc fusion polypeptide is administered to subjects at a dosage of 1×10^{12} to 1×10^{15} vg/kg.

In some embodiments of any of the methods described herein, said dosage is 1×10^{13} to 1×10^{14} vg/kg.

In some embodiments of any of the methods described herein, said AAV vector is administered to a subject at a dosage of 5×10^{11} -$5x10^{15}$ vg/kg.

In some embodiments of any of the methods described herein, said vector is an AAV vector encoding ENPP1-Fc and is administered to a subject at dosage of $1x10^{12}$-$1X10^{15}$ vg/kg. In some embodiments of any of the aforesaid methods, wherein administration of said AAV vector encoding ENPP1-Fc polypeptide to a subject produces a dose dependent increase in plasma pyrophosphate (PPi) and a dose dependent increase in plasma ENPP1 concentration in said subject.

In another aspect, the disclosure features a viral vector comprising a polynucleotide sequence encoding a polypeptide comprising the catalytic domain of an ENPP1 or an ENPP3 protein.

In some embodiments of any of the viral vectors described herein, polypeptide sequence comprises the extracellular domain of an ENPP1 or ENPP3 protein.

In some embodiments of any of the viral vectors described herein, the polypeptide comprises the transmembrane domain of an ENPP1 or ENPP3 protein.

In some embodiments of any of the viral vectors described herein, the polypeptide comprises the nuclease domain of an ENPP1 or ENPP3 protein.

In some embodiments of any of the viral vectors described herein, the polypeptide comprises residues 99-925(Pro Ser Cys to Gln Glu Asp) of SEQ ID NO: 1.

In some embodiments of any of the viral vectors described herein, the polypeptide comprises residues 31-875 (Leu Leu Val to Thr Thr Ile) of SEQ ID NO: 7.

In some embodiments of any of the viral vectors described herein, the polypeptide comprises residues 191-591 (Val Glu Glu to Gly Ser Leu) of SEQ ID NO: 1.

In some embodiments of any of the viral vectors described herein, the polypeptide comprises residues 140-510 (Leu Glu Glu to Glu Val Glu) of SEQ ID NO: 7.

In some embodiments of any of the viral vectors described herein, the polypeptide comprises residues 1-827 (Pro Ser Cys to Gln Glu Asp) of SEQ ID NO: 92.

In some embodiments of any of the viral vectors described herein, the polypeptide comprises residues 1-833 (Phe Thr Ala to Gln Glu Asp) of SEQ ID NO: 89 or residues 1-830 (Gly Leu Lys to Gln Glu Asp) of SEQ ID NO: 91

In some embodiments of any of the viral vectors described herein, the viral vector is not an insect viral vector.

In some embodiments of any of the viral vectors described herein, the viral vector infects or is capable of infecting mammalian cells.

In some embodiments of any of the viral vectors described herein, the polynucleotide sequence encodes a promoter sequence.

In some embodiments of any of the viral vectors described herein, said promoter is a liver specific promoter.

In some embodiments of any of the viral vectors described herein, the liver specific promoter is selected from the group consisting of: albumin promoter, phosphoenol pyruvate carboxykinase (PEPCK) promoter, and alpha-1-antitrypsin promoter.

In some embodiments of any of the viral vectors described herein, the polynucleotide sequence comprises a nucleotide sequence encoding a polyadenylation signal.

In some embodiments of any of the viral vectors described herein, the polynucleotide encodes a signal peptide amino-terminal to nucleotide sequence encoding the ENPP1 or ENPP3 protein.

In some embodiments of any of the viral vectors described herein, the signal peptide is an Azurocidin signal peptide.

In some embodiments of any of the viral vectors described herein, the viral vector is an Adeno-associated viral (AAV) vector.

In some embodiments of any of the viral vectors described herein, said AAV vector has a serotype selected from the group consisting of: AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, and AAV-rh74.

In some embodiments of any of the viral vectors described herein, said polynucleotide sequence encodes said Azurocidin signal peptide fused to said ENPP1 or said Azurocidin signal peptide fused to said ENPP3, and said ENPP1 or said ENPP3 fused to an Fc polypeptide to form in amino to carboxy terminal order Azurocidin signal peptide-ENPP1-Fc or Azurocidin signal peptide-ENPP3-Fc, respectively.

In some embodiments of any of the viral vectors described herein, said polynucleotide sequence encodes said Azurocidin signal peptide fused to said ENPP1 or said Azurocidin signal peptide fused to said ENPP3, and said ENPP1 or said ENPP3 fused to human serum albumin to form in amino to carboxy terminal order Azurocidin signal peptide-ENPP1-albumin or Azurocidin signal peptide-ENPP3-albumin, respectively.

In some embodiments of any of the viral vectors described herein, the polypeptide is a fusion protein comprising: (i) an ENPP1 protein or an ENPP3 protein and (ii) a half-life extending domain.

In some embodiments of any of the viral vectors described herein, the half-life extending domain is an IgG Fc domain or a functional fragment of the IgG Fc domain capable of extending the half-life of the polypeptide in a mammal, relative to the half-life of the polypeptide in the absence of the IgG Fc domain or functional fragment thereof.

In some embodiments of any of the viral vectors described herein, the half-life extending domain is an albumin domain or a functional fragment of the albumin domain capable of extending the half-life of the polypeptide in a mammal, relative to the half-life of the polypeptide in the absence of the albumin domain or functional fragment thereof.

In some embodiments of any of the viral vectors described herein, the half-life extending domain is carboxyterminal to the ENPP1 or ENPP3 protein in the fusion protein.

In some embodiments of any of the viral vectors described herein, the IgG Fc domain comprises the amino acid sequence as shown in SEQ ID NO: 34

In some embodiments of any of the viral vectors described herein, the albumin domain comprises the amino acid sequence as shown in SEQ ID NO: 35

In some embodiments of any of the viral vectors described herein, the polynucleotide encodes a linker sequence.

In some embodiments of any of the viral vectors described herein, the linker sequence is selected from the group consisting of SINs: 57 to 88.

In some embodiments of any of the viral vectors described herein, the linker sequence joins the ENPP1 or ENPP3 protein and the half-life extending domain of the fusion protein.

In some embodiments of any of the viral vectors described herein, the polypeptide comprises the amino acid sequence depicted in SEQ ID NO: 89, 91, 92 and 93.

In another aspect, the disclosure provides a method for producing a recombinant viral vector, the method comprising:

i. providing a cell or population of cells comprising a polynucleotide encoding a polypeptide comprising the catalytic domain of an ENPP1 or an ENPP3 protein, wherein the cell expresses viral proteins essential for packaging and/or assembly of the polynucleotide into a recombinant viral vector; and

ii. maintaining the cell or population of cells under conditions adequate for the assembly of packaging of said recombinant viral vector comprising the polynucleotide.

In some embodiments of any of the methods described herein, the mammalian cell is a rodent cell or a human cell.

In some embodiments of any of the methods described herein, the viral vector is any one of the viral vectors described herein.

In some embodiments, any of the methods described herein can further comprise purifying the recombinant viral vector from the cell or population of cells, or from the media in which the cell or population of cells were maintained.

In another aspect, the disclosure features the recombinant viral vector purified from the methods for producing and/or purifying a recombinant viral vector described herein.

In another aspect, the disclosure provides a pharmaceutical composition comprising any one of the viral vectors or recombinant viral vectors described herein and a pharmaceutically acceptable carrier.

In yet another aspect, the disclosure provides a method of preventing or reducing the progression of a disease in a mammal in need thereof, the method comprising: administering to said mammal a therapeutically effective amount of any one of the pharmaceutical compositions described herein to thereby prevent or reduce the progression of the disease or disorder.

In some embodiments of any of the methods described herein, the mammal is a human.

In some embodiments of any of the methods described herein, the disease is selected from the group consisting of: X-linked hypophosphatemia (XLH), Chronic kidney disease (CKD), Mineral bone disorders (MBD), vascular calcification, pathological calcification of soft tissue, pathological ossification of soft tissue, PXE, Generalized arterial calcification of infants (GACI), and Ossification of posterior longitudinal ligament (OPLL).

In another apect, the disclosure providesa method of treating or preventing a disease or disorder of pathological calcification or pathological ossification in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of any one of the viral vectors or pharmaceutical compositions described herein, thereby treating or preventing said disease or disorder.

In another aspect, the disclosure features a method of treating a subject having an ENPP1 protein deficiency, the method comprising administering to the subject a therapeutically effective amount of any one of the viral vectors or pharmaceutical compositions described herein, thereby treating said subject.

In some embodiments of any of the methods described herein, said disease or disorder or said ENPP1 protein deficiency is associated with a loss of function mutation in an NPP1 gene or a loss of function mutation in an ABCC6 gene in said subject.

In some embodiments of any of the methods described herein, the viral vector or pharmaceutical composition is administered at a dosage of 1×10^{12} to 1×10^{15} vg/kg of the subject or mammal.

In some embodiments of any of the methods described herein, the viral vector or pharmaceutical composition is administered at a dosage of 1×10^{13} to 1×10^{14} vg/kg of the subject or mammal.

In some embodiments of any of the methods described herein, the viral vector or pharmaceutical composition is administered at a dosage of 5×10^{11} -$5x10^{15}$ vg/kg of the subject or mammal.

In some embodiments of any of the methods described herein, the viral vector or pharmaceutical composition is administered at a dosage of $1x10^{12}$-$1x10^{15}$ vg/kg of the subject or mammal.

In some embodiments of any of the methods described herein, administration of said viral vector or pharmaceutical composition to the subject or mammal increases plasma pyrophosphate (PPi) and/or plasma ENPP1 or ENPP3 concentration in said subject or mammal.

In some embodiments, any of the aforesaid methods canfurther comprise detecting or measuring in a biological sample obtained from the subject or mammal one or more of the following parameters: (i) the concentration of pyrophosphate, (ii) the expression level of ENPP1 or ENPP3, and (iii) the enzymatic activity of ENPP1 or ENPP3.

In some embodiments of any of the methods described herein, the detecting or measuring occurs before administering the viral vector or pharmaceutical composition.

Brief Description of the Figures

Fig. 1 – Schematic showing AAV construct

Fig. 2- Figure showing increased amount of expression of ENPP1when using Azurocidin signal sequence as compared with NPP2 and NPP7 signal sequences.

Fig. 3 – Plasmid map of vector expressing ENPP1- Fc fusion

Fig. 4 – Schematic view showing the administration of viral particles comprising ENPP1 constructs to model mice.

Fig. 5 – Figure showing dose dependent increase in ENPP1 activity in blood plasma samples obtained from control, low dose and high dose mice cohorts collected at 7 days, 28 days and 56 days post administration of viral vector.

Fig. 6 - Figure showing dose dependent increase in ENPP1 concentration in blood plasma samples obtained from control, low dose and high dose mice cohorts collected at 7 days, 28 days and 56 days post administration of viral vector.

Fig. 7- Figure showing dose dependent increase in Plasma PPi concentration in blood plasma samples obtained from control, low dose and high dose mice cohorts collected at 7 days, 28 days and 56 days post administration of viral vector.

Fig. 8 – Figure showing persistent expression of Enpp1 for up to 112 days post viral vector administration.

Fig. 9 – Figure showing dose dependent increase in ENPP1 activity in blood plasma samples obtained from control, low dose and high dose mice cohorts collected at 7 days, 28 days, 56 days and 112 days post administration of viral vector.

Detailed Description according to the invention

The invention pertains to delivery of nucleic acid encoding mammal ENPP1 or mammal ENPP3 to a mammal having a deficiency in ENPP1 or ENPP3.

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, illustrative methods and materials are described. As used herein, each of the following terms has the meaning associated with it in this section.

The articles "*a*" and "*an*" are used herein to refer to one or to more than one (*i.e.*, to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

The following notation conventions are applied to the present disclosure for the sake of clarity. In any case, any teaching herein that does not follow this convention is still part of the present disclosure and can be fully understood in view of the context in which the teaching is disclosed. Protein symbols are disclosed in non-italicized capital letters. As non-limiting examples, 'ENPP1' refer to the protein. In certain embodiments, if the protein is a human protein, an 'h' is used before the protein symbol. In other embodiments, if the protein is a mouse protein, an 'm' is used before the symbol. Human ENPP1 is referred to as 'hENPP1', and mouse ENPP1 is referred to as 'mENPP1'. Human gene symbols are disclosed in italicized capital letters. As a non-limiting example, the human gene corresponding to the protein hENPP1 is *ENPP1*. Mouse gene symbols are disclosed with the first letter in upper case and the remaining

letters in lower case; further, the mouse gene symbol is italicized. As a non-limiting example, the mouse gene that makes the protein mEnpp1 is *Enpp1*. Notations about gene mutations are shown as uppercase text.

"Human ENPP1": Human NPP1 (NCBI accession NP_006199/ Uniprot-Swissprot P22413)

"Soluble human ENPP1": residues 96 to 925 of NCBI accession NP_006199

"Human ENPP3": Human NPP3 (UniProtKB/Swiss-Prot: O14638.2)

"Soluble human ENPP3": residues 49-875 of UniProtKB/Swiss-Prot: O14638.2

"*Reduction of calcification*": As used herein, reduction of calcification is observed by using non-invasive methods like X-rays, micro CT and MRI. Reduction of calcification is also inferred by using radio imaging with ^{99m}Tc-pyrophosphate (^{99m}PYP) uptake. The presence of calcifications in mice are evaluated via post-mortem by micro-computed tomography (CT) scans and histologic sections taken from the heart, aorta and kidneys with the use of dyes such as Hematoxylin and Eosin (H&E) and Alizarin red by following protocols established by Braddock et al. (*Nature Communications volume 6, Article number: 10006 (2015)*)

"*Enzymatically active*" with respect to ENPP1 or ENPP3: is defined as possessing ATP hydrolytic activity into AMP and PPi and/or AP3a hydrolysis to ATP. possessing substrate binding activity.

ATP hydrolytic activity may be determined as follows.

ATP Hydrolytic Activity of NPP1

NPP1 readily hydrolyzes ATP into AMP and PPi. The steady-state Michaelis-Menten enzymatic constants of NPP1 are determined using ATP as a substrate. NPP1 can be demonstrated to cleave ATP by HPLC analysis of the enzymatic reaction, and the identity of the substrates and products of the reaction are confirmed by using ATP, AMP, and ADP standards. The ATP substrate degrades over time in the presence of NPP1, with the accumulation of the enzymatic product AMP. Using varying concentrations of ATP substrate, the initial rate velocities for NPP1 are derived in the presence of ATP, and the data is fit to a curve to derive the enzymatic rate constants. At physiologic pH, the kinetic rate constants of NPP1 are Km=144 μM and $kcat_t$=7.8 s^{-1}.

ATP Hydrolytic Activity of NPP3

The enzymatic activity of NPP3 was measured with pNP-TMP or ATP as substrates. The NPP3 protein was incubated at 37°C in the presence of 100 mM Tris–HCl at pH 8.9 and either 5 mM pNP-TMP or 50 μM [γ-32P] ATP. The hydrolysis of pNP-TMP was stopped by a 10-fold dilution in 3% (w/v) trichloroacetic acid. Subsequently, the reaction mixture was neutralized with 60 μl 5 N NaOH and the formed p-nitrophenol (pNP) was quantified colorimetrically at 405 nm. The hydrolysis of ATP was arrested by the addition of 100 mM EDTA. One μl of the reaction mixture was analyzed by thin-layer chromatography on polyethyleneimine cellulose plates (Merck). Nucleotides and degradation products were separated by ascending chromatography in 750 mM KH2PO4 at pH 3.0. Radioactive spots were visualized by autoradiography. The nucleotidylated intermediate, formed during the hydrolysis of 50 μM [α-32P] ATP, was trapped according to Blytt et al. *(H.J. Blytt, J.E. Brotherton, L. Butler Anal. Biochem. 147 (1985), pp. 517-520)*, with slight modifications (*R. Gijsbers, H. Ceulemans, W. Stalmans, M. Bollen J. Biol. Chem., 276 (2001), pp. 1361-1368*). Following SDS–PAGE, the trapped intermediate was visualized by autoradiography. Bis-pNPP and pNPP were also tested as substrates for NPP3. The NPP3 isoforms were incubated in 100 mM Tris–HCl at pH 8.9 and either 5 mM bis-pNPP or pNPP for 2.5 h at 37°C. Subsequently, the formed pNP was quantified colorimetrically at 405 nm. *(Gijsbers R1, Aoki J, Arai H, Bollen M, FEBS Lett. 2003 Mar 13;538(1-3):60-4.)* At physiologic pH, NPP3 has a kcat value of about 2.59 (±0.04) s^{-1} and Km (< 8μM) values similar to ENPP1. (WO 2017/087936)

HPLC Protocol

The HPLC protocol used to measure ATP cleavage by NPP1, and for product identification, is modified from the literature (Stocchi et al., 1985, Anal. Biochem. 146:118-124). The reactions containing varying concentrations of ATP in 50 mM Tris pH 8.0, 140 mM NaCl, 5 mM KC1, 1 mM $MgCl_2$ and 1 mM $CaCl_2$ buffer are started by addition of 0.2-1 μM NPP1 and quenched at various time points by equal volume of 3M formic acid, or 0.5N KOH and re-acidified by glacial acetic acid to pH 6. The quenched reaction solution is diluted systematically, loaded onto a HPLC system (Waters, Milford Mass.), and substrates and products are monitored by UV absorbance at 254 or 259 nm. Substrates and products are

separated on a C18, 5um 250x4.6 mm HPLC column (Higgins Analytical, Mountain View, Calif.), using 15 mM ammonium acetate pH 6.0 solution, with a 0% to 10% (or 20%) methanol gradient. The products and substrate are quantified according to the integration of their correspondent peaks and the formula:

$$[\text{product/substrate}] = \frac{Area_{product/substrate} \,/\, \Sigma_{product/substrate}}{Area_{product} \,/\, \Sigma_{product} + Area_{substrate}/\Sigma_{substrate}} [\text{substrate}]$$

where [substrate] is the initial substrate concentration. The extinction coefficients of AMP, ADP and ATP used in the formula were 15.4 mM^{-1} cm'. If monitoring at 254 nm, substrate and product standards run on the same day as the reactions were used to convert integrated product/substrate peak areas to concentrations.

"*pathological calcification*": As used herein, the term refers to the abnormal deposition of calcium salts in soft tissues, secretory and excretory passages of the body causing it to harden. There are two types, dystrophic calcification which occurs in dying and dead tissue and metastatic calcification which elevated extracellular levels of calcium (hypercalcemia), exceeding the homeostatic capacity of cells and tissues. Calcification can involve cells as well as extracellular matrix components such as collagen in basement membranes and elastic fibers in arterial walls. Some examples of tissues prone to calcification include: Gastric mucosa – the inner epithelial lining of the stomach, Kidneys and lungs, Cornea, Systemic arteries and Pulmonary veins.

"*pathological ossification*": As used herein, the term refers to a pathological condition in which bone arises in tissues not in the osseous system and in connective tissues usually not manifesting osteogenic properties. Ossification is classified into three types depending on the nature of the tissue or organ being affected, endochondral ossification is ossification that occurs in and replaces cartilage. Intramembranous ossification is ossification of bone that occurs in and replaces connective tissue. Metaplastic ossification the development of bony substance in normally soft body structures; called also heterotrophic ossification.

A "deficiency" of NPP1 refers to a condition in which the subject has less than or equal to 5%-10% of normal levels of NPP1 in blood plasma. Normal levels of NPP1in healthy human subjects is approximately between 10 to 30 ng/ml. (Am J Pathol. 2001 Feb; 158(2): 543–554.)

A "low" level of PPi refers to a condition in which the subject has less than or equal to 2%-5% of normal levels of plasma pyrophosphate (PPi). Normal levels of Plasma PPi in healthy human subjects is approximately 1.8 to 2.6 μM. (Arthritis and Rheumatism, Vol. 22, No. 8 (August 1979))

"*Ectopic calcification*" refers to a condition characterized by a pathologic deposition of calcium salts in tissues or bone growth in soft tissues.

"*Ectopic calcification of soft tissue*" refers to inappropriate biomineralization, typically composed of calcium phosphate, hydroxyapatite, calcium oxalates and ocatacalcium phosphates occurring in soft tissues leading to loss of hardening of soft tissues. "Arterial calcification" refers to ectopic calcification that occurs in arteries and heart valves leading to hardening and or narrowing of arteries. Calcification in arteries is correlated with atherosclerotic plaque burden and increased risk of myocardial infarction, increased ischemic episodes in peripheral vascular disease, and increased risk of dissection following angioplasty.

"*Venous calcification*" refers to ectopic calcification that occurs in veins that reduces the elasticity of the veins and restricts blood flow which can then lead to increase in blood pressure and coronary defects

"*Vascular calcification*" refers to the pathological deposition of mineral in the vascular system. It has a variety of forms, including intimal calcification and medial calcification, but can also be found in the valves of the heart. Vascular calcification is associated with atherosclerosis, diabetes, certain heredity conditions, and kidney disease, especially CKD. Patients with vascular calcification are at higher risk for adverse cardiovascular events. Vascular calcification affects a wide variety of patients. Idiopathic infantile arterial calcification is a rare form of vascular calcification where the arteries of neonates calcify.

"*Brain calcification*" (BC) refers to a nonspecific neuropathology wherein deposition of calcium and other mineral in blood vessel walls and tissue parenchyma occurs leading to neuronal death and gliosis. Brain calcification is" often associated with various chronic and acute brain disorders including Down's syndrome, Lewy body disease, Alzheimer's disease, Parkinson's disease, vascular dementia, brain tumors, and various endocrinologic conditions

Calcification of heart tissue refers to accumulation of deposits of calcium (possibly including other minerals) in tissues of the heart, such as aorta tissue and coronary tissue.

"Chronic kidney disease (CKD)" As used herein, the term refers to abnormalities of kidney structure or function that persist for more than three months with implications for health. Generally excretory, endocrine and metabolic functions decline together in most chronic kidney diseases. Cardiovascular disease is the most common cause of death in patients with chronic kidney disease (CKD) and vascular calcification is one of the strongest predictors of cardiovascular risk. With decreasing kidney function, the prevalence of vascular calcification increases and calcification occurs years earlier in CKD patients than in the general population. Preventing, reducing and/or reversing vascular calcification may result in increased survival in patients with CKD.

Clinical symptoms of chronic kidney diseases include itching, muscle cramps, nausea, lack of appetite, swelling of feet and ankles, sleeplessness and labored breathing. Chronic kidney disease if left untreated tends to progress into End stage renal disease (ESRD). Common symptoms of ESRD include an inability to urinate, fatigue, malaise, weight loss, bone pain, changes in skin color, a frequent formation of bruises, and edema of outer extremities like fingers, toes, hands and legs. Calciphylaxis or calcific uremic arteriolopathy (CUA) is a condition that causes calcium to build up inside the blood vessels of the fat and skin. A subpopulation of patients suffering from ESRD can also develop Calciphylaxis. Common symptoms of Calciphylaxis include large purple net-like patterns on skin, deep and painful lumps that ulcerate creating open sores with black-brown crust that fails to heal, skin lesions on the lower limbs or areas with higher fat content, such as thighs, breasts, buttocks, and abdomen. A person with calciphylaxis may have higher than normal levels of calcium (hypercalcemia) and phosphate (hyperphosphatemia) in the blood. They may also have symptoms of hyperparathyroidism. Hyperparathyroidism occurs when the parathyroid glands make excess parathyroid hormone (PTH). Reduced plasma pyrophosphate (PPi) levels are also present in vascular calcification associated with end stage renal disease (ESRD).

Vascular calcifications associated with ESRD contributes to poor outcomes by increasing pulse pressure, causing or exacerbating hypertension, and inducing or intensifying myocardial infarctions and strokes. Most patients with ESRD do not die of renal failure, but from the cardiovascular complications of ESRD, and it is important to note that many very young patients

with ESRD on dialysis possess coronary artery calcifications. The histologic subtype of vascular calcification associated with CKD is known as Mönckeburg's sclerosis, which is a form of vessel hardening in which calcium deposits are found in the muscular layers of the medial vascular wall. This form of calcification is histologically distinct from intimal or neo-intimal vascular wall calcification commonly observed in atherosclerosis but identical to the vascular calcifications observed in human CKD patients, and in the rodent models of the disease described herein.

"Generalized arterial calcification of infants (GACI)" (also known as IACI)", as used herein, refers to a disorder affecting the circulatory system that becomes apparent before birth or within the first few months of life. It is characterized by abnormal accumulation of the mineral calcium (calcification) in the walls of the blood vessels that carry blood from the heart to the rest of the body (the arteries). Calcification often occurs along with thickening of the lining of the arterial walls (the intima). These changes lead to narrowing (stenosis) and stiffness of the arteries, which forces the heart to work harder to pump blood. As a result, heart failure may develop in affected individuals, with signs and symptoms including difficulty breathing, accumulation of fluid (edema) in the extremities, a bluish appearance of the skin or lips (cyanosis), severe high blood pressure (hypertension), and an enlarged heart (cardiomegaly). People with GACI may also have calcification in other organs and tissues, particularly around the joints. In addition, they may have hearing loss or softening and weakening of the bones referred to as rickets.

General arterial calcification (GACI) or Idiopathic Infantile Arterial Calcification (IIAC) characterized by abnormal accumulation of the mineral calcium (calcification) in the walls of the blood vessels that carry blood from the heart to the rest of the body (the arteries). The calcification often occurs along with thickening of the lining of the arterial walls (the intima). These changes lead to narrowing (stenosis) and stiffness of the arteries, which forces the heart to work harder to pump blood. As a result, heart failure may develop in affected individuals, with signs and symptoms including difficulty breathing, accumulation of fluid (edema) in the extremities, a bluish appearance of the skin or lips (cyanosis), severe high blood pressure (hypertension), and an enlarged heart (cardiomegaly).

"Arterial calcification" or "Vascular calcification" or "hardening of arteries", As used herein, the term refers to a process characterized by thickening and loss of elasticity of muscular arteries walls. The thickening and loss of elasticity occurs in two distinct sites, the intimal and medial layers of the vasculatures (Medial vascular calcification). Intimal calcification is associated with atherosclerotic plaques and medial calcification is characterized by vascular stiffening and arteriosclerosis. This results in a reduction of arterial elasticity and an increased propensity for morbidity and mortality due to the impairment of the cardiovascular system's hemodynamics.

"Mineral bone disorders (MBD)", as used herein, the term refers to a disorder characterized by abnormal hormone levels cause calcium and phosphorus levels in a person's blood to be out of balance. Mineral and bone disorder commonly occurs in people with CKD and affects most people with kidney failure receiving dialysis.

Osteopenia is a bone condition characterized by decreased bone density, which leads to bone weakening and an increased risk of bone fracture. Osteomalacia is a bone disorder characterized by decreased mineralization of newly formed bone. Osteomalacia is caused by severe vitamin D deficiency (which can be nutritional or caused by a hereditary syndrome) and by conditions that cause very low blood phosphate levels. Both osteomalacia and osteopenia increase the risk of breaking a bone. Symptoms of osteomalacia include bone pain and muscle weakness, bone tenderness, difficulty walking, and muscle spasms.

"Age related osteopenia", as used herein refers to a condition in which bone mineral density is lower than normal. Generally, patients with osteopenia have a bone mineral density T-score of between -1.0 and -2.5. Osteopenia if left untreated progresses into Osetoporosis where bones become brittle and are extremely prone to fracture.

"Ossification of posterior longitudinal ligament (OPLL)", as used herein, the term refers to a hyperostotic (excessive bone growth) condition that results in ectopic calcification of the posterior longitudinal ligament. The posterior longitudinal ligament connects and stabilizes the bones of the spinal column. The thickened or calcified ligament may compress the spinal cord, producing myelopathy. Symptoms of myelopathy include difficulty walking and difficulty with bowel and bladder control. OPLL may also cause radiculopathy, or compression of a nerve root. Symptoms of cervical radiculopathy include pain, tingling, or numbness in the neck, shoulder, arm, or hand.

Clinical symptoms and signs caused by OPLL are categorized as: (1) myelopathy, or a spinal cord lesion with motor and sensory disturbance of the upper and lower limbs, spasticity, and bladder dysfunction; (2) cervical radiculopathy, with pain and sensory disturbance of the upper limbs; and (3) axial discomfort, with pain and stiffness around the neck. The most common symptoms in the early stages of OPLL include dysesthesia and tingling sensation in hands, and clumsiness. With the progression of neurologic deficits, lower extremity symptoms, such as gait disturbance may appear. OPLL is detected on lateral plain radiographs, and the diagnosis and morphological details of cervical OPLL have been clearly demonstrated by magnetic resonance imaging (MRI) and computed tomography (CT).

"Pseudoxanthoma elasticum (PXE)", as used herein, the term refers a progressive disorder that is characterized by the accumulation of deposits of calcium and other minerals (mineralization) in elastic fibers. Elastic fibers are a component of connective tissue, which provides strength and flexibility to structures throughout the body. In PXE, mineralization can affect elastic fibers in the skin, eyes, and blood vessels, and less frequently in other areas such as the digestive tract. People with PXE may have yellowish bumps called papules on their necks, underarms, and other areas of skin that touch when a joint bends. Mineralization of the blood vessels that carry blood from the heart to the rest of the body (arteries) may cause other signs and symptoms of PXE. For example, people with this condition can develop narrowing of the arteries (arteriosclerosis) or a condition called claudication that is characterized by cramping and pain during exercise due to decreased blood flow to the arms and legs.

Pseudoxanthoma elasticum (PXE), also known as Grönblad–Strandberg syndrome, is a genetic disease that causes fragmentation and mineralization of elastic fibers in some tissues. The most common problems arise in the skin and eyes, and later in blood vessels in the form of premature atherosclerosis. PXE is caused by autosomal recessive mutations in the ABCC6 gene on the short arm of chromosome 16 (16p13.1). In some cases, a portion of infants survive GACI and end up developing Pseudoxanthoma elasticum (PXE) when they grow into adults. PXE is characterized by the accumulation of calcium and other minerals (mineralization) in elastic fibers, which are a component of connective tissue. Connective tissue provides strength and flexibility to structures throughout the body. Features characteristic of PXE that also occur in GACI include yellowish bumps called papules on the underarms and other areas of skin that touch when a joint bends (flexor areas); arterial stenosis, and abnormalities called angioid streaks

affecting tissue at the back of the eye (retinal hemorrhage), which is detected during an eye examination.

"End stage renal disease (ESRD):, as used herein, the term refers to an advanced stage of chronic kidney disease where kidneys of the patient are no longer functional. Common symptoms include fatigue associated with anemia (low blood iron), decreased appetite, nausea, vomiting, abnormal lab values including elevated potassium, abnormalities in hormones related to bone health, elevated phosphorus and/or decreased calcium, high blood pressure (hypertension), swelling in hands/legs/eyes/lower back (sacrum) and shortness of breath.

"Calcific uremic arteriolopathy (CUA)" or "Calciphylaxis", as used herein refers to a condition with high morbidity and mortality seen in patients with kidney disease, especially in those with end stage renal disease (ESRD). It is characterized by calcification of the small blood vessels located within the fatty tissue and deeper layers of the skin leading to blood clots, and the death of skin cells due to reduced blood flow caused by excessive calcification.

"Hypophosphatemic rickets", as used herein refers to a disorder in which the bones become soft and bend easily, due to low levels of phosphate in the blood. Symptoms usually begin in early childhood and can range in severity from bowing of the legs, bone deformities; bone pain; joint pain; poor bone growth; and short stature.

"*Hereditary Hypophosphatemic Rickets*" as used herein refers to a disorder related to low levels of phosphate in the blood (hypophosphatemia). Phosphate is a mineral that is essential for the normal formation of bones and teeth. Most commonly, it is caused by a mutation in the PHEX gene. Other genes that can be responsible for the condition include the CLCN5, DMP1, ENPP1, FGF23, and SLC34A3 genes. Other signs and symptoms of *hereditary hypophosphatemic rickets* can include premature fusion of the skull bones (craniosynostosis) and dental abnormalities. The disorder may also cause abnormal bone growth where ligaments and tendons attach to joints (enthesopathy). In adults, hypophosphatemia is characterized by a softening of the bones known as osteomalacia. Another rare type of the disorder is known as *hereditary hypophosphatemic rickets with hypercalciuria (HHRH)* wherein in addition to hypophosphatemia, this condition is characterized by the excretion of high levels of calcium in the urine (hypercalciuria).

"X-linked hypophosphatemia (XLH)", as used herein, the term X-linked hypophosphatemia (XLH), also called X-linked dominant hypophosphatemic rickets, or X-linked

Vitamin D-resistant rickets, is an X-linked dominant form of rickets (or osteomalacia) that differs from most cases of rickets in that vitamin D supplementation does not cure it. It can cause bone deformity including short stature and genu varum (bow leggedness). It is associated with a mutation in the PHEX gene sequence (Xp.22) and subsequent inactivity of the PHEX protein.

"Autosomal Recessive Hypophosphatemia Rickets type 2 (ARHR2)", as used herein, the term refers to a hereditary renal phosphate-wasting disorder characterized by hypophosphatemia, rickets and/or osteomalacia and slow growth. Autosomal recessive hypophosphatemic rickets type 2 (ARHR2) is caused by homozygous loss-of-function mutation in the ENPP1 gene.

"*Autosomal Dominant Hypophosphatemic Rickets (ADHR)*", as used herein refers to a rare hereditary disease in which excessive loss of phosphate in the urine leads to poorly formed bones (rickets), bone pain, and tooth abscesses. ADHR is caused by a mutation in the fibroblast growth factor 23 (FGF23). ADHR is characterized by impaired mineralization of bone, rickets and/or osteomalacia, suppressed levels of calcitriol (1, 25-dihydroxyvitamin D3), renal phosphate wasting, and low serum phosphate. Mutations in FGF23 render the protein more stable and uncleavable by proteases resulting in enhanced bioactivity of FGF23. The enhanced activity of FGF23 mutants reduce expression of sodium-phosphate co-transporters, NPT2a and NPT2c, on the apical surface of proximal renal tubule cells, resulting in renal phosphate wasting.

Hypophosphatemic rickets (previously called vitamin D-resistant rickets) is a disorder in which the bones become painfully soft and bend easily, due to low levels of phosphate in the blood. Symptoms may include bowing of the legs and other bone deformities; bone pain; joint pain; poor bone growth; and short stature. In some affected babies, the space between the skull bones closes too soon leading to craniosynostosis. Most patients display Abnormality of calcium-phosphate metabolism, Abnormality of dental enamel, Delayed eruption of teeth and long, narrow head (Dolichocephaly).

The terms "*adeno-associated viral vector*", "*AAV vector*", "*adeno-associated virus*", "*AAV virus*", "*AAV virion*", "*AAV viral particle*" and "*AAV particle*", as used interchangeably herein, refer to a viral particle composed of at least one AAV capsid protein (preferably by all of the capsid proteins of a particular AAV serotype) and an encapsidated recombinant viral genome. The particle comprises a recombinant viral genome having a heterologous polynucleotide comprising a sequence encoding human ENPP1 or human ENPP3 or a functionally equivalent variant thereof,) and a transcriptional regulatory region that at least

comprises a promoter flanked by the AAV inverted terminal repeats. The particle is typically referred to as an "*AAV vector particle*" or "*AAV vector*".

As used herein, the term "*vector*" means a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. In some embodiments, the vector is a plasmid, i.e., a circular double stranded DNA loop into which additional DNA segments may be ligated. In some embodiments, the vector is a viral vector, wherein additional nucleotide sequences may be ligated into the viral genome. In some embodiments, the vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). In other embodiments, the vectors (e.g., non-episomal mammalian vectors) is integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors (expression vectors) are capable of directing the expression of genes to which they are operatively linked.

As used herein, the term "*recombinant host cell*" (or simply "host cell"), as used herein, means a cell into which an exogenous nucleic acid and/or recombinant vector has been introduced. It should be understood that "recombinant host cell" and "host cell" mean not only the particular subject cell but also the progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term "host cell" as used herein.

The term "*recombinant viral genome*", as used herein, refers to an AAV genome in which at least one extraneous expression cassette polynucleotide is inserted into the naturally occurring AAV genome. The genome of the AAV according to the invention typically comprises the cis-acting 5′ and 3′ inverted terminal repeat sequences (ITRs) and an expression cassette.

The term "*expression cassette*", as used herein, refers to a nucleic acid construct, generated recombinantly or synthetically, with a series of specified nucleic acid elements, which permit transcription of a particular nucleic acid in a target cell. The expression cassette of the recombinant viral genome of the AAV vector according to the invention comprises a transcriptional regulatory region operatively linked to a nucleotide sequence encoding ENPP1 or ENPP3 or a functionally equivalent variant thereof.

The term "*transcriptional regulatory region*", as used herein, refers to a nucleic acid fragment capable of regulating the expression of one or more genes. The transcriptional regulatory region according to the invention includes a promoter and, optionally, an enhancer.

The term "*promoter*", as used herein, refers to a nucleic acid fragment that functions to control the transcription of one or more polynucleotides, located upstream the polynucleotide sequence(s), and which is structurally identified by the presence of a binding site for DNA-dependent RNA polymerase, transcription initiation sites, and any other DNA sequences including, but not limited to, transcription factor binding sites, repressor, and activator protein binding sites, and any other sequences of nucleotides known in the art to act directly or indirectly to regulate the amount of transcription from the promoter. Any kind of promoters may be used in the invention including inducible promoters, constitutive promoters and tissue-specific promoters.

The term "*enhancer*", as used herein, refers to a DNA sequence element to which transcription factors bind to increase gene transcription. Examples of enhancers may be, without limitation, RSV enhancer, CMV enhancer, HCR enhancer, etc. In another embodiment, the enhancer is a liver-specific enhancer, more preferably a hepatic control region enhancer (HCR).

The term "*operatively linked*", as used herein, refers to the functional relation and location of a promoter sequence with respect to a polynucleotide of interest (e.g. a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence). Generally, a promoter operatively linked is contiguous to the sequence of interest. However, an enhancer does not have to be contiguous to the sequence of interest to control its expression. In another embodiment, the promoter and the nucleotide sequence encoding ENPP1 or ENPP3 or a functionally equivalent variant thereof.

The term "*therapeutically effective amount*" refers to a nontoxic but sufficient amount of a viral vector encoding ENPP1 or ENPP3 to provide the desired biological result. That result may be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, a therapeutically effective amount of an AAV vector according to the invention is an amount sufficient to produce

The term "*Cap protein*", as used herein, refers to a polypeptide having at least one functional activity of a native AAV Cap protein (e.g. VP1, VP2, VP3). Examples of functional activities of Cap proteins include the ability to induce formation of a capsid, facilitate

accumulation of single-stranded DNA, facilitate AAV DNA packaging into capsids (i.e. encapsidation), bind to cellular receptors, and facilitate entry of the virion into host cells. In principle, any Cap protein can be used in the context of the present invention.

The term "*capsid*", as used herein, refers to the structure in which the viral genome is packaged. A capsid consists of several oligomeric structural subunits made of proteins. For instance, AAV have an icosahedral capsid formed by the interaction of three capsid proteins: VP1, VP2 and VP3.

The term "*Rep protein*", as used herein, refers to a polypeptide having at least one functional activity of a native AAV Rep protein (e.g. Rep 40, 52, 68, 78). A "functional activity" of a Rep protein is any activity associated with the physiological function of the protein, including facilitating replication of DNA through recognition, binding and nicking of the AAV origin of DNA replication as well as DNA helicase activity. Additional functions include modulation of transcription from AAV (or other heterologous) promoters and site-specific integration of AAV DNA into a host chromosome. In a particular embodiment, AAV rep genes derive from the serotypes AAV1, AAV2, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10 or AAVrh10; more preferably from an AAV serotype selected from the group consisting of AAV2, AAV5, AAV7, AAV8, AAV9, AAV10 and AAVrh10.

The expression "*viral proteins upon which AAV is dependent for replication*", as used herein, refers to polypeptides which perform functions upon which AAV is dependent for replication (i.e. "helper functions"). The helper functions include those functions required for AAV replication including, without limitation, those moieties involved in activation of AAV gene transcription, stage specific AAV mRNA splicing, AAV DNA replication, synthesis of cap expression products, and AAV capsid assembly. Viral-based accessory functions are derived from any of the known helper viruses such as adenovirus, herpesvirus (other than herpes simplex virus type-1), and vaccinia virus. Helper functions include, without limitation, adenovirus E1, E2a, VA, and E4 or herpesvirus UL5, ULB, UL52, and UL29, and herpesvirus polymerase. In another embodiment, the proteins upon which AAV is dependent for replication are derived from adenovirus.

The term "*adeno-associated virus ITRs*" or "*AAV ITRs*", as used herein, refers to the inverted terminal repeats present at both ends of the DNA strand of the genome of an adeno-associated virus. The ITR sequences are required for efficient multiplication of the AAV

genome. Another property of these sequences is their ability to form a hairpin. This characteristic contributes to its self-priming which allows the primase-independent synthesis of the second DNA strand. Procedures for modifying these ITR sequences are known in the art (*Brown T, "Gene Cloning", Chapman & Hall, London, GB, 1995; Watson R, et al., "Recombinant DNA", 2nd Ed. Scientific American Books, New York, N.Y., US, 1992; Alberts B, et al., "Molecular Biology of the Cell", Garland Publishing Inc., New York, N.Y., US, 2008; Innis M, et al., Eds., "PCR Protocols. A Guide to Methods and Applications", Academic Press Inc., San Diego, Calif., US, 1990; and Schleef M, Ed., "Plasmid for Therapy and Vaccination", Wiley-VCH Verlag GmbH, Weinheim, Del., 2001*).

The term "*tissue-specific*" promoter is only active in specific types of differentiated cells or tissues. Typically, the downstream gene in a tissue-specific promoter is one which is active to a much higher degree in the tissue(s) for which it is specific than in any other. In this case there may be little or substantially no activity of the promoter in any tissue other than the one(s) for which it is specific.

The term "*skeletal muscle-specific promoter*", as used herein, refers to a nucleic acid sequence that serves as a promoter (i.e. regulates expression of a selected nucleic acid sequence operably linked to the promoter), and which promotes expression of a selected nucleic acid sequence in specific tissue cells of skeletal muscle. Examples of skeletal muscle-specific promoters include, without limitation, myosin light chain promoter (MLC) and the muscle creatine kinase promoter (MCK).

The term "*liver specific promoter*", as used herein, refers to a nucleic acid sequence that serves as a promoter (i.e. regulates expression of a selected nucleic acid sequence operably linked to the promoter), and which promotes expression of a selected nucleic acid sequence in hepatocytes. Typically, a liver-specific promoter is more active in liver as compared to its activity in any other tissue in the body. The liver-specific promoter can be constitutive or inducible. Suitable liver-specific promoters include, without limitation, an [alpha]1-anti-trypsin (AAT) promoter, a thyroid hormone-binding globulin promoter, an alpha fetoprotein promoter, an alcohol dehydrogenase promoter, the factor VIII (FVIII) promoter, a HBV basic core promoter (BCP) and PreS2 promoter, an albumin promoter, a −460 to 73 bp phosphoenol pyruvate carboxykinase (PEPCK) promoter, a thyroxin-binding globulin (TBG) promoter, an Hepatic Control Region (HCR)-ApoCII hybrid promoter, an HCR-hAAT hybrid promoter, an

AAT promoter combined with the mouse albumin gene enhancer (Ealb) element, an apolipoprotein E promoter, a low density lipoprotein promoter, a pyruvate kinase promoter, a lecithin-cholesterol acyl transferase (LCAT) promoter, an apolipoprotein H (ApoH) promoter, the transferrin promoter, a transthyretin promoter, an alpha-fibrinogen and beta-fibrinogen promoters, an alpha 1-antichymotrypsin promoter, an alpha 2-HS glycoprotein promoter, an haptoglobin promoter, a ceruloplasmin promoter, a plasminogen promoter, promoters of the complement proteins (CIq, CIr, C2, C3, C4, C5, C6, C8, C9, complement Factor I and Factor H), C3 complement activator and the [alpha]-acid glycoprotein promoter. Additional tissue-specific promoters may be found in the Tissue-Specific Promoter Database, TiProD (Nucleic Acids Research, J4:D104-D107 (2006)). In another embodiment, the liver-specific promoter is selected from the group consisting of albumin promoter, phosphoenol pyruvate carboxykinase (PEPCK) promoter and alpha 1-antitrypsin promoter; more preferably alpha 1-antitrypsin promoter; even more preferably human alpha 1-antitrypsin promoter.

The term "*inducible promoter*", as used herein, refers to a promoter that is physiologically or developmentally regulated, e.g. by the application of a chemical inducer. For example, it can be a tetracycline-inducible promoter, a mifepristone (RU-486)-inducible promoter and the like.

The term "*constitutive promoter*", as used herein, refers to a promoter whose activity is maintained at a relatively constant level in all cells of an organism, or during most developmental stages, with little or no regard to cell environmental conditions. In another embodiment, the transcriptional regulatory region allows constitutive expression of ENPP1. Examples of constitutive promoters include, without limitation, the retroviral Rous sarcoma virus (RSV) LTR promoter (optionally with the RSV enhancer), the cytomegalovirus (CMV) promoter (optionally with the CMV enhancer), the SV40 promoter, the dihydrofolate reductase promoter, the β-actin promoter, the phosphoglycerol kinase (PGK) promoter, and the EF1a promoter (*Boshart M, et al., Cell 1985; 41:521-530*). Preferably, the constitutive promoter is suitable for expression of ENPP1 in liver and include, without limitation, a promoter of hypoxanthine phosphoribosyl transferase (HPTR), a promoter of the adenosine deaminase, a promoter of the pyruvate kinase, a promoter of β-actin, an elongation factor 1 alpha (EF1) promoter, a phosphoglycerate kinase (PGK) promoter, a ubiquitin (Ubc) promoter, an albumin promoter, and other constitutive promoters. Exemplary viral promoters which function constitutively in cells

include, for example, the SV40 early promoter region (*Bernoist and Chambon, 1981, Nature 290:304-310*), the promoter contained in the 3′ long terminal repeat of Rous sarcoma virus (*Yamamoto et al., 1980, Cell 22:787-797*), or the herpes thymidine kinase promoter (*Wagner et al., 1981, Proc. Natl. Acad. Sci. U.S.A. 78:1441-1445*).

The term "*polyadenylation signal*", as used herein, relates to a nucleic acid sequence that mediates the attachment of a polyadenine stretch to the 3′ terminus of the mRNA. Suitable polyadenylation signals include, without limitation, the SV40 early polyadenylation signal, the SV40 late polyadenylation signal, the HSV thymidine kinase polyadenylation signal, the protamine gene polyadenylation signal, the adenovirus 5 EIb polyadenylation signal, the bovine growth hormone polyadenylation signal, the human variant growth hormone polyadenylation signal and the like.

The term "*nucleotide or nucleic acid sequence*", is used herein interchangeably with "polynucleotide", and relates to any polymeric form of nucleotides of any length. Said nucleotide sequence encodes signal peptide and ENPP1 protein or a functionally equivalent variant thereof.

The term "*signal peptide*", as used herein, refers to a sequence of amino acid residues (ranging in length from 10-30 residues) bound at the amino terminus of a nascent protein of interest during protein translation. The signal peptide is recognized by the signal recognition particle (SRP) and cleaved by the signal peptidase following transport at the endoplasmic reticulum. (*Lodish et al., 2000, Molecular Cell Biology, 4th edition*).

The term "*subject*", as used herein, refers to an individualmammal, such as a human, a non-human primate (e.g. chimpanzees and other apes and monkey species), a farm animal (e.g. birds, fish, cattle, sheep, pigs, goats, and horses), a domestic mammal (e.g. dogs and cats), or a laboratory animal (e.g. rodents, such as mice, rats and guinea pigs). The term includes a subject of any age or sex. In another embodiment the subject is a mammal, preferably a human.

A disease or disorder is "*alleviated*" if the severity of a symptom of the disease or disorder, the frequency with which such a symptom is experienced by a patient, or both, is reduced.

As used herein the terms "*alteration*," "*defect*," "*variation*" or "*mutation*" refer to a mutation in a gene in a cell that affects the function, activity, expression (transcription or translation) or conformation of the polypeptide it encodes, including missense and nonsense mutations, insertions, deletions, frameshifts and premature terminations.

A "*disease*" is a state of health of an animal wherein the animal cannot maintain homeostasis, and wherein if the disease is not ameliorated then the animal's health continues to deteriorate.

A "*disorder*" in an animal is a state of health in which the animal is able to maintain homeostasis, but in which the animal's state of health is less favorable than it would be in the absence of the disorder. Left untreated, a disorder does not necessarily cause a further decrease in the animal's state of health.

As used herein, the term "*immune response" or "immune reaction*" refers to the host's immune system to antigen in an invading (infecting) pathogenic organism, or to introduction or expression of foreign protein. The immune response is generally humoral and local; antibodies produced by B cells combine with antigen in an antigen-antibody complex to inactivate or neutralize antigen. Immune response is often observed when human proteins are injected into mouse model systems. Generally, the mouse model system is made immune tolerant by injecting immune suppressors prior to the introduction of a foreign antigen to ensure better viability.

As used herein, the term "*immunesuppression*" is a deliberate reduction of the activation or efficacy of the host immune system using immunesuppresant drugs to facilitate immune tolerance towards foreign antigens such as foreign proteins, organ transplants, bone marrow and tissue transplantation. Non limiting examples of immunosuppressant drugs include anti-CD4(GK1.5) antibody, Cyclophosphamide, Azathioprine (Imuran), Mycophenolate mofetil (Cellcept), Cyclosporine (Neoral, Sandimmune, Gengraf), Methotrexate (Rheumatrex), Leflunomide (Arava), Cyclophosphamide (Cytoxan) and Chlorambucil (Leukeran).

As used herein, the term "*ENPP*" or "*NPP*" refers to ectonucleotide pyrophosphatase/ phosphodiesterase.

As used herein, the term "*ENPP1 protein*" or "*ENPP1 polypeptide*" refers to ectonucleotide pyrophosphatase/phosphodiesterase-1 protein encoded by the *ENPP1* gene. The encoded protein is a type II transmembrane glycoprotein and cleaves a variety of substrates, including phosphodiester bonds of nucleotides and nucleotide sugars and pyrophosphate bonds of nucleotides and nucleotide sugars. ENPP1 protein has a transmembrane domain and soluble extracellular domain. The extracellular domain is further subdivided into somatomedin B domain, catalytic domain and the nuclease domain. The sequence and structure of wild-type

ENPP1 is described in detail in PCT Application Publication No. WO 2014/126965 to Braddock, *et al.*, which is incorporated herein in its entirety by reference.

Mammal ENPP1 and ENPP3 polypeptides, mutants, or mutant fragments thereof, have been previously disclosed in International PCT Application Publications No. *WO/2014/126965-Braddock et al., WO/2016/187408-Braddock et al., WO/2017/087936-Braddock et al., and WO2018/027024-Braddock et al.*, all of which are incorporated by reference in their entireties herein.

As used herein, the term "*ENPP3 protein*" or "*ENPP3 polypeptide*" refers to ectonucleotide pyrophosphatase/phosphodiesterase-3 protein encoded by the *ENPP3* gene. The encoded protein is a type II transmembrane glycoprotein and cleaves a variety of substrates, including phosphodiester bonds of nucleotides and nucleotide sugars and pyrophosphate bonds of nucleotides and nucleotide sugars. ENPP3 protein has a transmembrane domain and soluble extracellular domain. The sequence and structure of wild-type ENPP3 is described in detail in PCT Application Publication No. WO/2017/087936 to Braddock, *et al.*, which is incorporated herein in its entirety by reference.

As used herein, the term "*ENPP1 precursor protein*" refers to ENPP1 with its signal peptide sequence at the ENPP1 N-terminus. Upon proteolysis, the signal sequence is cleaved from ENPP1 to provide the ENPP1 protein. Signal peptide sequences useful within the invention include, but are not limited to, Albumin signal sequence, Azurocidin signal sequence, ENPP1 signal peptide sequence, ENPP2 signal peptide sequence, ENPP7 signal peptide sequence, and/or ENPP5 signal peptide sequence.

As used herein, the term "*ENPP3 precursor protein*" refers to ENPP3 with its signal peptide sequence at the ENPP3 N-terminus. Upon proteolysis, the signal sequence is cleaved from ENPP3 to provide the ENPP3 protein. Signal peptide sequences useful within the invention include, but are not limited to, Albumin signal peptide sequence, Azurocidin signal peptide sequence, ENPP1 signal peptide sequence, ENPP2 signal peptide sequence, ENPP7 signal peptide sequence, and/or ENPP5 signal peptide sequence.

As used herein, the term "*Azurocidin signal peptide sequence*" refers to the signal peptide derived from human azurocidin. Azurocidin, also known as cationic antimicrobial protein CAP37 or heparin-binding protein (HBP), is a protein that in humans is encoded by the AZU1 gene. The nucleotide sequence encoding Azurocin signal peptide

(MTRLTVLALLAGLLASSRA) is fused with the nucleotide sequence of NPP1 or NPP3 gene which when encoded generates ENPP1 precursor protein or ENPP3 precursor protein. (*Optimized signal peptides for the development of high expressing CHO cell lines, Kober et al., Biotechnol Bioeng. 2013 Apr;110(4):1164-73*)

As used herein, the term "*ENPP1-Fc construct*" refers to ENPP1 recombinantly fused and/or chemically conjugated (including both covalent and non-covalent conjugations) to an FcR binding domain of an IgG molecule (preferably, a human IgG). In certain embodiments, the C-terminus of ENPP1 is fused or conjugated to the N-terminus of the FcR binding domain.

As used herein, the term "*ENPP3-Fc construct*" refers to ENPP3 recombinantly fused and/or chemically conjugated (including both covalent and non-covalent conjugations) to an FcR binding domain of an IgG molecule (preferably, a human IgG). In certain embodiments, the C-terminus of ENPP1 is fused or conjugated to the N-terminus of the FcR binding domain.

As used herein, the term "*Fc*" refers to a human IgG (immunoglobulin) Fc domain. Subtypes of IgG such as IgG1, IgG2, IgG3, and IgG4 are contemplated for use as Fc domains.

As used herein, the "*Fc region or Fc polypeptide*" is the portion of an IgG molecule that correlates to a crystallizable fragment obtained by papain digestion of an IgG molecule. The Fc region comprises the C-terminal half of the two heavy chains of an IgG molecule that are linked by disulfide bonds. It has no antigen binding activity but contains the carbohydrate moiety and the binding sites for complement and Fc receptors, including the FcRn receptor. The Fc fragment contains the entire second constant domain CH2 (residues 231-340 of human IgG1, according to the Kabat numbering system) and the third constant domain CH3 (residues 341-447). The term "IgG hinge-Fc region" or "hinge-Fc fragment" refers to a region of an IgG molecule consisting of the Fc region (residues 231 -447) and a hinge region (residues 216-230) extending from the N-terminus of the Fc region. The term "constant domain" refers to the portion of an immunoglobulin molecule having a more conserved amino acid sequence relative to the other portion of the immunoglobulin, the variable domain, which contains the antigen binding site. The constant domain contains the CH1, CH2 and CH3 domains of the heavy chain and the CHL domain of the light chain.

As used herein, the term "*fragment*," as applied to a nucleic acid, refers to a subsequence of a larger nucleic acid. A "fragment" of a nucleic acid can be at least about 15, 50-100, 100-500, 500-1000, 1000-1500 nucleotides, 1500-2500, or 2500 nucleotides (and any integer value in

between). As used herein, the term "fragment," as applied to a protein or peptide, refers to a subsequence of a larger protein or peptide, and can be at least about 20, 50, 100, 200, 300 or 400 amino acids in length (and any integer value in between).

"*Isolated*" means altered or removed from the natural state. For example, a nucleic acid or a polypeptide naturally present in a living animal is not "isolated," but the same nucleic acid or polypeptide partially or completely separated from the coexisting materials of its natural state is "isolated." An isolated nucleic acid or protein can exist in substantially purified form, or can exist in a non-native environment such as, for example, a host cell.

An "*oligonucleotide*" or "*polynucleotide*" is a nucleic acid ranging from at least 2, in certain embodiments at least 8, 15 or 25 nucleotides in length, but may be up to 50, 100, 1000, or 5000 nucleotides long or a compound that specifically hybridizes to a polynucleotide.

As used herein, the term "*patient*," "*individu*al" or "*subject*" refers to a human.

As used herein, the term "*pharmaceutical composition*" or "*composition*" refers to a mixture of at least one compound useful within the invention with a pharmaceutically acceptable carrier. The pharmaceutical composition facilitates administration of the compound to a patient. Multiple techniques of administering a compound exist in the art including, but not limited to, subcutaneous, intravenous, oral, aerosol, inhalational, rectal, vaginal, transdermal, intranasal, buccal, sublingual, parenteral, intrathecal, intragastrical, ophthalmic, pulmonary, and topical administration.

As used herein, the term "*pharmaceutically acceptable*" refers to a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively non-toxic, *i.e.*, the material may be administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained; for example, phosphate-buffered saline (PBS)

As used herein the term "*plasma pyrophosphate (PPi) levels*" refers to the amount of pyrophosphate present in plasma of animals. In certain embodiments, animals include rat, mouse, cat, dog, human, cow and horse. It is necessary to measure PPi in plasma rather than serum because of release from platelets. There are several ways to measure PPi, one of which is by enzymatic assay using uridine-diphosphoglucose (UDPG) pyrophosphorylase (*Lust & Seegmiller, 1976, Clin. Chim. Acta 66:241-249; Cheung & Suhadolnik, 1977, Anal. Biochem.*

83:61-63) with modifications. Typically, normal PPi levels in healthy subjects range from about 1μm to about 3 μM, in some cases between 1-2 μm. Subjects who have defective ENPP1 expression tend to exhibit low ppi levels which range from at least 10% below normal levels, at least 20% below normal levels, at least 30% below normal levels, at least 40% below normal levels, at least 50% below normal levels, at least 60% below normal levels, at least 70% below normal levels, at least 80% below normal levels and combinations thereof. In patients afflicted with GACI, the ppi levels are found to be less than 1 μm and in some cases are below the level of detection. In patients afflicted with PXE, the ppi levels are below 0.5 μm. (*Arterioscler Thromb Vasc Biol. 2014 Sep;34(9):1985-9; Braddock et al., Nat Commun. 2015; 6: 10006.*)

As used herein, the term "*polypeptide*" refers to a polymer composed of amino acid residues, related naturally occurring structural variants, and synthetic non-naturally occurring analogs thereof linked via peptide bonds.

As used herein, the term "*PPi*" refers to pyrophosphate.

As used herein, the term "*prevent" or "prevention*" means no disorder or disease development if none had occurred, or no further disorder or disease development if there had already been development of the disorder or disease. Also considered is the ability of one to prevent some or all of the symptoms associated with the disorder or disease.

"*Sample*" or "*biological sample*" as used herein means a biological material isolated from a subject. The biological sample may contain any biological material suitable for detecting a mRNA, polypeptide or other marker of a physiologic or pathologic process in a subject, and may comprise fluid, tissue, cellular and/or non-cellular material obtained from the individual.

As used herein, "*substantially purified*" refers to being essentially free of other components. For example, a substantially purified polypeptide is a polypeptide that has been separated from other components with which it is normally associated in its naturally occurring state. Non-limiting embodiments include 95% purity, 99% purity, 99.5% purity, 99.9% purity and 100% purity.

As used herein, the term "*treatment*" or "*treating*" is defined as the application or administration of a therapeutic agent, *i.e.*, a compound useful within the invention (alone or in combination with another pharmaceutical agent), to a patient, or application or administration of a therapeutic agent to an isolated tissue or cell line from a patient (*e.g.*, for diagnosis or *ex vivo* applications), who has a disease or disorder, a symptom of a disease or disorder or the potential

to develop a disease or disorder, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve or affect the disease or disorder, the symptoms of the disease or disorder, or the potential to develop the disease or disorder. Such treatments may be specifically tailored or modified, based on knowledge obtained from the field of pharmacogenomics.

The terms "*prevent," "preventing," and "prevention*", as used herein, refer to inhibiting the inception or decreasing the occurrence of a disease in a subject. Prevention may be complete (e.g. the total absence of pathological cells in a subject) or partial. Prevention also refers to a reduced susceptibility to a clinical condition.

As used herein, the term "*wild-type*" refers to a gene or gene product isolated from a naturally occurring source. A wild-type gene is most frequently observed in a population and is thus arbitrarily designed the "normal" or "wild-type" form of the human NPP1 or NPP3 genes. In contrast, the term "*functionally equivalent*" refers to a NPP1 or NPP3 gene or gene product that displays modifications in sequence and/or functional properties (*i.e.*, altered characteristics) when compared to the wild-type gene or gene product. Naturally occurring mutants can be isolated; these are identified by the fact that they have altered characteristics (including altered nucleic acid sequences) when compared to the wild-type gene or gene product.

The term "*functional equivalent variant*", as used herein, relates to a polypeptide substantially homologous to the sequences of ENPP1 or ENPP3 (defined above) and that preserves the enzymatic and biological activities of ENPP1 or ENPP3, respectively. Methods for determining whether a variant preserves the biological activity of the native ENPP1 or ENPP3 are widely known to the skilled person and include any of the assays used in the experimental part of said application. Particularly, functionally equivalent variants of ENPP1 or ENPP3 delivered by viral vectors is encompassed by the present invention.

The functionally equivalent variants of ENPP1 or ENPP3 are polypeptides substantially homologous to the native ENPP1 or ENPP3 respectively. The expression "substantially homologous", relates to a protein sequence when said protein sequence has a degree of identity with respect to the ENPP1 or ENPP3 sequences described above of at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% respectively.

The degree of identity between two polypeptides is determined using computer algorithms and methods that are widely known for the persons skilled in the art. The identity

between two amino acid sequences is preferably determined by using the BLASTP algorithm (*BLAST Manual, Altschul, S., et al., NCBI NLM NIH Bethesda, Md. 20894, Altschul, S., et al., J. Mol. Biol. 215: 403-410 (1990)*), though other similar algorithms can also be used. BLAST and BLAST 2.0 are used, with the parameters described herein, to determine percent sequence identity. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information.

"*Functionally equivalent variants*" of ENPP1 or ENPP3 may be obtained by replacing nucleotides within the polynucleotide accounting for codon preference in the host cell that is to be used to produce the ENPP1 or ENPP3 respectively. Such "codon optimization" can be determined via computer algorithms which incorporate codon frequency tables such as "Human high.cod" for codon preference as provided by the University of Wisconsin Package Version 9.0, Genetics Computer Group, Madison, Wis.

"About" as used herein when referring to a measurable value such as an amount, a temporal duration, and the like, is meant to encompass variations of ±20% or ±10%, in certain embodiments ±5%, in certain embodiments ±1%, in certain embodiments ±0.1% from the specified value, as such variations are appropriate to perform the disclosed methods.

The disclosure provides a representative example of protein sequence and nucleic acid sequences of the invention. The protein sequences described can be converted into nucleic acid sequences by performing revere translation and codon optimization. There are several tools available in art such as Expasy (https://www.expasy.org/)and bioinformatics servers (http://www.bioinformatics.org)that enable such conversions

Ranges: throughout this disclosure, various aspects according to the invention can be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope according to the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 2.7, 3, 4, 5, 5.3, and 6. This applies regardless of the breadth of the range.

Viral Vectors for *in vivo* expression of ENPP1 and ENPP3

Genetic material such as a polynucleotide comprising an NPP1 or an NPP3 sequence can be introduced to a mammal in order to compensate for a deficiency in ENPP1 or ENPP3 polypeptide

Certain modified viruses are often used as vectors to carry a coding sequence because after administration to a mammal, a virus infects a cell and expresses the encoded protein. Modified viruses useful according to the invention are derived from viruses which include, for example: parvovirus, picornavirus, pseudorabies virus, hepatitis virus A, B or C, papillomavirus, papovavirus (such as polyoma and SV40) or herpes virus (such as Epstein-Barr Virus, Varicella Zoster Virus, Cytomegalovirus, Herpes Zoster and Herpes Simplex Virus types 1 and 2), an RNA virus or a retrovirus, such as the Moloney murine leukemia virus or a lentivirus (i.e. derived from Human Immunodeficiency Virus, Feline Immunodeficiency Virus, equine infectious anemia virus, etc.). Among DNA viruses useful according to the invention are: Adeno-associated viruses adenoviruses, Alphaviruses, and Lentiviruses.

A viral vector is generally administered by injection, most often intravenously (by IV) directly into the body, or directly into a specific tissue, where it is taken up by individual cells. Alternately, a viral vector may be administered by contacting the viral vector *ex vivo* with a sample of the patient's cells, thereby allowing the viral vector to infect the cells, and cells containing the vector are then returned to the patient. Once the viral vector is delivered, the coding sequence expressed and results in a functioning protein. Generally, the infection and transduction of cells by viral vectors occur by a series of sequential events as follows: interaction of the viral capsid with receptors on the surface of the target cell, internalization by endocytosis, intracellular trafficking through the endocytic/ proteasomal compartment, endosomal escape, nuclear import, virion uncoating, and viral DNA double-strand conversion that leads to the transcription and expression of the recombinant coding sequence interest. (*Colella et al., Mol Ther Methods Clin Dev. 2017 Dec 1;8:87-104.).*

Adeno-Associated Viral Vectors according to the invention

AAV refers to viruses belonging to the genus Dependovirus of the Parvoviridae family. The AAV genome is approximately 4.7 kilobases long and is composed of linear single-stranded deoxyribonucleic acid (ssDNA) which may be either positive- or negative-sensed. The genome

comprises inverted terminal repeats (ITRs) at both ends of the DNA strand, and two open reading frames (ORFs): rep and cap. The rep frame is made of four overlapping genes encoding non-structural replication (Rep) proteins required for the AAV life cycle. The cap frame contains overlapping nucleotide sequences of structural VP capsid proteins: VP1, VP2 and VP3, which interact together to form a capsid of an icosahedral symmetry.

The terminal 145 nucleotides are self-complementary and are organized so that an energetically stable intramolecular duplex forming a T-shaped hairpin may be formed. These hairpin structures function as an origin for viral DNA replication, serving as primers for the cellular DNA polymerase complex. Following wild type AAV infection in mammalian cells the rep genes (i.e. Rep78 and Rep52) are expressed from the P5 promoter and the P19 promoter, respectively, and both Rep proteins have a function in the replication of the viral genome. A splicing event in the rep ORF results in the expression of actually four Rep proteins (i.e. Rep78, Rep68, Rep52 and Rep40). However, it has been shown that the unspliced mRNA, encoding Rep78 and Rep52 proteins, in mammalian cells are sufficient for AAV vector production. Also in insect cells the Rep78 and Rep52 proteins suffice for AAV vector production.

The AAV vector typically lacks rep and cap frames. Such AAV vectors can be replicated and packaged into infectious viral particles when present in a host cell that has been transfected with a vector encoding and expressing rep and cap gene products (i.e. AAV Rep and Cap proteins), and wherein the host cell has been transfected with a vector which encodes and expresses a protein from the adenovirus open reading frame E4orf6.

In one embodiment, the invention relates to an adeno-associated viral (AAV) expression vector comprising a sequence encoding mammal ENPP1 or mammal ENPP3, and upon administration to a mammal the vector expresses an ENPP1 or ENPP3 precursor in a cell, the precursor including an Azurocidin signal peptide fused at its carboxy terminus to the amino terminus of ENPP1 or ENPP3. The ENPP1 or ENPP3 precursor may include a stabilizing domain, such as an IgG Fc region or human albumin. Upon secretion of the precursor from the cell, the signal peptide is cleaved off and enzymatically active soluble mammal ENPP1 or ENPP3 is provided extracellularly.

An AAV expression vector may include an expression cassette comprising a transcriptional regulatory region operatively linked to a nucleotide sequence comprising a transcriptional regulatory region operatively linked to a recombinant nucleic acid sequence

encoding a polypeptide comprising a Azurocidin signal peptide sequence and an ectonucleotide pyrophosphatase/phosphodiesterase (ENPP1) polypeptide sequence.

In some embodiments, the expression cassette comprises a promoter and enhancer, the Kozak sequence GCCACCATGG, a nucleotide sequence encoding mammal NPP1 protein or a nucleotide sequence encoding mammal NPP3 protein, other suitable regulatory elements and a polyadenylation signal.

In some embodiments, the AAV recombinant genome of the AAV vector according to the invention lacks the rep open reading frame and/or the cap open reading frame.

The AAV vector according to the invention comprises a capsid from any serotype. In general, the AAV serotypes have genomic sequences of significant homology at the amino acid and the nucleic acid levels, provide an identical set of genetic functions, and replicate and assemble through practically identical mechanisms. In particular, the AAV of the present invention may belong to the serotype 1 of AAV (AAV1), AAV2, AAV3 (including types 3A and 3B), AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAVrh10, AAV11, avian AAV, bovine AAV, canine AAV, equine AAV, or ovine AAV.

Examples of the sequences of the genome of the different AAV serotypes may be found in the literature or in public databases such as GenBank. For example, GenBank accession numbers NC_001401.2 (AAV2), NC_001829.1 (AAV4), NC_006152.1 (AAV5), AF028704.1 (AAV6), NC_006260.1 (AAV7), NC_006261.1 (AAV8), AX753250.1 (AAV9) and AX753362.1 (AAV10).

In some embodiments, the adeno-associated viral vector according to the invention comprises a capsid derived from a serotype selected from the group consisting of the AAV2, AAV5, AAV7, AAV8, AAV9, AAV10 and AAVrh10 serotypes. In another embodiment, the serotype of the AAV is AAV8. If the viral vector comprises sequences encoding the capsid proteins, these may be modified so as to comprise an exogenous sequence to direct the AAV to a particular cell type or types, or to increase the efficiency of delivery of the targeted vector to a cell, or to facilitate purification or detection of the AAV, or to reduce the host response.

The published application, US 2017/0290926 –Smith et al., the contents of which are incorporated by reference in their entirety herein, describes in detail the process by which AAV vectors are generated, delivered and administered.

Adeno Viral Vectors Useful According to the Invention

Adenovirus can be manipulated such that it encodes and expresses the desired gene product, (e.g., ENPP1 or ENPP3), and at the same time is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. In addition, adenovirus has a natural tropism for airway epithelial. The viruses are able to infect quiescent cells as are found in the airways, offering a major advantage over retroviruses. Adenovirus expression is achieved without integration of the viral DNA into the host cell chromosome, thereby alleviating concerns about insertional mutagenesis. Furthermore, adenoviruses have been used as live enteric vaccines for many years with an excellent safety profile (*Schwartz, A. R. et al. (1974) Am. Rev. Respir. Dis. 109:233–238*). Finally, adenovirus mediated gene transfer has been demonstrated in a number of instances including transfer of alpha-1-antitrypsin and CFTR to the lungs of cotton rats (*Rosenfeld, M. A. et al. (1991) Science 252:431–434; Rosenfeld et al., (1992) Cell 68:143–155*). Furthermore, extensive studies to attempt to establish adenovirus as a causative agent in human cancer were uniformly negative (*Green, M. et al. (1979) Proc. Natl. Acad. Sci. USA 76:6606*).

Pseudo-Adenovirus Vectors (PAV)—PAVs contain adenovirus inverted terminal repeats and the minimal adenovirus 5′ sequences required for helper virus dependent replication and packaging of the vector. These vectors contain no potentially harmful viral genes, have a theoretical capacity for foreign material of nearly 36 kb, may be produced in reasonably high titers and maintain the tropism of the parent virus for dividing and non-dividing human target cell types. The PAV vector can be maintained as either a plasmid-borne construct or as an infectious viral particle. As a plasmid construct, PAV is composed of the minimal sequences from wild type adenovirus type 2 necessary for efficient replication and packaging of these sequences and any desired additional exogenous genetic material, by either a wild-type or defective helper virus.

The US patent publication, US 7,318,919- Gregory et al., describes in detail the process by which adenoviral vectors are generated, delivered and their corresponding use for treatment of diseases, the contents of which are incorporated by reference in their entirety herein. The present invention contemplates the use of Adenoviral vectors to deliver nucleotides encoding ENPP1 or ENPP3 to a subject in need thereof and the methods of treatment using the same.

Herpes Simplex Vectors Useful According to the Invention

A Herpes Simplex Vector (HSV based viral vector) is suitable for use as a vector to introduce a nucleic acid sequence into numerous cell types. The mature HSV virion consists of an enveloped icosahedral capsid with a viral genome consisting of a linear double-stranded DNA molecule that is 152 kb. In another embodiment, the HSV based viral vector is deficient in at least one essential HSV gene. In some embodiments, the HSV based viral vector that is deficient in at least one essential HSV gene is replication deficient. Most replication deficient HSV vectors contain a deletion to remove one or more intermediate-early, early, or late HSV genes to prevent replication. For example, the HSV vector may be deficient in an immediate early gene selected from the group consisting of: ICP4, ICP22, ICP27, ICP47, and a combination thereof. Advantages of the HSV vector are its ability to enter a latent stage that can result in long-term DNA expression and its large viral DNA genome that can accommodate exogenous DNA inserts of up to 25 kb.

HSV-based vectors are described in, for example, U.S. Pat. Nos. *5,837,532- Preston et al., 5,846,782- Wickham et al., and 5,804,413- Deluca et al.*, and International Patent Applications *WO 91/02788 – Preston et al., WO 96/04394- Preston et al., WO 98/15637-Deluca et al., and WO 99/06583-Glorioso et al.*, which are incorporated herein by reference. The HSV vector can be deficient in replication-essential gene functions of only the early regions of the HSV genome, only the immediate-early regions of the HSV genome, only the late regions of the HSV genome, or both the early and late regions of the HSV genome. The production of HSV vectors involves using standard molecular biological techniques well known in the art.

Replication deficient HSV vectors are typically produced in complementing cell lines that provide gene functions not present in the replication deficient HSV vectors, but required for viral propagation, at appropriate levels in order to generate high titers of viral vector stock. The expression of the nucleic acid sequence encoding the protein is controlled by a suitable expression control sequence operably linked to the nucleic acid sequence. An “expression control sequence” is any nucleic acid sequence that promotes, enhances, or controls expression (typically and preferably transcription) of another nucleic acid sequence.

Suitable expression control sequences include constitutive promoters, inducible promoters, repressible promoters, and enhancers. The nucleic acid sequence encoding the protein in the vector can be regulated by its endogenous promoter or, preferably, by a non-native promoter sequence. Examples of suitable non-native promoters include the human

cytomegalovirus (HCMV) promoters, such as the HCMV immediate-early promoter (HCMV IEp), promoters derived from human immunodeficiency virus (HIV), such as the HIV long terminal repeat promoter, the phosphoglycerate kinase (PGK) promoter, Rous sarcoma virus (RSV) promoters, such as the RSV long terminal repeat, mouse mammary tumor virus (MMTV) promoters, the Lap2 promoter, or the herpes thymidine kinase promoter (*Wagner et al., Proc. Natl. Acad. Sci., 78, 1444-1445 (1981)*), promoters derived from SV40 or Epstein Barr virus, and the like. In another embodiment, the promoter is HCMV IEp.

The promoter can also be an inducible promoter, i.e., a promoter that is up- and/or down-regulated in response to an appropriate signal. For example, an expression control sequence up-regulated by a pharmaceutical agent is particularly useful in pain management applications. For example, the promoter can be a pharmaceutically-inducible promoter (e.g., responsive to tetracycline).The promoter can be introduced into the genome of the vector by methods known in the art, for example, by the introduction of a unique restriction site at a given region of the genome.

The US patent publication, US *7,531,167 –Glorioso et al.,* describes in detail the process by which Herpes Simplex vectors are generated, delivered and their corresponding use for treatment of diseases, the contents of which are incorporated by reference in their entirety herein. The present invention contemplates the use of Herpes Simplex vectors to deliver nucleotides encoding ENPP1 or ENPP3 to a subject in need thereof and the methods of treatment using the same.

Alphaviral Vectors Useful According to the Invention

Alphaviral expression vectors have been developed from different types of alphavirus, including Sindbis virus (SIN), Semliki Forest Virus (SFV) and Venezuelan equine encephalitis (VEE) virus. The alphavirus replicon contains at its 5′ end an open reading frame encoding viral replicase (Rep) which is translated when viral RNA is transfected into cells. Rep is expressed as a polyprotein which is subsequently processed into four subunits (nsps 1 to 4). Unprocessed Rep can copy the RNA vector into negative-strand RNA, a process that only takes place during the first 3 to 4 hours after transfection or infection. Once processed, the Rep will use the negative-strand RNA as a template for synthesizing more replicon molecules. Processed Rep can also recognize an internal sequence in the negative-strand RNA, or subgenomic promoter, from

which it will synthesize a subgenomic positive-strand RNA corresponding to the 3′ end of the replicon. This subgenomic RNA will be translated to produce the heterologous protein in large amounts.

A non-cytopathic mutant isolated from SIN containing a single amino acid change (P for L) in position 726 in nsp2 (SIN P726L vector in nsp2) showed Rep hyper processing (*Frolov et al., 1999, J. Virol. 73: 3854-65*). This mutant was capable of efficiently establishing continuous replication in BHK cells. This non-cytopathic SIN vector has been widely used in vitro as it is capable of providing long-lasting transgene expression with good stability levels and expression levels that were about 4% of those obtained with the original SIN vector (*Agapov et al., 1998, Proc. Natl. Acad. Sci. USA. 95: 12989-94*). Likewise, the Patent application *WO2008065225 – Smerdou et al.,* describes a non-cytopathic SFV vector has mutations R649H/P718T in the replicase nsp2 subunit. The aforesaid vector allows obtaining cell lines capable of constitutively and stably expressing the gene of interest by means of culturing in the presence of an antibiotic the resistance gene of which is incorporated in the alphaviral vector (*Casales et al. 2008. Virology. 376:242-51*).

The invention contemplates designing a vector comprising a DNA sequence complementary to an alphavirus replicon in which a sequence of a gene of interest such as NPP1 or NPP3 has been incorporated along with recognition sequences for site-specific recombination. By means of said vector, it is possible to obtain and select cells in which the alphaviral replicon, including the sequence of the gene of interest, has been integrated in the cell genome, such that the cells stably express ENPP1 or ENPP3 polypeptide. The invention also contemplates generating an expression vector in which the alphaviral replicon is under the control of an inducible promoter. Said vector when incorporated to cells which have additionally been modified by means of incorporating an expression cassette encoding a transcriptional activator which, in the presence of a given ligand, is capable of positively regulating the activity of the promoter which regulates alphavirus replicon transcription.

The US patent publication, US *10,011,847-Aranda et al.,* describes in detail the process by which Alphaviral vectors are generated, delivered and their corresponding use for treatment of diseases, the contents of which are incorporated by reference in their entirety herein. The present invention contemplates the use of Alphaviral vectors to deliver nucleotides encoding ENPP1 or ENPP3 to a subject in need thereof and methods of treatment using the same.

Lentiviral Vectors Useful According to the Invention

Lentiviruses belong to a genus of viruses of the Retroviridae family and are characterized by a long incubation period. Lentiviruses can deliver a significant amount of viral RNA into the DNA of the host cell and have the unique ability among retroviruses of being able to infect non-dividing cells. Lentiviral vectors, especially those derived from HIV-1, are widely studied and frequently used vectors. The evolution of the lentiviral vectors backbone and the ability of viruses to deliver recombinant DNA molecules (transgenes) into target cells have led to their use in restoration of functional genes in genetic therapy and in vitro recombinant protein production.

The invention contemplates a lentiviral vector comprising a suitable promoter and a transgene to express protein of interest such as ENPP1 or ENPP3. Typically, the backbone of the vector is from a simian immunodeficiency virus (SIV), such as SIV1 or African green monkey SIV (SIV-AGM). In one embodiment, the promoter is preferably a hybrid human CMV enhancer/EF1a (hCEF) promoter. The present invention encompasses methods of manufacturing Lentiviral vectors, compositions comprising Lentiviral vectors expressing genes of interest, and use in gene therapy to express ENPP1 or ENPP3 protein in order to treat diseases of calcification or ossification. The lentiviral vectors according to the invention can also be used in methods of gene therapy to promote secretion of therapeutic proteins. By way of further example, the invention provides secretion of therapeutic proteins into the lumen of the respiratory tract or the circulatory system. Thus, administration of a vector according to the invention and its uptake by airway cells may enable the use of the lungs (or nose or airways) as a “factory” to produce a therapeutic protein that is then secreted and enters the general circulation at therapeutic levels, where it can travel to cells/tissues of interest to elicit a therapeutic effect. In contrast to intracellular or membrane proteins, the production of such secreted proteins does not rely on specific disease target cells being transduced, which is a significant advantage and achieves high levels of protein expression. Thus, other diseases which are not respiratory tract diseases, such as cardiovascular diseases and blood disorders can also be treated by the Lentiviral vectors. Lentiviral vectors, such as those according to the invention, can integrate into the genome of transduced cells and lead to long-lasting expression, making them suitable for transduction of stem/progenitor cells.

The US patent application publication, *US 2017/0096684-Alton et al.*, describes in detail the process by which Lentiviral vectors are generated, delivered and their corresponding use for treatment of diseases, the contents of which are incorporated by reference in their entirety herein. The present invention contemplates the use of Lentiviral vectors to deliver nucleotides encoding ENPP1 or ENPP3 to a subject in need thereof and the methods of treatment using the same.

Sequences

SEQ ID NO: 1 – ENPP1 Amino Acid Sequence – Wild Type

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Met Glu Arg Asp Gly Cys Ala Gly Gly Gly Ser Arg Gly Gly Glu Gly
1               5                  10                  15
Gly Arg Ala Pro Arg Glu Gly Pro Ala Gly Asn Gly Arg Asp Arg Gly
            20                  25                  30
Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala Ser
        35                  40                  45
Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala
    50                  55                  60
Arg Ala Arg Thr Ala Lys Asp Pro Asn Thr Tyr Lys Val Leu Ser Leu
65                  70                  75                  80
Val Leu Ser Val Cys Val Leu Thr Thr Ile Leu Gly Cys Ile Phe Gly
                85                  90                  95
Leu Lys Pro Ser Cys Ala Lys Glu Val Lys Ser Cys Lys Gly Arg Cys
            100                 105                 110
Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala Ala Cys Val Glu
        115                 120                 125
Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys Ile Glu Pro Glu
    130                 135                 140
His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu Lys Arg Leu Thr
145                 150                 155                 160
Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp Lys Gly Asp Cys
                165                 170                 175
Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp Val Glu
            180                 185                 190
Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro Ala Gly Phe Glu
        195                 200                 205
Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe Arg Ala Glu Tyr
    210                 215                 220
Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser Lys Leu Lys Lys
225                 230                 235                 240
Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr Lys Thr
                245                 250                 255
Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu Ser His
            260                 265                 270
Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala Ser Phe
        275                 280                 285
Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys Gly Glu
    290                 295                 300
Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly Thr Phe
305                 310                 315                 320
Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro Asp Ile
                325                 330                 335
Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Leu Ala
            340                 345                 350
Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His Phe Tyr
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        355                 360                 365
Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr Gly Pro
    370                 375                 380
Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly Met Val
385                 390                 395                 400
Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg Cys Leu
                405                 410                 415
Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser Cys Lys
            420                 425                 430
Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn Ile Lys
        435                 440                 445
Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val Pro Asp
    450                 455                 460
Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu Ser Cys
465                 470                 475                 480
Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe Leu Pro
                485                 490                 495
Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu Thr Phe
            500                 505                 510
Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu Arg Lys
        515                 520                 525
Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser Asn Met
    530                 535                 540
Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys His Gly Ile Glu
545                 550                 555                 560
Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu
                565                 570                 575
Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn
            580                 585                 590
His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His Pro Lys Glu Val
        595                 600                 605
His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp Asn Leu
    610                 615                 620
Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe Gln Thr
625                 630                 635                 640
Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His Glu Thr
                645                 650                 655
Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr Ile Cys
            660                 665                 670
Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp Ile Leu
        675                 680                 685
Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser Phe Ser
    690                 695                 700
Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile Pro Leu
705                 710                 715                 720
Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val Ser
                725                 730                 735
Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser Gly Ile
            740                 745                 750
Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln Ser
        755                 760                 765
Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys Tyr
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    770                 775                 780
Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val Phe Asp
785                 790                 795                 800
Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln Lys
                805                 810                 815
Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe Phe
            820                 825                 830
Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His Cys
        835                 840                 845
Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp Asn
    850                 855                 860
Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu Glu
865                 870                 875                 880
Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile Thr
                885                 890                 895
Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile Leu
            900                 905                 910
Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp
        915                 920                 925
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NPP1 amino acid sequence shown above comprises cytoplasmic domain, transmembrane domain, SMB1 domain, SMB2 domain, phosphodiesterase/catalytic domain, linker domain and nuclease domain. The SMB1 domain, SMB2 domain, catalytic domain, linker domain and the nuclease domain are jointly referred to as the extracellular domain. Residues 1-76 (Met Glu Arg to Thr Tyr Lys) correspond to the cytoplasmic domain. Residues 77-97 (Val Leu Ser to Phe Gly Leu) correspond to the transmembrane domain. Residues 99-925 (Pro Ser Cys to Gln Glu Asp) correspond to the extracellular domain. Residues 104-144 (Glu Val Lys to Glu Pro Glu) correspond to SMB1 domain and residues 145-189 (His Ile Trp to Glu Lys Ser) correspond to SMB2 domain. Residues 597-647 correspond to linker domain that connects catalytic and nuclease domains. Residues 191-591 (Val Glu Glu to Gly Ser Leu) correspond to the catalytic/phosphodiesterase domain. Residues 654-925(His Glu Thr to Gln Glu Asp) correspond to the nuclease domain. The residue numbering and domain classification are based on human NPP1 sequence (NCBI accession NP_006199/Uniprot-Swissprot P22413)

SEQ ID No: 2 – Azurocidin-ENPP1-FC

MTRLTVLALLAGLLASSRA**APSCAKEVKSCKGRCFERTFGNCRCDAACVELGNCCLDYQETCIEPEHI
WTCNKFRCGEKRLTRSLCACSDDCKDKGDCCINYSSVCQGEKSWVEEPCESINEPQCPAGFETPPTLLFS
LDGFRAEYLHTWGGLLPVISKLKKCGTYTKNMRPVYPTKTFPNHYSIVTGLYPESHGIIDNKMYDPKMNA
SFSLKSKEKFNPEWYKGEPIWVTAKYQGLKSGTFFWPGSDVEINGIFPDIYKMYNGSVPFEERILAVLQW

LQLPKDERPHFYTLYLEEPDSSGHSYGPVSSEVIKALQRVDGMVGMLMDGLKELNLHRCLNLILISDHGM
EQGSCKKYIYLNKYLGDVKNIKVIYGPAARLRPSDVPDKYYSFNYEGIARNLSCREPNQHFKPYLKHFLP
KRLHFAKSDRIEPLTFYLDPQWQLALNPSERKYCGSGFHGSDNVFSNMQALFVGYGPGFKHGIEADTFEN
IEVYNLMCDLLNLTPAPNNGTHGSLNHLLKNPVYTPKHPKEVHPLVQCPFTRNPRDNLGCSCNPSILPIE
DFQTQFNLTVAEEKIIKHETLPYGRPRVLQKENTICLLSQHQFMSGYSQDILMPLWTSYTVDRNDSFSTE
DFSNCLYQDFRIPLSPVHKCSFYKNNTKVSYGFLSPPQLNKNSSGIYSEALLTTNIVPMYQSFQVIWRYF
HDTLLRKYAEERNGVNVVSGPVFDFDYDGRCDSLENLRQKRRVIRNQEILIPTHFFIVLTSCKDTSQTPL
HCENLDTLAFILPHRTDNSESCVHGKHDSSWVEELLMLHRARITDVEHITGLSFYQQRKEPVSDILKLKT
HLPTFSQEDLIN**DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY**
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
QGNVFSCSVMHEALHNHYTQKSLSLSPGK

Single underline – Azurocidin signal sequence, Double underline – Beginning and end of ENPP1 sequence, Bold residues- Fc sequence, ** indicates the cleavage point of the signal sequence.

SEQ ID No: 3 – Azurocidin-ENPP1-Alb

MTRLTVLALLAGLLASSRA**APSCAKEVKSCKGRCFERTFGNCRCDAACVELGNCCLDYQETCIEPEHI
WTCNKFRCGEKRLTRSLCACSDDCKDKGDCCINYSSVCQGEKSWVEEPCESINEPQCPAGFETPPTLLFS
LDGFRAEYLHTWGGLLPVISKLKKCGTYTKNMRPVYPTKTFPNHYSIVTGLYPESHGIIDNKMYDPKMNA
SFSLKSKEKFNPEWYKGEPIWVTAKYQGLKSGTFFWPGSDVEINGIFPDIYKMYNGSVPFEERILAVLQW
LQLPKDERPHFYTLYLEEPDSSGHSYGPVSSEVIKALQRVDGMVGMLMDGLKELNLHRCLNLILISDHGM
EQGSCKKYIYLNKYLGDVKNIKVIYGPAARLRPSDVPDKYYSFNYEGIARNLSCREPNQHFKPYLKHFLP
KRLHFAKSDRIEPLTFYLDPQWQLALNPSERKYCGSGFHGSDNVFSNMQALFVGYGPGFKHGIEADTFEN
IEVYNLMCDLLNLTPAPNNGTHGSLNHLLKNPVYTPKHPKEVHPLVQCPFTRNPRDNLGCSCNPSILPIE
DFQTQFNLTVAEEKIIKHETLPYGRPRVLQKENTICLLSQHQFMSGYSQDILMPLWTSYTVDRNDSFSTE
DFSNCLYQDFRIPLSPVHKCSFYKNNTKVSYGFLSPPQLNKNSSGIYSEALLTTNIVPMYQSFQVIWRYF
HDTLLRKYAEERNGVNVVSGPVFDFDYDGRCDSLENLRQKRRVIRNQEILIPTHFFIVLTSCKDTSQTPL
HCENLDTLAFILPHRTDNSESCVHGKHDSSWVEELLMLHRARITDVEHITGLSFYQQRKEPVSDILKLKT
HLPTFSQEDLIN**MKWVTFLLLLFVSGSAFSRGVFRREAHKSEIAHRYNDLGEQHFKGLVLIAFSQYLQKC**
SYDEHAKLVQEVTDFAKTCVADESAANCDKSLHTLFGDKLCAIPNLRENYGELADCCTKQEPERNECFLQ
HKDDNPSLPPFERPEAEAMCTSFKENPTTFMGHYLHEVARRHPYFYAPELLYYAEQYNEILTQCCAEADK
ESCLTPKLDGVKEKALVSSVRQRMKCSSMQKFGERAFKAWAVARLSQTFPNADFAEITKLATDLTKVNKE
CCHGDLLECADDRAELAKYMCENQATISSKLQTCCDKPLLKKAHCLSEVEHDTMPADLPAIAADFVEDQE
VCKNYAEAKDVFLGTFLYEYSRRHPDYSVSLLLRLAKKYEATLEKCCAEANPPACYGTVLAEFQPLVEEP
KNLVKTNCDLYEKLGEYGFQNAILVRYTQKAPQVSTPTLVEAARNLGRVGTKCCTLPEDQRLPCVEDYLS
AILNRVCLLHEKTPVSEHVTKCCSGSLVERRPCFSALTVDETYVPKEFKAETFTFHSDICTLPEKEKQIK
KQTALAELVKHKPKATAEQLKTVMDDFAQFLDTCCKAADKDTCFSTEGPNLVTRCKDALARSWSHPQFEK

Single underline – Azurocidin signal sequence, Double underline – Beginning and end of ENPP1 sequence, Bold residues- Albumin sequence, ** indicates the cleavage point of the signal sequence.

SEQ ID No: 4 – Azurocidin-ENPP1

MTRLTVLALLAGLLASSRA**APSCAKEVKSCKGRCFERTFGNCRCDAACVELGNCCLDYQETCIEPEHI
WTCNKFRCGEKRLTRSLCACSDDCKDKGDCCINYSSVCQGEKSWVEEPCESINEPQCPAGFETPPTLLFS
LDGFRAEYLHTWGGLLPVISKLKKCGTYTKNMRPVYPTKTFPNHYSIVTGLYPESHGIIDNKMYDPKMNA
SFSLKSKEKFNPEWYKGEPIWVTAKYQGLKSGTFFWPGSDVEINGIFPDIYKMYNGSVPFEERILAVLQW
LQLPKDERPHFYTLYLEEPDSSGHSYGPVSSEVIKALQRVDGMVGMLMDGLKELNLHRCLNLILISDHGM

EQGSCKKYIYLNKYLGDVKNIKVIYGPAARLRPSDVPDKYYSFNYEGIARNLSCREPNQHFKPYLKHFLP
KRLHFAKSDRIEPLTFYLDPQWQLALNPSERKYCGSGFHGSDNVFSNMQALFVGYGPGFKHGIEADTFEN
IEVYNLMCDLLNLTPAPNNGTHGSLNHLLKNPVYTPKHPKEVHPLVQCPFTRNPRDNLGCSCNPSILPIE
DFQTQFNLTVAEEKIIKHETLPYGRPRVLQKENTICLLSQHQFMSGYSQDILMPLWTSYTVDRNDSFSTE
DFSNCLYQDFRIPLSPVHKCSFYKNNTKVSYGFLSPPQLNKNSSGIYSEALLTTNIVPMYQSFQVIWRYF
HDTLLRKYAEERNGVNVVSGPVFDFDYDGRCDSLENLRQKRRVIRNQEILIPTHFFIVLTSCKDTSQTAP
SCAKEVKSCKGRCFERTFGNCRCDAACVELGNCCLDYQETCIEPEHIWTCNKFRCGEKRLTRSLCACSDD
CKDKGDCCINYSSVCQGEKSWVEEPCESINEPQCPAGFETPPTLLFSLDGFRAEYLHTWGGLLPVISKLK
KCGTYTKNMRPVYPTKTFPNHYSIVTGLYPESHGIIDNKMYDPKMNASFSLKSKEKFNPEWYKGEPIWVT
AKYQGLKSGTFFWPGSDVEINGIFPDIYKMYNGSVPFEERILAVLQWLQLPKDERPHFYTLYLEEPDSSG
HSYGPVSSEVIKALQRVDGMVGMLMDGLKELNLHRCLNLILISDHGMEQGSCKKYIYLNKYLGDVKNIKV
IYGPAARLRPSDVPDKYYSFNYEGIARNLSCREPNQHFKPYLKHFLPKRLHFAKSDRIEPLTFYLDPQWQ
LALNPSERKYCGSGFHGSDNVFSNMQALFVGYGPGFKHGIEADTFENIEVYNLMCDLLNLTPAPNNGTHG
SLNHLLKNPVYTPKHPKEVHPLVQCPFTRNPRDNLGCSCNPSILPIEDFQTQFNLTVAEEKIIKHETLPY
GRPRVLQKENTICLLSQHQFMSGYSQDILMPLWTSYTVDRNDSFSTEDFSNCLYQDFRIPLSPVHKCSFY
KNNTKVSYGFLSPPQLNKNSSGIYSEALLTTNIVPMYQSFQVIWRYFHDTLLRKYAEERNGVNVVSGPVF
DFDYDGRCDSLENLRQKRRVIRNQEILIPTHFFIVLTSCKDTSQTPLHCENLDTLAFILPHRTDNSESCV
HGKHDSSWVEELLMLHRARITDVEHITGLSFYQQRKEPVSDILKLKTHLPTFSQED

Single underline – Azurocidin signal sequence, Double underline – Beginning and end of ENPP1 sequence, ** indicates the cleavage point of the signal sequence.

SEQ ID NO: 5 – ENPP2 Amino Acid Sequence – Wild Type

```
Met Ala Arg Arg Ser Ser Phe Gln Ser Cys Gln Ile Ile Ser Leu Phe
1               5                  10                  15
Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly Phe Thr Ala His Arg
            20                  25                  30
Ile Lys Arg Ala Glu Gly Trp Glu Glu Gly Pro Pro Thr Val Leu Ser
        35                  40                  45
Asp Ser Pro Trp Thr Asn Ile Ser Gly Ser Cys Lys Gly Arg Cys Phe
    50                  55                  60
Glu Leu Gln Glu Ala Gly Pro Pro Asp Cys Arg Cys Asp Asn Leu Cys
65                  70                  75                  80
Lys Ser Tyr Thr Ser Cys Cys His Asp Phe Asp Glu Leu Cys Leu Lys
                85                  90                  95
Thr Ala Arg Gly Trp Glu Cys Thr Lys Asp Arg Cys Gly Glu Val Arg
            100                 105                 110
Asn Glu Glu Asn Ala Cys His Cys Ser Glu Asp Cys Leu Ala Arg Gly
        115                 120                 125
Asp Cys Cys Thr Asn Tyr Gln Val Val Cys Lys Gly Glu Ser His Trp
    130                 135                 140
Val Asp Asp Asp Cys Glu Glu Ile Lys Ala Ala Glu Cys Pro Ala Gly
145                 150                 155                 160
Phe Val Arg Pro Pro Leu Ile Ile Phe Ser Val Asp Gly Phe Arg Ala
                165                 170                 175
Ser Tyr Met Lys Lys Gly Ser Lys Val Met Pro Asn Ile Glu Lys Leu
            180                 185                 190
Arg Ser Cys Gly Thr His Ser Pro Tyr Met Arg Pro Val Tyr Pro Thr
        195                 200                 205
Lys Thr Phe Pro Asn Leu Tyr Thr Leu Ala Thr Gly Leu Tyr Pro Glu
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    210                 215                 220
Ser His Gly Ile Val Gly Asn Ser Met Tyr Asp Pro Val Phe Asp Ala
225                 230                 235                 240
Thr Phe His Leu Arg Gly Arg Glu Lys Phe Asn His Arg Trp Trp Gly
                245                 250                 255
Gly Gln Pro Leu Trp Ile Thr Ala Thr Lys Gln Gly Val Lys Ala Gly
            260                 265                 270
Thr Phe Phe Trp Ser Val Val Ile Pro His Glu Arg Arg Ile Leu Thr
        275                 280                 285
Ile Leu Gln Trp Leu Thr Leu Pro Asp His Glu Arg Pro Ser Val Tyr
    290                 295                 300
Ala Phe Tyr Ser Glu Gln Pro Asp Phe Ser Gly His Lys Tyr Gly Pro
305                 310                 315                 320
Phe Gly Pro Glu Met Thr Asn Pro Leu Arg Glu Ile Asp Lys Ile Val
                325                 330                 335
Gly Gln Leu Met Asp Gly Leu Lys Gln Leu Lys Leu His Arg Cys Val
            340                 345                 350
Asn Val Ile Phe Val Gly Asp His Gly Met Glu Asp Val Thr Cys Asp
        355                 360                 365
Arg Thr Glu Phe Leu Ser Asn Tyr Leu Thr Asn Val Asp Asp Ile Thr
    370                 375                 380
Leu Val Pro Gly Thr Leu Gly Arg Ile Arg Ser Lys Phe Ser Asn Asn
385                 390                 395                 400
Ala Lys Tyr Asp Pro Lys Ala Ile Ile Ala Asn Leu Thr Cys Lys Lys
                405                 410                 415
Pro Asp Gln His Phe Lys Pro Tyr Leu Lys Gln His Leu Pro Lys Arg
            420                 425                 430
Leu His Tyr Ala Asn Asn Arg Arg Ile Glu Asp Ile His Leu Leu Val
        435                 440                 445
Glu Arg Arg Trp His Val Ala Arg Lys Pro Leu Asp Val Tyr Lys Lys
    450                 455                 460
Pro Ser Gly Lys Cys Phe Phe Gln Gly Asp His Gly Phe Asp Asn Lys
465                 470                 475                 480
Val Asn Ser Met Gln Thr Val Phe Val Gly Tyr Gly Ser Thr Phe Lys
                485                 490                 495
Tyr Lys Thr Lys Val Pro Pro Phe Glu Asn Ile Glu Leu Tyr Asn Val
            500                 505                 510
Met Cys Asp Leu Leu Gly Leu Lys Pro Ala Pro Asn Asn Gly Thr His
        515                 520                 525
Gly Ser Leu Asn His Leu Leu Arg Thr Asn Thr Phe Arg Pro Thr Met
    530                 535                 540
Pro Glu Glu Val Thr Arg Pro Asn Tyr Pro Gly Ile Met Tyr Leu Gln
545                 550                 555                 560
Ser Asp Phe Asp Leu Gly Cys Thr Cys Asp Asp Lys Val Glu Pro Lys
                565                 570                 575
Asn Lys Leu Asp Glu Leu Asn Lys Arg Leu His Thr Lys Gly Ser Thr
            580                 585                 590
Glu Ala Glu Thr Arg Lys Phe Arg Gly Ser Arg Asn Glu Asn Lys Glu
        595                 600                 605
Asn Ile Asn Gly Asn Phe Glu Pro Arg Lys Glu Arg His Leu Leu Tyr
    610                 615                 620
Gly Arg Pro Ala Val Leu Tyr Arg Thr Arg Tyr Asp Ile Leu Tyr His
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625 630 635 640
Thr Asp Phe Glu Ser Gly Tyr Ser Glu Ile Phe Leu Met Pro Leu Trp
645 650 655
Thr Ser Tyr Thr Val Ser Lys Gln Ala Glu Val Ser Ser Val Pro Asp
660 665 670
His Leu Thr Ser Cys Val Arg Pro Asp Val Arg Val Ser Pro Ser Phe
675 680 685
Ser Gln Asn Cys Leu Ala Tyr Lys Asn Asp Lys Gln Met Ser Tyr Gly
690 695 700
Phe Leu Phe Pro Pro Tyr Leu Ser Ser Ser Pro Glu Ala Lys Tyr Asp
705 710 715 720
Ala Phe Leu Val Thr Asn Met Val Pro Met Tyr Pro Ala Phe Lys Arg
725 730 735
Val Trp Asn Tyr Phe Gln Arg Val Leu Val Lys Lys Tyr Ala Ser Glu
740 745 750
Arg Asn Gly Val Asn Val Ile Ser Gly Pro Ile Phe Asp Tyr Asp Tyr
755 760 765
Asp Gly Leu His Asp Thr Glu Asp Lys Ile Lys Gln Tyr Val Glu Gly
770 775 780
Ser Ser Ile Pro Val Pro Thr His Tyr Tyr Ser Ile Ile Thr Ser Cys
785 790 795 800
Leu Asp Phe Thr Gln Pro Ala Asp Lys Cys Asp Gly Pro Leu Ser Val
805 810 815
Ser Ser Phe Ile Leu Pro His Arg Pro Asp Asn Glu Glu Ser Cys Asn
820 825 830
Ser Ser Glu Asp Glu Ser Lys Trp Val Glu Glu Leu Met Lys Met His
835 840 845
Thr Ala Arg Val Arg Asp Ile Glu His Leu Thr Ser Leu Asp Phe Phe
850 855 860
Arg Lys Thr Ser Arg Ser Tyr Pro Glu Ile Leu Thr Leu Lys Thr Tyr
865 870 875 880

Leu His Thr Tyr Glu Ser Glu Ile
885

SEQ. ID NO:6 - Extracellular Domain of ENPP3:

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

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Val Ile Leu Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr Leu Tyr Thr
        115                 120                 125
Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys Thr Cys Gly Ile
    130                 135                 140
His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr Phe Pro Asn
145                 150                 155                 160
His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly Ile Ile
                165                 170                 175
Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser Leu Ser
            180                 185                 190
Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro Met Trp
        195                 200                 205
Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe Trp Pro
    210                 215                 220
Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr Met Pro
225                 230                 235                 240
Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu Leu Lys
                245                 250                 255
Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr Met Tyr
            260                 265                 270
Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val Ser Ala
        275                 280                 285
Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala Phe Gly Met Leu
    290                 295                 300
Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn Ile Ile
305                 310                 315                 320
Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys Met Glu
                325                 330                 335
Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr Met Tyr Glu
            340                 345                 350
Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro His Asp Phe Phe
        355                 360                 365
Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg Lys Pro
    370                 375                 380
Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys Arg Leu
385                 390                 395                 400
His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His Leu Phe Val Asp
                405                 410                 415
Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys Gly Gly
            420                 425                 430
Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala Ile Phe
        435                 440                 445
Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu Pro Phe
    450                 455                 460
Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg Ile Gln
465                 470                 475                 480
Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His Leu Leu Lys
                485                 490                 495
Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys Phe Ser
            500                 505                 510
Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu Asp Cys Phe
        515                 520                 525
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Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn Gln Met
    530                 535                 540
Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val Asn Leu
545                 550                 555                 560
Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val Asp His Cys Leu
                565                 570                 575
Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala Met Arg Met
            580                 585                 590
Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp Thr Ser Pro
        595                 600                 605
Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp Val Arg Val Pro
    610                 615                 620
Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys Asn Ile
625                 630                 635                 640
Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser Asp Ser
                645                 650                 655
Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro Met Tyr Glu Glu
            660                 665                 670
Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu Leu Ile Lys His
        675                 680                 685
Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile Phe Asp
    690                 695                 700
Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr Lys His
705                 710                 715                 720
Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val Val Leu
                725                 730                 735
Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro Gly Trp
            740                 745                 750
Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn Val Glu
        755                 760                 765
Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu Arg Phe
    770                 775                 780
Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr Gly Leu
785                 790                 795                 800
Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu Gln Leu
                805                 810                 815
Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile
            820                 825
```

SEQ. ID NO: 7 - NPP3 Amino Acid Sequence:

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Met Glu Ser Thr Leu Thr Leu Ala Thr Glu Gln Pro Val Lys Lys Asn
1               5                   10                  15
Thr Leu Lys Lys Tyr Lys Ile Ala Cys Ile Val Leu Leu Ala Leu Leu
            20                  25                  30
Val Ile Met Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys Leu
        35                  40                  45
Glu Lys Gln Gly Ser Cys Arg Lys Lys Cys Phe Asp Ala Ser Phe Arg
    50                  55                  60
Gly Leu Glu Asn Cys Arg Cys Asp Val Ala Cys Lys Asp Arg Gly Asp
65                  70                  75                  80
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Cys Cys Trp Asp Phe Glu Asp Thr Cys Val Glu Ser Thr Arg Ile Trp
                85                  90                  95
Met Cys Asn Lys Phe Arg Cys Gly Glu Thr Arg Leu Glu Ala Ser Leu
            100                 105                 110
Cys Ser Cys Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys Cys Ala Asp
        115                 120                 125
Tyr Lys Ser Val Cys Gln Gly Glu Thr Ser Trp Leu Glu Glu Asn Cys
    130                 135                 140
Asp Thr Ala Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp Leu Pro Pro
145                 150                 155                 160
Val Ile Leu Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr Leu Tyr Thr
                165                 170                 175
Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys Thr Cys Gly Ile
            180                 185                 190
His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr Phe Pro Asn
        195                 200                 205
His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly Ile Ile
    210                 215                 220
Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser Leu Ser
225                 230                 235                 240
Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro Met Trp
                245                 250                 255
Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe Trp Pro
            260                 265                 270
Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr Met Pro
        275                 280                 285
Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu Leu Lys
    290                 295                 300
Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr Met Tyr
305                 310                 315                 320
Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val Ser Ala
                325                 330                 335
Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala Phe Gly Met Leu
            340                 345                 350
Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn Ile Ile
        355                 360                 365
Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys Met Glu
    370                 375                 380
Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr Met Tyr Glu
385                 390                 395                 400
Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro His Asp Phe Phe
                405                 410                 415
Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg Lys Pro
            420                 425                 430
Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys Arg Leu
        435                 440                 445
His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His Leu Phe Val Asp
    450                 455                 460
Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys Gly Gly
465                 470                 475                 480
Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala Ile Phe
                485                 490                 495
```

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Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu Pro Phe
            500                 505                 510
Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg Ile Gln
        515                 520                 525
Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His Leu Leu Lys
    530                 535                 540
Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys Phe Ser
545                 550                 555                 560
Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu Asp Cys Phe
                565                 570                 575
Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn Gln Met
            580                 585                 590
Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val Asn Leu
        595                 600                 605
Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val Asp His Cys Leu
    610                 615                 620
Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala Met Arg Met
625                 630                 635                 640
Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp Thr Ser Pro
                645                 650                 655
Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp Val Arg Val Pro
            660                 665                 670
Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys Asn Ile
          675                 680                 685
Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser Asp Ser
      690                 695                 700
Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro Met Tyr Glu Glu
705                 710                 715                 720
Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu Leu Ile Lys His
                725                 730                 735
Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile Phe Asp
            740                 745                 750
Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr Lys His
        755                 760                 765
Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val Val Leu
    770                 775                 780
Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro Gly Trp
785                 790                 795                 800
Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn Val Glu
                805                 810                 815
Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu Arg Phe
            820                 825                 830
Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr Gly Leu
        835                 840                 845
Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu Gln Leu
    850                 855                 860
Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile
865                 870                 875
```

NPP3 amino acid sequence shown above comprises cytoplasmic domain, transmembrane domain, phosphodiesterase/catalytic domain and Nuclease

domain. The catalytic domain and the nuclease domain are jointly referred to as the extracellular domain. Residues 1-11 (Met Glu Ser to Ala Thr Glu) correspond to the cytoplasmic domain. Residues 12-30 (Gln Pro Val to Leu Leu Ala) correspond to the transmembrane domain. Residues 31-875 (Leu Leu Val to Thr Thr Ile) correspond to the extracellular domain. Residues 140-510 (Leu Glu Glu to Glu Val Glu) correspond to the catalytic/phosphodiesterase domain. Residues 605 to 875 (Lys Val Asn to Thr Thr Ile) correspond to the nuclease domain. The residue numbering and domain classification are based on human NPP3 sequence (UniProtKB/Swiss-Prot: O14638.2)

SEQ ID No: 8 – Azurocidin-ENPP3-FC

MTRLTVLALLAGLLASSRA**AKQGSCRKKCFDASFRGLENCRCDVACKDRGDCCWDFEDTCVES
TRIWMCNKFRCGETRLEASLCSCSDDCLQRKDCCADYKSVCQGETSWLEENCDTAQQSQCPEGFDLPPVI
LFSMDGFRAEYLYTWDTLMPNINKLKTCGIHSKYMRAMYPTKTFPNHYTIVTGLYPESHGIIDNNMYDVN
LNKNFSLSSKEQNNPAWWHGQPMNLTAMYQGLKAATYFWPGSEVAINGSFPSIYMPYNGSVPFEERISTL
LKWLDLPKAERPRFYTMYFEEPDSSGHAGGPVSARVIKALQVVDHAFGMLMEGLKQRNLHNCVNIILLAD
HGMDQTYCNKMEYMTDYFPRINFFYMYEGPAPRIRAHNIPHDFFSFNSEEIVRNLSCRKPDQHFKPYLTP
DLPKRLHYAKNVRIDKVHLFVDQQWLAVRSKSNTNCGGGNHGYNNEFRSMEAIFLAHGPSFKEKTEVEPF
ENIEVYNLMCDLLRIQPAPNNGTHGSLNHLLKVPFYEPSHAEEVSKFSVCGFANPLPTESLDCFCPHLQN
STQLEQVNQMLNLTQEEITATVKVNLPFGRPRVLQKNVDHCLLYHREYVSGFGKAMRMPMWSSYTVPQLG
DTSPLPPTVPDCLRADVRVPPSESQKCSFYLADKNITHGFLYPPASNRTSDSQYDALITSNLVPMYEEFR
KMWDYFHSVLLIKHATERNGVNVVSGPIFDYNYDGHFDAPDEITKHLANTDVPIPTHYFVVLTSCKNKSH
TPENCPGWLDVLPFIIPHRPTNVESCPEGKPEALWVEERFTAHIARVRDVELLTGLDFYQDKVQPVSEIL
QLKTYLPTFETTI**DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW
YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPGK**

Single underline – Azurocidin signal sequence, Double underline – Beginning and end of ENPP3 sequence, Bold residues- Fc sequence, ** indicates the cleavage point of the signal sequence.

SEQ ID No: 9 – Azurocidin-ENPP3-Albumin

MTRLTVLALLAGLLASSRA**AKQGSCRKKCFDASFRGLENCRCDVACKDRGDCCWDFEDTCVES
TRIWMCNKFRCGETRLEASLCSCSDDCLQRKDCCADYKSVCQGETSWLEENCDTAQQSQCPEGFDLPPVI
LFSMDGFRAEYLYTWDTLMPNINKLKTCGIHSKYMRAMYPTKTFPNHYTIVTGLYPESHGIIDNNMYDVN
LNKNFSLSSKEQNNPAWWHGQPMNLTAMYQGLKAATYFWPGSEVAINGSFPSIYMPYNGSVPFEERISTL
LKWLDLPKAERPRFYTMYFEEPDSSGHAGGPVSARVIKALQVVDHAFGMLMEGLKQRNLHNCVNIILLAD
HGMDQTYCNKMEYMTDYFPRINFFYMYEGPAPRIRAHNIPHDFFSFNSEEIVRNLSCRKPDQHFKPYLTP
DLPKRLHYAKNVRIDKVHLFVDQQWLAVRSKSNTNCGGGNHGYNNEFRSMEAIFLAHGPSFKEKTEVEPF
ENIEVYNLMCDLLRIQPAPNNGTHGSLNHLLKVPFYEPSHAEEVSKFSVCGFANPLPTESLDCFCPHLQN
STQLEQVNQMLNLTQEEITATVKVNLPFGRPRVLQKNVDHCLLYHREYVSGFGKAMRMPMWSSYTVPQLG
DTSPLPPTVPDCLRADVRVPPSESQKCSFYLADKNITHGFLYPPASNRTSDSQYDALITSNLVPMYEEFR
KMWDYFHSVLLIKHATERNGVNVVSGPIFDYNYDGHFDAPDEITKHLANTDVPIPTHYFVVLTSCKNKSH
TPENCPGWLDVLPFIIPHRPTNVESCPEGKPEALWVEERFTAHIARVRDVELLTGLDFYQDKVQPVSEIL

QLKTYLPTFETTI**MKWVTFLLLLFVSGSAFSRGVFRREAHKSEIAHRYNDLGEQHFKGLVLIAFSQYLQK
CSYDEHAKLVQEVTDFAKTCVADESAANCDKSLHTLFGDKLCAIPNLRENYGELADCCTKQEPERNECFL
QHKDDNPSLPPFERPEAEAMCTSFKENPTTFMGHYLHEVARRHPYFYAPELLYYAEQYNEILTQCCAEAD
KESCLTPKLDGVKEKALVSSVRQRMKCSSMQKFGERAFKAWAVARLSQTFPNADFAEITKLATDLTKVNK
ECCHGDLLECADDRAELAKYMCENQATISSKLQTCCDKPLLKKAHCLSEVEHDTMPADLPAIAADFVEDQ
EVCKNYAEAKDVFLGTFLYEYSRRHPDYSVSLLLRLAKKYEATLEKCCAEANPPACYGTVLAEFQPLVEE
PKNLVKTNCDLYEKLGEYGFQNAILVRYTQKAPQVSTPTLVEAARNLGRVGTKCCTLPEDQRLPCVEDYL
SAILNRVCLLHEKTPVSEHVTKCCSGSLVERRPCFSALTVDETYVPKEFKAETFTFHSDICTLPEKEKQI
KKQTALAELVKHKPKATAEQLKTVMDDFAQFLDTCCKAADKDTCFSTEGPNLVTRCKDALARSWSHPQFE
K**

Single underline – Azurocidin signal sequence, Double underline – Beginning and end of ENPP3 sequence, Bold residues- Albumin sequence, ** indicates the cleavage point of the signal sequence.

SEQ ID No: 10 – Azurocidin-ENPP3

MTRLTVLALLAGLLASSRA**AKQGSCRKKCFDASFRGLENCRCDVACKDRGDCCWDFEDTCVES
TRIWMCNKFRCGETRLEASLCSCSDDCLQRKDCCADYKSVCQGETSWLEENCDTAQQSQCPEGFDLPPVI
LFSMDGFRAEYLYTWDTLMPNINKLKTCGIHSKYMRAMYPTKTFPNHYTIVTGLYPESHGIIDNNMYDVN
LNKNFSLSSKEQNNPAWWHGQPMNLTAMYQGLKAATYFWPGSEVAINGSFPSIYMPYNGSVPFEERISTL
LKWLDLPKAERPRFYTMYFEEPDSSGHAGGPVSARVIKALQVVDHAFGMLMEGLKQRNLHNCVNIILLAD
HGMDQTYCNKMEYMTDYFPRINFFYMYEGPAPRIRAHNIPHDFFSFNSEEIVRNLSCRKPDQHFKPYLTP
DLPKRLHYAKNVRIDKVHLFVDQQWLAVRSKSNTNCGGGNHGYNNEFRSMEAIFLAHGPSFKEKTEVEPF
ENIEVYNLMCDLLRIQPAPNNGTHGSLNHLLKVPFYEPSHAEEVSKFSVCGFANPLPTESLDCFCPHLQN
STQLEQVNQMLNLTQEEITATVKVNLPFGRPRVLQKNVDHCLLYHREYVSGFGKAMRMPMWSSYTVPQLG
DTSPLPPTVPDCLRADVRVPPSESQKCSFYLADKNITHGFLYPPASNRTSDSQYDALITSNLVPMYEEFR
KMWDYFHSVLLIKHATERNGVNVVSGPIFDYNYDGHFDAPDEITKHLANTDVPIPTHYFVVLTSCKNKSH
TPENCPGWLDVLPFIIPHRPTNVESCPEGKPEALWVEERFTAHIARVRDVELLTGLDFYQDKVQPVSEIL
QLKTYLPTFETTI

Single underline – Azurocidin signal sequence, Double underline – Beginning and end of ENPP3 sequence, ** indicates the cleavage point of the signal sequence.

SEQ. ID NO:11 – ENPP4 Amino Acid Sequence – Wild Type

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

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            100                 105                 110
Trp Asn Glu Ala Val Pro Ile Trp Val Thr Asn Gln Leu Gln Glu Asn
        115                 120                 125
Arg Ser Ser Ala Ala Ala Met Trp Pro Gly Thr Asp Val Pro Ile His
    130                 135                 140
Asp Thr Ile Ser Ser Tyr Phe Met Asn Tyr Asn Ser Ser Val Ser Phe
145                 150                 155                 160
Glu Glu Arg Leu Asn Asn Ile Thr Met Trp Leu Asn Asn Ser Asn Pro
                165                 170                 175
Pro Val Thr Phe Ala Thr Leu Tyr Trp Glu Glu Pro Asp Ala Ser Gly
            180                 185                 190
His Lys Tyr Gly Pro Glu Asp Lys Glu Asn Met Ser Arg Val Leu Lys
        195                 200                 205
Lys Ile Asp Asp Leu Ile Gly Asp Leu Val Gln Arg Leu Lys Met Leu
    210                 215                 220
Gly Leu Trp Glu Asn Leu Asn Val Ile Ile Thr Ser Asp His Gly Met
225                 230                 235                 240
Thr Gln Cys Ser Gln Asp Arg Leu Ile Asn Leu Asp Ser Cys Ile Asp
                245                 250                 255
His Ser Tyr Tyr Thr Leu Ile Asp Leu Ser Pro Val Ala Ala Ile Leu
            260                 265                 270
Pro Lys Ile Asn Arg Thr Glu Val Tyr Asn Lys Leu Lys Asn Cys Ser
        275                 280                 285
Pro His Met Asn Val Tyr Leu Lys Glu Asp Ile Pro Asn Arg Phe Tyr
    290                 295                 300
Tyr Gln His Asn Asp Arg Ile Gln Pro Ile Ile Leu Val Ala Asp Glu
305                 310                 315                 320
Gly Trp Thr Ile Val Leu Asn Glu Ser Ser Gln Lys Leu Gly Asp His
                325                 330                 335
Gly Tyr Asp Asn Ser Leu Pro Ser Met His Pro Phe Leu Ala Ala His
            340                 345                 350
Gly Pro Ala Phe His Lys Gly Tyr Lys His Ser Thr Ile Asn Ile Val
        355                 360                 365
Asp Ile Tyr Pro Met Met Cys His Ile Leu Gly Leu Lys Pro His Pro
    370                 375                 380
Asn Asn Gly Thr Phe Gly His Thr Lys Cys Leu Leu Val Asp Gln Trp
385                 390                 395                 400
Cys Ile Asn Leu Pro Glu Ala Ile Ala Ile Val Ile Gly Ser Leu Leu
                405                 410                 415
Val Leu Thr Met Leu Thr Cys Leu Ile Ile Ile Met Gln Asn Arg Leu
            420                 425                 430

Ser Val Pro Arg Pro Phe Ser Arg Leu Gln Leu Gln Glu Asp Asp Asp
        435                 440                 445
Asp Pro Leu Ile Gly
    450
```

SEQ. ID NO: 12 - ENPP51 Amino Acid Sequence

Met Thr Ser Lys Phe Leu Leu Val Ser Phe Ile Leu Ala Ala Leu Ser

```
1               5                  10                  15
Leu Ser Thr Thr Phe Ser Leu Gln**Pro Ser Cys Ala Lys Glu Val Lys
            20                  25                  30
Ser Cys Lys Gly Arg Cys Phe Glu Arg Thr Phe Ser Asn Cys Arg Cys
        35                  40                  45
Asp Ala Ala Cys Val Ser Leu Gly Asn Cys Cys Leu Asp Phe Gln Glu
    50                  55                  60
Thr Cys Val Glu Pro Thr His Ile Trp Thr Cys Asn Lys Phe Arg Cys
65                  70                  75                  80
Gly Glu Lys Arg Leu Ser Arg Phe Val Cys Ser Cys Ala Asp Asp Cys
                85                  90                  95
Lys Thr His Asn Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln Asp
            100                 105                 110
Lys Lys Ser Trp Val Glu Glu Thr Cys Glu Ser Ile Asp Thr Pro Glu
        115                 120                 125
Cys Pro Ala Glu Phe Glu Ser Pro Pro Thr Leu Leu Phe Ser Leu Asp
    130                 135                 140
Gly Phe Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro Val
145                 150                 155                 160
Ile Ser Lys Leu Lys Asn Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro
                165                 170                 175
Met Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly
            180                 185                 190
Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro
        195                 200                 205
Lys Met Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro
    210                 215                 220
Leu Trp Tyr Lys Gly Gln Pro Ile Trp Val Thr Ala Asn His Gln Glu
225                 230                 235                 240
Val Lys Ser Gly Thr Tyr Phe Trp Pro Gly Ser Asp Val Glu Ile Asp
                245                 250                 255
Gly Ile Leu Pro Asp Ile Tyr Lys Val Tyr Asn Gly Ser Val Pro Phe
            260                 265                 270
Glu Glu Arg Ile Leu Ala Val Leu Glu Trp Leu Gln Leu Pro Ser His
        275                 280                 285
Glu Arg Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser
    290                 295                 300
Gly His Ser His Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln
305                 310                 315                 320
Lys Val Asp Arg Leu Val Gly Met Leu Met Asp Gly Leu Lys Asp Leu
                325                 330                 335
Gly Leu Asp Lys Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met
            340                 345                 350
Glu Gln Gly Ser Cys Lys Lys Tyr Val Tyr Leu Asn Lys Tyr Leu Gly
        355                 360                 365
Asp Val Asn Asn Val Lys Val Val Tyr Gly Pro Ala Ala Arg Leu Arg
    370                 375                 380
Pro Thr Asp Val Pro Glu Thr Tyr Tyr Ser Phe Asn Tyr Glu Ala Leu
385                 390                 395                 400
Ala Lys Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Arg Pro Tyr
                405                 410                 415
Leu Lys Pro Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg
```

```
            420                 425                 430
Ile Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu
        435                 440                 445
Asn Pro Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp
    450                 455                 460
Asn Leu Phe Ser Asn Met Gln Ala Leu Phe Ile Gly Tyr Gly Pro Ala
465                 470                 475                 480
Phe Lys His Gly Ala Glu Val Asp Ser Phe Glu Asn Ile Glu Val Tyr
                485                 490                 495
Asn Leu Met Cys Asp Leu Leu Gly Leu Ile Pro Ala Pro Asn Asn Gly
            500                 505                 510
Ser His Gly Ser Leu Asn His Leu Leu Lys Lys Pro Ile Tyr Asn Pro
        515                 520                 525
Ser His Pro Lys Glu Glu Gly Phe Leu Ser Gln Cys Pro Ile Lys Ser
    530                 535                 540
Thr Ser Asn Asp Leu Gly Cys Thr Cys Asp Pro Trp Ile Val Pro Ile
545                 550                 555                 560
Lys Asp Phe Glu Lys Gln Leu Asn Leu Thr Thr Glu Asp Val Asp Asp
                565                 570                 575
Ile Tyr His Met Thr Val Pro Tyr Gly Arg Pro Arg Ile Leu Leu Lys
            580                 585                 590
Gln His Arg Val Cys Leu Leu Gln Gln Gln Gln Phe Leu Thr Gly Tyr
        595                 600                 605
Ser Leu Asp Leu Leu Met Pro Leu Trp Ala Ser Tyr Thr Phe Leu Ser
    610                 615                 620
Asn Asp Gln Phe Ser Arg Asp Asp Phe Ser Asn Cys Leu Tyr Gln Asp
625                 630                 635                 640
Leu Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Tyr Tyr Lys Ser
                645                 650                 655
Asn Ser Lys Leu Ser Tyr Gly Phe Leu Thr Pro Pro Arg Leu Asn Arg
            660                 665                 670
Val Ser Asn His Ile Tyr Ser Glu Ala Leu Leu Thr Ser Asn Ile Val
        675                 680                 685
Pro Met Tyr Gln Ser Phe Gln Val Ile Trp His Tyr Leu His Asp Thr
    690                 695                 700
Leu Leu Gln Arg Tyr Ala His Glu Arg Asn Gly Ile Asn Val Val Ser
705                 710                 715                 720
Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Tyr Asp Ser Leu Glu
                725                 730                 735
Ile Leu Lys Gln Asn Ser Arg Val Ile Arg Ser Gln Glu Ile Leu Ile
            740                 745                 750
Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Gln Leu Ser Glu
        755                 760                 765
Thr Pro Leu Glu Cys Ser Ala Leu Glu Ser Ser Ala Tyr Ile Leu Pro
    770                 775                 780
His Arg Pro Asp Asn Ile Glu Ser Cys Thr His Gly Lys Arg Glu Ser
785                 790                 795                 800
Ser Trp Val Glu Glu Leu Leu Thr Leu His Arg Ala Arg Val Thr Asp
                805                 810                 815
Val Glu Leu Ile Thr Gly Leu Ser Phe Tyr Gln Asp Arg Gln Glu Ser
            820                 825                 830
Val Ser Glu Leu Leu Arg Leu Lys Thr His Leu Pro Ile Phe Ser Gln
```

835 840 845

Glu Asp
850

Singly underlined:signal peptide sequence; double-underlined: beginning and end of NPP1; ** = cleavage position at the signal peptide sequence

SEQ. ID NO: 13 - ENPP51 – ALB Amino Acid Sequence:

Met Thr Ser Lys Phe Leu Leu Val Ser Phe Ile Leu Ala Ala Leu Ser
1 5 10 15
Leu Ser Thr Thr Phe Ser Leu Gln**Pro Ser Cys Ala Lys Glu Val Lys
20 25 30
Ser Cys Lys Gly Arg Cys Phe Glu Arg Thr Phe Ser Asn Cys Arg Cys
35 40 45
Asp Ala Ala Cys Val Ser Leu Gly Asn Cys Cys Leu Asp Phe Gln Glu
50 55 60
Thr Cys Val Glu Pro Thr His Ile Trp Thr Cys Asn Lys Phe Arg Cys
65 70 75 80
Gly Glu Lys Arg Leu Ser Arg Phe Val Cys Ser Cys Ala Asp Asp Cys
85 90 95
Lys Thr His Asn Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln Asp
100 105 110
Lys Lys Ser Trp Val Glu Glu Thr Cys Glu Ser Ile Asp Thr Pro Glu
115 120 125
Cys Pro Ala Glu Phe Glu Ser Pro Pro Thr Leu Leu Phe Ser Leu Asp
130 135 140
Gly Phe Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro Val
145 150 155 160
Ile Ser Lys Leu Lys Asn Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro
165 170 175
Met Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly
180 185 190
Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro
195 200 205
Lys Met Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro
210 215 220
Leu Trp Tyr Lys Gly Gln Pro Ile Trp Val Thr Ala Asn His Gln Glu
225 230 235 240
Val Lys Ser Gly Thr Tyr Phe Trp Pro Gly Ser Asp Val Glu Ile Asp
245 250 255
Gly Ile Leu Pro Asp Ile Tyr Lys Val Tyr Asn Gly Ser Val Pro Phe
260 265 270
Glu Glu Arg Ile Leu Ala Val Leu Glu Trp Leu Gln Leu Pro Ser His
275 280 285
Glu Arg Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser
290 295 300
Gly His Ser His Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln

305 310 315 320
Lys Val Asp Arg Leu Val Gly Met Leu Met Asp Gly Leu Lys Asp Leu
325 330 335
Gly Leu Asp Lys Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met
340 345 350
Glu Gln Gly Ser Cys Lys Lys Tyr Val Tyr Leu Asn Lys Tyr Leu Gly
355 360 365
Asp Val Asn Asn Val Lys Val Val Tyr Gly Pro Ala Ala Arg Leu Arg
370 375 380
Pro Thr Asp Val Pro Glu Thr Tyr Tyr Ser Phe Asn Tyr Glu Ala Leu
385 390 395 400
Ala Lys Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Arg Pro Tyr
405 410 415
Leu Lys Pro Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg
420 425 430
Ile Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu
435 440 445
Asn Pro Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp
450 455 460
Asn Leu Phe Ser Asn Met Gln Ala Leu Phe Ile Gly Tyr Gly Pro Ala
465 470 475 480
Phe Lys His Gly Ala Glu Val Asp Ser Phe Glu Asn Ile Glu Val Tyr
485 490 495
Asn Leu Met Cys Asp Leu Leu Gly Leu Ile Pro Ala Pro Asn Asn Gly
500 505 510
Ser His Gly Ser Leu Asn His Leu Leu Lys Lys Pro Ile Tyr Asn Pro
515 520 525
Ser His Pro Lys Glu Glu Gly Phe Leu Ser Gln Cys Pro Ile Lys Ser
530 535 540
Thr Ser Asn Asp Leu Gly Cys Thr Cys Asp Pro Trp Ile Val Pro Ile
545 550 555 560
Lys Asp Phe Glu Lys Gln Leu Asn Leu Thr Thr Glu Asp Val Asp Asp
565 570 575
Ile Tyr His Met Thr Val Pro Tyr Gly Arg Pro Arg Ile Leu Leu Lys
580 585 590
Gln His Arg Val Cys Leu Leu Gln Gln Gln Gln Phe Leu Thr Gly Tyr
595 600 605
Ser Leu Asp Leu Leu Met Pro Leu Trp Ala Ser Tyr Thr Phe Leu Ser
610 615 620
Asn Asp Gln Phe Ser Arg Asp Asp Phe Ser Asn Cys Leu Tyr Gln Asp
625 630 635 640
Leu Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Tyr Tyr Lys Ser
645 650 655
Asn Ser Lys Leu Ser Tyr Gly Phe Leu Thr Pro Pro Arg Leu Asn Arg
660 665 670
Val Ser Asn His Ile Tyr Ser Glu Ala Leu Leu Thr Ser Asn Ile Val
675 680 685
Pro Met Tyr Gln Ser Phe Gln Val Ile Trp His Tyr Leu His Asp Thr
690 695 700
Leu Leu Gln Arg Tyr Ala His Glu Arg Asn Gly Ile Asn Val Val Ser
705 710 715 720
Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Tyr Asp Ser Leu Glu

```
                725                 730                 735
Ile Leu Lys Gln Asn Ser Arg Val Ile Arg Ser Gln Glu Ile Leu Ile
            740                 745                 750
Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Gln Leu Ser Glu
        755                 760                 765
Thr Pro Leu Glu Cys Ser Ala Leu Glu Ser Ser Ala Tyr Ile Leu Pro
    770                 775                 780
His Arg Pro Asp Asn Ile Glu Ser Cys Thr His Gly Lys Arg Glu Ser
785                 790                 795                 800
Ser Trp Val Glu Glu Leu Leu Thr Leu His Arg Ala Arg Val Thr Asp
                805                 810                 815
Val Glu Leu Ile Thr Gly Leu Ser Phe Tyr Gln Asp Arg Gln Glu Ser
            820                 825                 830
Val Ser Glu Leu Leu Arg Leu Lys Thr His Leu Pro Ile Phe Ser Gln
        835                 840                 845
Glu Asp Gly Gly Ser Gly Gly Ser Met Lys Trp Val Thr Phe Leu Leu
    850                 855                 860
Leu Leu Phe Val Ser Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg
865                 870                 875                 880
Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu
                885                 890                 895
Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln
            900                 905                 910
Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu Val Thr Asp
        915                 920                 925
Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys
    930                 935                 940
Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu
945                 950                 955                 960
Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro
                965                 970                 975
Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Ser Leu
            980                 985                 990
Pro Pro Phe Glu Arg Pro Glu Ala  Glu Ala Met Cys Thr  Ser Phe Lys
        995                 1000                1005
Glu Asn  Pro Thr Thr Phe Met  Gly His Tyr Leu His  Glu Val Ala
    1010                1015                1020
Arg Arg  His Pro Tyr Phe Tyr  Ala Pro Glu Leu Leu  Tyr Tyr Ala
    1025                1030                1035
Glu Gln  Tyr Asn Glu Ile Leu  Thr Gln Cys Cys Ala  Glu Ala Asp
    1040                1045                1050
Lys Glu  Ser Cys Leu Thr Pro  Lys Leu Asp Gly Val  Lys Glu Lys
    1055                1060                1065
Ala Leu  Val Ser Ser Val Arg  Gln Arg Met Lys Cys  Ser Ser Met
    1070                1075                1080
Gln Lys  Phe Gly Glu Arg Ala  Phe Lys Ala Trp Ala  Val Ala Arg
    1085                1090                1095
Leu Ser  Gln Thr Phe Pro Asn  Ala Asp Phe Ala Glu  Ile Thr Lys
    1100                1105                1110
Leu Ala  Thr Asp Leu Thr Lys  Val Asn Lys Glu Cys  Cys His Gly
    1115                1120                1125
Asp Leu  Leu Glu Cys Ala Asp  Asp Arg Ala Glu Leu  Ala Lys Tyr
```

```
    1130                1135                1140
Met Cys  Glu Asn Gln Ala Thr  Ile Ser Ser Lys Leu  Gln Thr Cys
    1145                1150                1155
Cys Asp  Lys Pro Leu Leu Lys  Lys Ala His Cys Leu  Ser Glu Val
    1160                1165                1170
Glu His  Asp Thr Met Pro Ala  Asp Leu Pro Ala Ile  Ala Ala Asp
    1175                1180                1185
Phe Val  Glu Asp Gln Glu Val  Cys Lys Asn Tyr Ala  Glu Ala Lys
    1190                1195                1200
Asp Val  Phe Leu Gly Thr Phe  Leu Tyr Glu Tyr Ser  Arg Arg His
    1205                1210                1215
Pro Asp  Tyr Ser Val Ser Leu  Leu Leu Arg Leu Ala  Lys Lys Tyr
    1220                1225                1230
Glu Ala  Thr Leu Glu Lys Cys  Cys Ala Glu Ala Asn  Pro Pro Ala
    1235                1240                1245
Cys Tyr  Gly Thr Val Leu Ala  Glu Phe Gln Pro Leu  Val Glu Glu
    1250                1255                1260
Pro Lys  Asn Leu Val Lys Thr  Asn Cys Asp Leu Tyr  Glu Lys Leu
    1265                1270                1275
Gly Glu  Tyr Gly Phe Gln Asn  Ala Ile Leu Val Arg  Tyr Thr Gln
    1280                1285                1290
Lys Ala  Pro Gln Val Ser Thr  Pro Thr Leu Val Glu  Ala Ala Arg
    1295                1300                1305
Asn Leu  Gly Arg Val Gly Thr  Lys Cys Cys Thr Leu  Pro Glu Asp
    1310                1315                1320
Gln Arg  Leu Pro Cys Val Glu  Asp Tyr Leu Ser Ala  Ile Leu Asn
    1325                1330                1335
Arg Val  Cys Leu Leu His Glu  Lys Thr Pro Val Ser  Glu His Val
    1340                1345                1350
Thr Lys  Cys Cys Ser Gly Ser  Leu Val Glu Arg Arg  Pro Cys Phe
    1355
Ser Ala  Leu Thr Val Asp Glu  Thr Tyr Val Pro Lys  Glu Phe Lys
    1370                1375                1380
Ala Glu  Thr Phe Thr Phe His  Ser Asp Ile Cys Thr  Leu Pro Glu
    1385                1390                1395
Lys Glu  Lys Gln Ile Lys Lys  Gln Thr Ala Leu Ala  Glu Leu Val
    1400                1405                1410
Lys His  Lys Pro Lys Ala Thr  Ala Glu Gln Leu Lys  Thr Val Met
    1415                1420                1425
Asp Asp  Phe Ala Gln Phe Leu  Asp Thr Cys Cys Lys  Ala Ala Asp
    1430                1435                1440
Lys Asp  Thr Cys Phe Ser Thr  Glu Gly Pro Asn Leu  Val Thr Arg
    1445                1450                1455
Cys Lys  Asp Ala Leu Ala Arg  Ser Trp Ser His Pro  Gln Phe Glu
    1460                1465                1470
Lys
```

Singly underlined:signal peptide sequence; double-underlined: beginning and end of NPP1; ** = cleavage position at the signal peptide sequence; bold residues indicate albumin sequence

SEQ. ID NO: 14 - ENPP5-NPP3-Fc sequence

```
Met Thr Ser Lys Phe Leu Leu Val Ser Phe Ile Leu Ala Ala Leu Ser
1               5                  10                  15
Leu Ser Thr Thr Phe Ser**Lys Gln Gly Ser Cys Arg Lys Lys Cys Phe
            20                  25                  30
Asp Ala Ser Phe Arg Gly Leu Glu Asn Cys Arg Cys Asp Val Ala Cys
        35                  40                  45
Lys Asp Arg Gly Asp Cys Cys Trp Asp Phe Glu Asp Thr Cys Val Glu
    50                  55                  60
Ser Thr Arg Ile Trp Met Cys Asn Lys Phe Arg Cys Gly Glu Arg Leu
65                  70                  75                  80
Glu Ala Ser Leu Cys Ser Cys Ser Asp Asp Cys Leu Gln Arg Lys Asp
                85                  90                  95
Cys Cys Ala Asp Tyr Lys Ser Val Cys Gln Gly Glu Thr Ser Trp Leu
            100                 105                 110
Glu Glu Asn Cys Asp Thr Ala Gln Gln Ser Gln Cys Pro Glu Gly Phe
        115                 120                 125
Asp Leu Pro Pro Val Ile Leu Phe Ser Met Asp Gly Phe Arg Ala Glu
    130                 135                 140
Tyr Leu Tyr Thr Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys
145                 150                 155                 160
Thr Cys Gly Ile His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys
                165                 170                 175
Thr Phe Pro Asn His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser
            180                 185                 190
His Gly Ile Ile Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn
        195                 200                 205
Phe Ser Leu Ser Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly
    210                 215                 220
Gln Pro Met Trp Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr
225                 230                 235                 240
Tyr Phe Trp Pro Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser
                245                 250                 255
Ile Tyr Met Pro Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser
            260                 265                 270
Thr Leu Leu Lys Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe
        275                 280                 285
Tyr Thr Met Tyr Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly
    290                 295                 300
Pro Val Ser Ala Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala
305                 310                 315                 320
Phe Gly Met Leu Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys
                325                 330                 335
Val Asn Ile Ile Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys
            340                 345                 350
Asn Lys Met Glu Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe
        355                 360                 365
Tyr Met Tyr Glu Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro
```

```
    370                 375                 380
His Asp Phe Phe Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser
385                 390                 395                 400
Cys Arg Lys Pro Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu
                405                 410                 415
Pro Lys Arg Leu His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His
            420                 425                 430
Leu Phe Val Asp Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr
        435                 440                 445
Asn Cys Gly Gly Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met
    450                 455                 460
Glu Ala Ile Phe Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu
465                 470                 475                 480
Val Glu Pro Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu
                485                 490                 495
Leu Arg Ile Gln Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn
            500                 505                 510
His Leu Leu Lys Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val
        515                 520                 525
Ser Lys Phe Ser Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser
    530                 535                 540
Leu Asp Cys Phe Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln
545                 550                 555                 560
Val Asn Gln Met Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val
                565                 570                 575
Lys Val Asn Leu Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val
            580                 585                 590
Asp His Cys Leu Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys
        595                 600                 605
Ala Met Arg Met Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly
    610                 615                 620
Asp Thr Ser Pro Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp
625                 630                 635                 640
Val Arg Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala
                645                 650                 655
Asp Lys Asn Ile Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg
            660                 665                 670
Thr Ser Asp Ser Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro
        675                 680                 685
Met Tyr Glu Glu Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu
    690                 695                 700
Leu Ile Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly
705                 710                 715                 720
Pro Ile Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu
                725                 730                 735
Ile Thr Lys His Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr
            740                 745                 750
Phe Val Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn
        755                 760                 765
Cys Pro Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro
    770                 775                 780
Thr Asn Val Glu Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val
```

785 790 795 800
Glu Glu Arg Phe Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu
805 810 815
Leu Thr Gly Leu Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu
820 825 830
Ile Leu Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile **Asp**
835 840 845
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
850 855 860
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
865 870 875 880
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
885 890 895
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
900 905 910
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
915 920 925
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
930 935 940
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
945 950 955 960
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
965 970 975
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
980 985 990
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
995 1000 1005
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
1010 1015 1020
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
1025 1030 1035
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
1040 1045 1050
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
1055 1060 1065
Ser Leu Ser Pro Gly Lys
1070

Singly underlined:signal peptide sequence; double-underlined: beginning and end of NPP33; ** = cleavage position at the signal peptide sequence; bold residues indicate albumin sequence

SEQ. ID NO: 15- ENPP5-NPP3-Albumin sequence

Met Thr Ser Lys Phe Leu Leu Val Ser Phe Ile Leu Ala Ala Leu Ser
1 5 10 15
Leu Ser Thr Thr Phe Ser**Lys Gln Gly Ser Cys Arg Lys Lys Cys Phe
20 25 30

```
Asp Ala Ser Phe Arg Gly Leu Glu Asn Cys Arg Cys Asp Val Ala Cys
        35                  40                  45
Lys Asp Arg Gly Asp Cys Cys Trp Asp Phe Glu Asp Thr Cys Val Glu
    50                  55                  60
Ser Thr Arg Ile Trp Met Cys Asn Lys Phe Arg Cys Gly Glu Arg Leu
65                  70                  75                  80
Glu Ala Ser Leu Cys Ser Cys Ser Asp Asp Cys Leu Gln Arg Lys Asp
                85                  90                  95
Cys Cys Ala Asp Tyr Lys Ser Val Cys Gln Gly Glu Thr Ser Trp Leu
            100                 105                 110
Glu Glu Asn Cys Asp Thr Ala Gln Gln Ser Gln Cys Pro Glu Gly Phe
        115                 120                 125
Asp Leu Pro Pro Val Ile Leu Phe Ser Met Asp Gly Phe Arg Ala Glu
    130                 135                 140
Tyr Leu Tyr Thr Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys
145                 150                 155                 160
Thr Cys Gly Ile His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys
                165                 170                 175
Thr Phe Pro Asn His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser
            180                 185                 190
His Gly Ile Ile Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn
        195                 200                 205
Phe Ser Leu Ser Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly
    210                 215                 220
Gln Pro Met Trp Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr
225                 230                 235                 240
Tyr Phe Trp Pro Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser
                245                 250                 255
Ile Tyr Met Pro Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser
            260                 265                 270
Thr Leu Leu Lys Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe
        275                 280                 285
Tyr Thr Met Tyr Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly
    290                 295                 300
Pro Val Ser Ala Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala
305                 310                 315                 320
Phe Gly Met Leu Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys
                325                 330                 335
Val Asn Ile Ile Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys
            340                 345                 350
Asn Lys Met Glu Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe
        355                 360                 365
Tyr Met Tyr Glu Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro
    370                 375                 380
His Asp Phe Phe Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser
385                 390                 395                 400
Cys Arg Lys Pro Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu
                405                 410                 415
Pro Lys Arg Leu His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His
            420                 425                 430
Leu Phe Val Asp Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr
        435                 440                 445
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Asn Cys Gly Gly Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met
450 455 460
Glu Ala Ile Phe Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu
465 470 475 480
Val Glu Pro Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu
485 490 495
Leu Arg Ile Gln Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn
500 505 510
His Leu Leu Lys Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val
515 520 525
Ser Lys Phe Ser Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser
530 535 540
Leu Asp Cys Phe Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln
545 550 555 560
Val Asn Gln Met Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val
565 570 575
Lys Val Asn Leu Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val
580 585 590
Asp His Cys Leu Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys
595 600 605
Ala Met Arg Met Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly
610 615 620
Asp Thr Ser Pro Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp
625 630 635 640
Val Arg Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala
645 650 655
Asp Lys Asn Ile Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg
660 665 670
Thr Ser Asp Ser Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro
675 680 685
Met Tyr Glu Glu Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu
690 695 700
Leu Ile Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly
705 710 715 720
Pro Ile Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu
725 730 735
Ile Thr Lys His Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr
740 745 750
Phe Val Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn
755 760 765
Cys Pro Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro
770 775 780
Thr Asn Val Glu Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val
785 790 795 800
Glu Glu Arg Phe Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu
805 810 815
Leu Thr Gly Leu Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu
820 825 830
Ile Leu Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile **Gly**
835 840 845
Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Met Lys Trp
850 855 860

```
Val Thr Phe Leu Leu Leu Leu Phe Val Ser Gly Ser Ala Phe Ser Arg
865                 870                 875                 880
Gly Val Phe Arg Arg Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr
                885                 890                 895
Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe
            900                 905                 910
Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val
        915                 920                 925
Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
    930                 935                 940
Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
945                 950                 955                 960
Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys
                965                 970                 975
Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
            980                 985                 990
Asp Asn Pro Ser Leu Pro Pro Phe  Glu Arg Pro Glu Ala  Glu Ala Met
        995                 1000                1005
Cys Thr  Ser Phe Lys Glu Asn  Pro Thr Thr Phe Met  Gly His Tyr
    1010                1015                1020
Leu His  Glu Val Ala Arg Arg  His Pro Tyr Phe Tyr  Ala Pro Glu
    1025                1030                1035
Leu Leu  Tyr Tyr Ala Glu Gln  Tyr Asn Glu Ile Leu  Thr Gln Cys
    1040                1045                1050
Cys Ala  Glu Ala Asp Lys Glu  Ser Cys Leu Thr Pro  Lys Leu Asp
    1055                1060                1065
Gly Val  Lys Glu Lys Ala Leu  Val Ser Ser Val Arg  Gln Arg Met
    1070                1075                1080
Lys Cys  Ser Ser Met Gln Lys  Phe Gly Glu Arg Ala  Phe Lys Ala
    1085                1090                1095
Trp Ala  Val Ala Arg Leu Ser  Gln Thr Phe Pro Asn  Ala Asp Phe
    1100                1105                1110
Ala Glu  Ile Thr Lys Leu Ala  Thr Asp Leu Thr Lys  Val Asn Lys
    1115                1120                1125
Glu Cys  Cys His Gly Asp Leu  Leu Glu Cys Ala Asp  Asp Arg Ala
    1130                1135                1140
Glu Leu  Ala Lys Tyr Met Cys  Glu Asn Gln Ala Thr  Ile Ser Ser
    1145                1150                1155
Lys Leu  Gln Thr Cys Cys Asp  Lys Pro Leu Leu Lys  Lys Ala His
    1160                1165                1170
Cys Leu  Ser Glu Val Glu His  Asp Thr Met Pro Ala  Asp Leu Pro
    1175                1180                1185
Ala Ile  Ala Ala Asp Phe Val  Glu Asp Gln Glu Val  Cys Lys Asn
    1190                1195                1200
Tyr Ala  Glu Ala Lys Asp Val  Phe Leu Gly Thr Phe  Leu Tyr Glu
    1205                1210                1215
Tyr Ser  Arg Arg His Pro Asp  Tyr Ser Val Ser Leu  Leu Leu Arg
    1220                1225                1230
Leu Ala  Lys Lys Tyr Glu Ala  Thr Leu Glu Lys Cys  Cys Ala Glu
    1235                1240                1245
Ala Asn  Pro Pro Ala Cys Tyr  Gly Thr Val Leu Ala  Glu Phe Gln
    1250                1255                1260
```

Pro Leu Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys Asp
1265 1270 1275
Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu
1280 1285 1290
Val Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu
1295 1300 1305
Val Glu Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys
1310 1315 1320
Thr Leu Pro Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu
1325 1330 1335
Ser Ala Ile Leu Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro
1340 1345 1350
Val Ser Glu His Val Thr Lys Cys Cys Ser Gly Ser Leu Val Glu
1355 1360 1365
Arg Arg Pro Cys Phe Ser Ala Leu Thr Val Asp Glu Thr Tyr Val
1370 1375 1380
Pro Lys Glu Phe Lys Ala Glu Thr Phe Thr Phe His Ser Asp Ile
1385 1390 1395
Cys Thr Leu Pro Glu Lys Glu Lys Gln Ile Lys Lys Gln Thr Ala
1400 1405 1410
Leu Ala Glu Leu Val Lys His Lys Pro Lys Ala Thr Ala Glu Gln
1415 1420 1425
Leu Lys Thr Val Met Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys
1430 1435 1440
Cys Lys Ala Ala Asp Lys Asp Thr Cys Phe Ser Thr Glu Gly Pro
1445 1450 1455
Asn Leu Val Thr Arg Cys Lys Asp Ala Leu Ala
1460 1465

Singly underlined:signal peptide sequence; double-underlined: beginning and end of NPP3; ** = cleavage position at the signal peptide sequence; bold residues indicate albumin sequence

SEQ. ID NO: 16 - ENPP5 Protein Export Signal Sequence

Met Thr Ser Lys Phe Leu Leu Val Ser Phe Ile Leu Ala Ala Leu Ser
1 5 10 15
Leu Ser Thr Thr Phe Ser Xaa
20

SEQ. ID NO: 17 - ENPP5-1-Fc

Met Thr Ser Lys Phe Leu Leu Val Ser Phe Ile Leu Ala Ala Leu Ser
1 5 10 15
Leu Ser Thr Thr Phe Ser**Gly Leu Lys Pro Ser Cys Ala Lys Glu Val
20 25 30
Lys Ser Cys Lys Gly Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg

```
        35                  40                  45
Cys Asp Ala Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln
    50                  55                  60
Glu Thr Cys Ile Glu Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg
65                  70                  75                  80
Cys Gly Glu Lys Arg Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp
                85                  90                  95
Cys Lys Asp Lys Gly Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln
            100                 105                 110
Gly Glu Lys Ser Trp Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro
        115                 120                 125
Gln Cys Pro Ala Gly Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu
    130                 135                 140
Asp Gly Phe Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro
145                 150                 155                 160
Val Ile Ser Lys Leu Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg
                165                 170                 175
Pro Val Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr
            180                 185                 190
Gly Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp
        195                 200                 205
Pro Lys Met Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn
    210                 215                 220
Pro Glu Trp Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln
225                 230                 235                 240
Gly Leu Lys Ser Gly Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile
                245                 250                 255
Asn Gly Ile Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro
            260                 265                 270
Phe Glu Glu Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys
        275                 280                 285
Asp Glu Arg Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser
    290                 295                 300
Ser Gly His Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu
305                 310                 315                 320
Gln Arg Val Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu
                325                 330                 335
Leu Asn Leu His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly
            340                 345                 350
Met Glu Gln Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu
        355                 360                 365
Gly Asp Val Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu
    370                 375                 380
Arg Pro Ser Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly
385                 390                 395                 400
Ile Ala Arg Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro
                405                 410                 415
Tyr Leu Lys His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp
            420                 425                 430
Arg Ile Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala
        435                 440                 445
Leu Asn Pro Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser
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    450                 455                 460
Asp Asn Val Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro
465                 470                 475                 480
Gly Phe Lys His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val
                485                 490                 495
Tyr Asn Leu Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn
            500                 505                 510
Gly Thr His Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr
        515                 520                 525
Pro Lys His Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr
    530                 535                 540
Arg Asn Pro Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu
545                 550                 555                 560
Pro Ile Glu Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu
                565                 570                 575
Lys Ile Ile Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu
            580                 585                 590
Gln Lys Glu Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser
        595                 600                 605
Gly Tyr Ser Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val
    610                 615                 620
Asp Arg Asn Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr
625                 630                 635                 640
Gln Asp Phe Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr
                645                 650                 655
Lys Asn Asn Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu
            660                 665                 670
Asn Lys Asn Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn
        675                 680                 685
Ile Val Pro Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His
    690                 695                 700
Asp Thr Leu Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val
705                 710                 715                 720
Val Ser Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser
                725                 730                 735
Leu Glu Asn Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile
            740                 745                 750
Leu Ile Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr
        755                 760                 765
Ser Gln Thr Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile
    770                 775                 780
Leu Pro His Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His
785                 790                 795                 800
Asp Ser Ser Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile
                805                 810                 815
Thr Asp Val Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys
            820                 825                 830
Glu Pro Val Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe
        835                 840                 845
Ser Gln Glu Asp Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
    850                 855                 860
Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
```

865 870 875 880
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
885 890 895
Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
900 905 910
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
915 920 925
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
930 935 940
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
945 950 955 960
Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
965 970 975
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
980 985 990
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
995 1000 1005
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
1010 1015 1020
Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
1025 1030 1035
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
1040 1045 1050
Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
1055 1060 1065
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
1070 1075

Singly underlined:signal peptide sequence; double-underlined: beginning and end of NPP3; ** = cleavage position at the signal peptide sequence; bold residues indicate Fc sequence

SEQ. ID NO: 18 - ENPP7-1-Fc Amino Acid Sequence

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

```
Gly Glu Lys Ser Trp Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro
        115                 120                 125
Gln Cys Pro Ala Gly Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu
    130                 135                 140
Asp Gly Phe Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro
145                 150                 155                 160
Val Ile Ser Lys Leu Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg
                165                 170                 175
Pro Val Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr
            180                 185                 190
Gly Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp
        195                 200                 205
Pro Lys Met Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn
    210                 215                 220
Pro Glu Trp Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln
225                 230                 235                 240
Gly Leu Lys Ser Gly Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile
                245                 250                 255
Asn Gly Ile Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro
            260                 265                 270
Phe Glu Glu Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys
        275                 280                 285
Asp Glu Arg Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser
    290                 295                 300
Ser Gly His Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu
305                 310                 315                 320
Gln Arg Val Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu
                325                 330                 335
Leu Asn Leu His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly
            340                 345                 350
Met Glu Gln Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu
        355                 360                 365
Gly Asp Val Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu
    370                 375                 380
Arg Pro Ser Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly
385                 390                 395                 400
Ile Ala Arg Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro
                405                 410                 415
Tyr Leu Lys His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp
            420                 425                 430
Arg Ile Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala
        435                 440                 445
Leu Asn Pro Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser
    450                 455                 460
Asp Asn Val Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro
465                 470                 475                 480
Gly Phe Lys His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val
                485                 490                 495
Tyr Asn Leu Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn
            500                 505                 510
Gly Thr His Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr
        515                 520                 525
```

Pro Lys His Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr
530 535 540
Arg Asn Pro Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu
545 550 555 560
Pro Ile Glu Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu
565 570 575
Lys Ile Ile Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu
580 585 590
Gln Lys Glu Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser
595 600 605
Gly Tyr Ser Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val
610 615 620
Asp Arg Asn Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr
625 630 635 640
Gln Asp Phe Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr
645 650 655
Lys Asn Asn Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu
660 665 670
Asn Lys Asn Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn
675 680 685
Ile Val Pro Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His
690 695 700
Asp Thr Leu Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val
705 710 715 720
Val Ser Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser
725 730 735
Leu Glu Asn Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile
740 745 750
Leu Ile Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr
755 760 765
Ser Gln Thr Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile
770 775 780
Leu Pro His Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His
785 790 795 800
Asp Ser Ser Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile
805 810 815
Thr Asp Val Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys
820 825 830
Glu Pro Val Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe
835 840 845
Ser Gln Glu Asp Leu Ile Asn **Asp Lys Thr His Thr Cys Pro Pro Cys**
850 855 860
Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
865 870 875 880
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
885 890 895
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
900 905 910
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
915 920 925
Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
930 935 940

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
945 950 955 960
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
965 970 975
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
980 985 990
Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
995 1000 1005
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
1010 1015 1020
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
1025 1030 1035
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
1040 1045 1050
Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
1055 1060 1065
Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
1070 1075 1080

Singly underlined:signal peptide sequence; double-underlined: beginning and end of NPP1; ** = cleavage position at the signal peptide sequence; bold residues indicate Fc sequence

SEQ. ID NO: 19 - ENPP71 (lacking NPP1 N-Terminus GLK) Amino Acid Sequence:

Met Arg Gly Pro Ala Val Leu Leu Thr Val Ala Leu Ala Thr Leu Leu
1 5 10 15
Ala Pro Gly Ala Gly Ala**Pro Ser Cys Ala Lys Glu Val Lys Ser Cys
20 25 30
Lys Gly Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala
35 40 45
Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys
50 55 60
Ile Glu Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu
65 70 75 80
Lys Arg Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp
85 90 95
Lys Gly Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys
100 105 110
Ser Trp Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro
115 120 125
Ala Gly Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe
130 135 140
Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser
145 150 155 160
Lys Leu Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr
165 170 175
Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr

```
            180                 185                 190
Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met
        195                 200                 205
Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp
    210                 215                 220
Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys
225                 230                 235                 240
Ser Gly Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile
                245                 250                 255
Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu
            260                 265                 270
Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg
        275                 280                 285
Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His
    290                 295                 300
Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val
305                 310                 315                 320
Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu
                325                 330                 335
His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln
            340                 345                 350
Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val
        355                 360                 365
Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser
    370                 375                 380
Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg
385                 390                 395                 400
Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys
                405                 410                 415
His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu
            420                 425                 430
Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro
        435                 440                 445
Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val
    450                 455                 460
Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys
465                 470                 475                 480
His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu
                485                 490                 495
Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His
            500                 505                 510
Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His
        515                 520                 525
Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro
    530                 535                 540
Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu
545                 550                 555                 560
Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile
                565                 570                 575
Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu
            580                 585                 590
Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser
```

595 600 605
Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn
610 615 620
Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe
625 630 635 640
Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn
645 650 655
Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn
660 665 670
Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro
675 680 685
Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu
690 695 700
Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly
705 710 715 720
Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn
725 730 735
Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro
740 745 750
Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr
755 760 765
Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His
770 775 780
Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser
785 790 795 800
Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val
805 810 815
Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val
820 825 830
Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu
835 840 845
Asp

Singly underlined:signal peptide sequence; double-underlined: beginning and end of NPP3; ** = cleavage position at the signal peptide sequence

SEQ. ID NO: 20 -ENPP71 (lacking NPP1 N-Terminus GLK) – Fc Amino Acid Sequence:

Met Arg Gly Pro Ala Val Leu Leu Thr Val Ala Leu Ala Thr Leu Leu
1 5 10 15
Ala Pro Gly Ala Gly Ala**Pro Ser Cys Ala Lys Glu Val Lys Ser Cys
20 25 30
Lys Gly Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala
35 40 45
Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys
50 55 60
Ile Glu Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu
65 70 75 80

Lys Arg Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp
85 90 95
Lys Gly Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys
100 105 110
Ser Trp Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro
115 120 125
Ala Gly Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe
130 135 140
Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser
145 150 155 160
Lys Leu Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr
165 170 175
Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr
180 185 190
Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met
195 200 205
Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp
210 215 220
Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys
225 230 235 240
Ser Gly Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile
245 250 255
Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu
260 265 270
Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg
275 280 285
Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His
290 295 300
Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val
305 310 315 320
Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu
325 330 335
His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln
340 345 350
Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val
355 360 365
Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser
370 375 380
Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg
385 390 395 400
Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys
405 410 415
His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu
420 425 430
Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro
435 440 445
Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val
450 455 460
Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys
465 470 475 480
His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu
485 490 495

Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His
500 505 510
Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His
515 520 525
Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro
530 535 540
Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu
545 550 555 560
Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile
565 570 575
Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu
580 585 590
Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser
595 600 605
Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn
610 615 620
Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe
625 630 635 640
Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn
645 650 655
Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn
660 665 670
Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro
675 680 685
Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu
690 695 700
Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly
705 710 715 720
Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn
725 730 735
Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro
740 745 750
Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr
755 760 765
Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His
770 775 780
Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser
785 790 795 800
Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val
805 810 815
Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val
820 825 830
Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu
835 840 845
Asp Leu Ile Asn **Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro**
850 855 860
Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
865 870 875 880
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
885 890 895
Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
900 905 910

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
915 920 925
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
930 935 940
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
945 950 955 960
Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
965 970 975
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
980 985 990
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
995 1000 1005
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
1010 1015 1020
Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
1025 1030 1035
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
1040 1045 1050
Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
1055 1060 1065
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
1070 1075

Singly underlined:signal peptide sequence; double-underlined: beginning and end of NPP1; ** = cleavage position at the signal peptide sequence; bold residues indicate Fc sequence

SEQ. ID NO: 21 - ENPP7-1 (lacking NPP1 N-Terminus GLK) - ALB Amino Acid Sequence

Met Arg Gly Pro Ala Val Leu Leu Thr Val Ala Leu Ala Thr Leu Leu
1 5 10 15
Ala Pro Gly Ala Gly Ala**Pro Ser Cys Ala Lys Glu Val Lys Ser Cys
20 25 30
Lys Gly Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala
35 40 45
Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys
50 55 60
Ile Glu Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu
65 70 75 80
Lys Arg Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp
85 90 95
Lys Gly Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys
100 105 110
Ser Trp Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro
115 120 125
Ala Gly Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe
130 135 140
Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser
145 150 155 160
Lys Leu Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr

```
                 165                 170                 175
Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr
            180                 185                 190
Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met
        195                 200                 205
Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp
    210                 215                 220
Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys
225                 230                 235                 240
Ser Gly Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile
                245                 250                 255
Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu
            260                 265                 270
Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg
        275                 280                 285
Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His
    290                 295                 300
Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val
305                 310                 315                 320
Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu
                325                 330                 335
His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln
            340                 345                 350
Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val
        355                 360                 365
Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser
    370                 375                 380
Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg
385                 390                 395                 400
Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys
                405                 410                 415
His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu
            420                 425                 430
Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro
        435                 440                 445
Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val
    450                 455                 460
Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys
465                 470                 475                 480
His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu
                485                 490                 495
Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His
            500                 505                 510
Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His
        515                 520                 525
Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro
    530                 535                 540
Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu
545                 550                 555                 560
Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile
                565                 570                 575
Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu
```

580 585 590
Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser
595 600 605
Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn
610 615 620
Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe
625 630 635 640
Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn
645 650 655
Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn
660 665 670
Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro
675 680 685
Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu
690 695 700
Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly
705 710 715 720
Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn
725 730 735
Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro
740 745 750
Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr
755 760 765
Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His
770 775 780
Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser
785 790 795 800
Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val
805 810 815
Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val
820 825 830
Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu
835 840 845
Asp Arg Ser Gly Ser Gly Gly Ser **Met Lys Trp Val Thr Phe Leu Leu**
850 855 860
Leu Leu Phe Val Ser Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg
865 870 875 880
Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu
885 890 895
Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln
900 905 910
Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu Val Thr Asp
915 920 925
Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys
930 935 940
Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu
945 950 955 960
Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro
965 970 975
Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Ser Leu
980 985 990
Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met Cys Thr Ser Phe Lys

995 1000 1005

Glu Asn Pro Thr Thr Phe Met Gly His Tyr Leu His Glu Val Ala
1010 1015 1020
Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Tyr Tyr Ala
1025 1030 1035
Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys Ala Glu Ala Asp
1040 1045 1050
Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val Lys Glu Lys
1055 1060 1065
Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys Ser Ser Met
1070 1075 1080
Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
1085 1090 1095
Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr Lys
1100 1105 1110
Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly
1115 1120 1125
Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr
1130 1135 1140
Met Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys
1145 1150 1155
Cys Asp Lys Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val
1160 1165 1170
Glu His Asp Thr Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp
1175 1180 1185
Phe Val Glu Asp Gln Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys
1190 1195 1200
Asp Val Phe Leu Gly Thr Phe Leu Tyr Glu Tyr Ser Arg Arg His
1205 1210 1215
Pro Asp Tyr Ser Val Ser Leu Leu Leu Arg Leu Ala Lys Lys Tyr
1220 1225 1230
Glu Ala Thr Leu Glu Lys Cys Cys Ala Glu Ala Asn Pro Pro Ala
1235 1240 1245
Cys Tyr Gly Thr Val Leu Ala Glu Phe Gln Pro Leu Val Glu Glu
1250 1255 1260
Pro Lys Asn Leu Val Lys Thr Asn Cys Asp Leu Tyr Glu Lys Leu
1265 1270 1275
Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val Arg Tyr Thr Gln
1280 1285 1290
Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu Ala Ala Arg
1295 1300 1305
Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu Pro Glu Asp
1310 1315 1320
Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile Leu Asn
1325 1330 1335
Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His Val
1340 1345 1350
Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe
1355 1360 1365
Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys
1370 1375 1380
Ala Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu

```
    1385                1390                1395
Lys Glu  Lys Gln Ile Lys Lys  Gln Thr Ala Leu Ala  Glu Leu Val
    1400                1405                1410
Lys His  Lys Pro Lys Ala Thr  Ala Glu Gln Leu Lys  Thr Val Met
    1415                1420                1425
Asp Asp  Phe Ala Gln Phe Leu  Asp Thr Cys Cys Lys  Ala Ala Asp
    1430                1435                1440
Lys Asp  Thr Cys Phe Ser Thr  Glu Gly Pro Asn Leu  Val Thr Arg
    1445                1450                1455
Cys Lys  Asp Ala Leu Ala Arg  Ser Trp Ser His Pro  Gln Phe Glu
    1460                1465                1470
Lys
```

Singly underlined:signal peptide sequence; double-underlined: beginning and end of NPP1; ** = cleavage position at the signal peptide sequence; bold residues indicate albumin sequence

SEQ. ID NO: 22 - ENPP7-NPP3-Fc sequence:

```
Met Arg Gly Pro Ala Val Leu Leu Thr Val Ala Leu Ala Thr Leu Leu
1               5                  10                  15
Ala Pro Gly Ala**Lys Gln Gly Ser Cys Arg Lys Lys Cys Phe Asp Ala
            20                  25                  30
Ser Phe Arg Gly Leu Glu Asn Cys Arg Cys Asp Val Ala Cys Lys Asp
        35                  40                  45
Arg Gly Asp Cys Cys Trp Asp Phe Glu Asp Thr Cys Val Glu Ser Thr
    50                  55                  60
Arg Ile Trp Met Cys Asn Lys Phe Arg Cys Gly Glu Arg Leu Glu Ala
65                  70                  75                  80
Ser Leu Cys Ser Cys Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys Cys
                85                  90                  95
Ala Asp Tyr Lys Ser Val Cys Gln Gly Glu Thr Ser Trp Leu Glu Glu
            100                 105                 110
Asn Cys Asp Thr Ala Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp Leu
        115                 120                 125
Pro Pro Val Ile Leu Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr Leu
    130                 135                 140
Tyr Thr Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys Thr Cys
145                 150                 155                 160
Gly Ile His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr Phe
                165                 170                 175
Pro Asn His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly
            180                 185                 190
Ile Ile Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser
        195                 200                 205
Leu Ser Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro
    210                 215                 220
Met Trp Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe
225                 230                 235                 240
Trp Pro Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr
```

245 250 255
Met Pro Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu
260 265 270
Leu Lys Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr
275 280 285
Met Tyr Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val
290 295 300
Ser Ala Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala Phe Gly
305 310 315 320
Met Leu Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn
325 330 335
Ile Ile Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys
340 345 350
Met Glu Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr Met
355 360 365
Tyr Glu Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro His Asp
370 375 380
Phe Phe Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg
385 390 395 400
Lys Pro Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys
405 410 415
Arg Leu His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His Leu Phe
420 425 430
Val Asp Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys
435 440 445
Gly Gly Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala
450 455 460
Ile Phe Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu
465 470 475 480
Pro Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg
485 490 495
Ile Gln Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His Leu
500 505 510
Leu Lys Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys
515 520 525
Phe Ser Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu Asp
530 535 540
Cys Phe Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn
545 550 555 560
Gln Met Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val
565 570 575
Asn Leu Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val Asp His
580 585 590
Cys Leu Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala Met
595 600 605
Arg Met Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp Thr
610 615 620
Ser Pro Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp Val Arg
625 630 635 640
Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys
645 650 655
Asn Ile Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser

660 665 670
Asp Ser Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro Met Tyr
675 680 685
Glu Glu Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu Leu Ile
690 695 700
Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile
705 710 715 720
Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr
725 730 735
Lys His Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val
740 745 750
Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro
755 760 765
Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn
770 775 780
Val Glu Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu
785 790 795 800
Arg Phe Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr
805 810 815
Gly Leu Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu
820 825 830
Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile **Asp Lys Thr**
835 840 845
His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
850 855 860
Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
865 870 875 880
Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
885 890 895
Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
900 905 910
Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
915 920 925
Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
930 935 940
Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
945 950 955 960
Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
965 970 975
Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
980 985 990
Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
995 1000 1005
Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
1010 1015 1020
Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
1025 1030 1035
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
1040 1045 1050
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
1055 1060 1065
Ser Pro Gly Lys

1070

Singly underlined:signal peptide sequence; double-underlined: beginning and end of NPP3; ** = cleavage position at the signal peptide sequence; bold residues indicate Fc sequence

SEQ. ID NO: 23 - ENPP7-1-Albumin

```
Met Arg Gly Pro Ala Val Leu Leu Thr Val Ala Leu Ala Thr Leu Leu
1               5                  10                  15
Ala Pro Gly Ala Gly Leu Lys**Pro Ser Cys Ala Lys Glu Val Lys Ser
            20                  25                  30
Cys Lys Gly Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp
        35                  40                  45
Ala Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr
    50                  55                  60
Cys Ile Glu Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly
65                  70                  75                  80
Glu Lys Arg Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys
                85                  90                  95
Asp Lys Gly Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu
            100                 105                 110
Lys Ser Trp Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys
        115                 120                 125
Pro Ala Gly Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly
    130                 135                 140
Phe Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile
145                 150                 155                 160
Ser Lys Leu Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val
                165                 170                 175
Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu
            180                 185                 190
Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys
        195                 200                 205
Met Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu
    210                 215                 220
Trp Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu
225                 230                 235                 240
Lys Ser Gly Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly
                245                 250                 255
Ile Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu
            260                 265                 270
Glu Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu
        275                 280                 285
Arg Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly
    290                 295                 300
His Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg
305                 310                 315                 320
Val Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn
                325                 330                 335
Leu His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu
```

```
            340                 345                 350
Gln Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp
        355                 360                 365
Val Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro
    370                 375                 380
Ser Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala
385                 390                 395                 400
Arg Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu
                405                 410                 415
Lys His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile
            420                 425                 430
Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn
        435                 440                 445
Pro Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn
    450                 455                 460
Val Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe
465                 470                 475                 480
Lys His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn
                485                 490                 495
Leu Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr
            500                 505                 510
His Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys
        515                 520                 525
His Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn
    530                 535                 540
Pro Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile
545                 550                 555                 560
Glu Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile
                565                 570                 575
Ile Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys
            580                 585                 590
Glu Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr
        595                 600                 605
Ser Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg
    610                 615                 620
Asn Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp
625                 630                 635                 640
Phe Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn
                645                 650                 655
Asn Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys
            660                 665                 670
Asn Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val
        675                 680                 685
Pro Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr
    690                 695                 700
Leu Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser
705                 710                 715                 720
Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu
                725                 730                 735
Asn Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile
            740                 745                 750
Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln
```

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        755                 760                 765
Thr Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro
    770                 775                 780
His Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His Asp Ser
785                 790                 795                 800
Ser Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp
                805                 810                 815
Val Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro
            820                 825                 830
Val Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln
        835                 840                 845
Glu Asp Gly Gly Ser Gly Gly Ser Met Lys Trp Val Thr Phe Leu Leu
    850                 855                 860
Leu Leu Phe Val Ser Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg
865                 870                 875                 880
Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu
                885                 890                 895
Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln
            900                 905                 910
Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu Val Thr Asp
        915                 920                 925
Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys
    930                 935                 940
Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu
945                 950                 955                 960
Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro
                965                 970                 975
Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Ser Leu
            980                 985                 990
Pro Pro Phe Glu Arg Pro Glu Ala  Glu Ala Met Cys Thr  Ser Phe Lys
        995                1000                1005
Glu Asn  Pro Thr Thr Phe Met  Gly His Tyr Leu His  Glu Val Ala
    1010                1015                1020
Arg Arg  His Pro Tyr Phe Tyr  Ala Pro Glu Leu Leu  Tyr Tyr Ala
    1025                1030                1035
Glu Gln  Tyr Asn Glu Ile Leu  Thr Gln Cys Cys Ala  Glu Ala Asp
    1040                1045                1050
Lys Glu  Ser Cys Leu Thr Pro  Lys Leu Asp Gly Val  Lys Glu Lys
    1055                1060                1065
Ala Leu  Val Ser Ser Val Arg  Gln Arg Met Lys Cys  Ser Ser Met
    1070                1075                1080
Gln Lys  Phe Gly Glu Arg Ala  Phe Lys Ala Trp Ala  Val Ala Arg
    1085                1090                1095
Leu Ser  Gln Thr Phe Pro Asn  Ala Asp Phe Ala Glu  Ile Thr Lys
    1100                1105                1110
Leu Ala  Thr Asp Leu Thr Lys  Val Asn Lys Glu Cys  Cys His Gly
    1115                1120                1125
Asp Leu  Leu Glu Cys Ala Asp  Asp Arg Ala Glu Leu  Ala Lys Tyr
    1130                1135                1140
Met Cys  Glu Asn Gln Ala Thr  Ile Ser Ser Lys Leu  Gln Thr Cys
    1145                1150                1155
Cys Asp  Lys Pro Leu Leu Lys  Lys Ala His Cys Leu  Ser Glu Val
```

```
    1160                1165                1170
Glu His  Asp Thr Met Pro Ala  Asp Leu Pro Ala Ile  Ala Ala Asp
    1175                1180                1185
Phe Val  Glu Asp Gln Glu Val  Cys Lys Asn Tyr Ala  Glu Ala Lys
    1190                1195                1200
Asp Val  Phe Leu Gly Thr Phe  Leu Tyr Glu Tyr Ser  Arg Arg His
    1205                1210                1215
Pro Asp  Tyr Ser Val Ser Leu  Leu Leu Arg Leu Ala  Lys Lys Tyr
    1220                1225                1230
Glu Ala  Thr Leu Glu Lys Cys  Cys Ala Glu Ala Asn  Pro Pro Ala
    1235                1240                1245
Cys Tyr  Gly Thr Val Leu Ala  Glu Phe Gln Pro Leu  Val Glu Glu
    1250                1255                1260
Pro Lys  Asn Leu Val Lys Thr  Asn Cys Asp Leu Tyr  Glu Lys Leu
    1265                1270                1275
Gly Glu  Tyr Gly Phe Gln Asn  Ala Ile Leu Val Arg  Tyr Thr Gln
    1280                1285                1290
Lys Ala  Pro Gln Val Ser Thr  Pro Thr Leu Val Glu  Ala Ala Arg
    1295                1300                1305
Asn Leu  Gly Arg Val Gly Thr  Lys Cys Cys Thr Leu  Pro Glu Asp
    1310                1315                1320
Gln Arg  Leu Pro Cys Val Glu  Asp Tyr Leu Ser Ala  Ile Leu Asn
    1325                1330                1335
Arg Val  Cys Leu Leu His Glu  Lys Thr Pro Val Ser  Glu His Val
    1340                1345                1350
Thr Lys  Cys Cys Ser Gly Ser  Leu Val Glu Arg Arg  Pro Cys Phe
    1355                1360                1365
Ser Ala  Leu Thr Val Asp Glu  Thr Tyr Val Pro Lys  Glu Phe Lys
    1370                1375                1380
Ala Glu  Thr Phe Thr Phe His  Ser Asp Ile Cys Thr  Leu
    1385                1390                1395
```

Singly underlined:signal peptide sequence; double-underlined: beginning and end of NPP3; ** = cleavage position at the signal peptide sequence; bold residues indicate Fc sequence

SEQ. ID NO: 24 - ENPP7-NPP3-Albumin

```
Met Arg Gly Pro Ala Val Leu Leu Thr Val Ala Leu Ala Thr Leu Leu
1               5                  10                  15
Ala Pro Gly Ala**Lys Gln Gly Ser Cys Arg Lys Lys Cys Phe Asp Ala
            20                  25                  30
Ser Phe Arg Gly Leu Glu Asn Cys Arg Cys Asp Val Ala Cys Lys Asp
        35                  40                  45
Arg Gly Asp Cys Cys Trp Asp Phe Glu Asp Thr Cys Val Glu Ser Thr
    50                  55                  60
Arg Ile Trp Met Cys Asn Lys Phe Arg Cys Gly Glu Arg Leu Glu Ala
65                  70                  75                  80
Ser Leu Cys Ser Cys Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys Cys
```

```
                85                  90                  95
Ala Asp Tyr Lys Ser Val Cys Gln Gly Glu Thr Ser Trp Leu Glu Glu
            100                 105                 110
Asn Cys Asp Thr Ala Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp Leu
        115                 120                 125
Pro Pro Val Ile Leu Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr Leu
    130                 135                 140
Tyr Thr Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys Thr Cys
145                 150                 155                 160
Gly Ile His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr Phe
                165                 170                 175
Pro Asn His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly
            180                 185                 190
Ile Ile Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser
        195                 200                 205
Leu Ser Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro
    210                 215                 220
Met Trp Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe
225                 230                 235                 240
Trp Pro Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr
                245                 250                 255
Met Pro Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu
            260                 265                 270
Leu Lys Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr
        275                 280                 285
Met Tyr Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val
    290                 295                 300
Ser Ala Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala Phe Gly
305                 310                 315                 320
Met Leu Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn
                325                 330                 335
Ile Ile Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys
            340                 345                 350
Met Glu Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr Met
        355                 360                 365
Tyr Glu Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro His Asp
    370                 375                 380
Phe Phe Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg
385                 390                 395                 400
Lys Pro Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys
                405                 410                 415
Arg Leu His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His Leu Phe
            420                 425                 430
Val Asp Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys
        435                 440                 445
Gly Gly Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala
    450                 455                 460
Ile Phe Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu
465                 470                 475                 480
Pro Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg
                485                 490                 495
Ile Gln Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His Leu
```

500 505 510
Leu Lys Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys
515 520 525
Phe Ser Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu Asp
530 535 540
Cys Phe Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn
545 550 555 560
Gln Met Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val
565 570 575
Asn Leu Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val Asp His
580 585 590
Cys Leu Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala Met
595 600 605
Arg Met Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp Thr
610 615 620
Ser Pro Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp Val Arg
625 630 635 640
Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys
645 650 655
Asn Ile Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser
660 665 670
Asp Ser Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro Met Tyr
675 680 685
Glu Glu Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu Leu Ile
690 695 700
Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile
705 710 715 720
Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr
725 730 735
Lys His Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val
740 745 750
Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro
755 760 765
Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn
770 775 780
Val Glu Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu
785 790 795 800
Arg Phe Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr
805 810 815
Gly Leu Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu
820 825 830
Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile Gly Gly Gly
835 840 845
Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser **Met Lys Trp Val Thr**
850 855 860
Phe Leu Leu Leu Leu Phe Val Ser Gly Ser Ala Phe Ser Arg Gly Val
865 870 875 880
Phe Arg Arg Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp
885 890 895
Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln
900 905 910
Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu

915 920 925
Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn
930 935 940
Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile
945 950 955 960
Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys
965 970 975
Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn
980 985 990
Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met Cys Thr
995 1000 1005
Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly His Tyr Leu His
1010 1015 1020
Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
1025 1030 1035
Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys Ala
1040 1045 1050
Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val
1055 1060 1065
Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys
1070 1075 1080
Ser Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala
1085 1090 1095
Val Ala Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu
1100 1105 1110
Ile Thr Lys Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys
1115 1120 1125
Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu
1130 1135 1140
Ala Lys Tyr Met Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu
1145 1150 1155
Gln Thr Cys Cys Asp Lys Pro Leu Leu Lys Lys Ala His Cys Leu
1160 1165 1170
Ser Glu Val Glu His Asp Thr Met Pro Ala Asp Leu Pro Ala Ile
1175 1180 1185
Ala Ala Asp Phe Val Glu Asp Gln Glu Val Cys Lys Asn Tyr Ala
1190 1195 1200
Glu Ala Lys Asp Val Phe Leu Gly Thr Phe Leu Tyr Glu Tyr Ser
1205 1210 1215
Arg Arg His Pro Asp Tyr Ser Val Ser Leu Leu Leu Arg Leu Ala
1220 1225 1230
Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys Cys Ala Glu Ala Asn
1235 1240 1245
Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu Phe Gln Pro Leu
1250 1255 1260
Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys Asp Leu Tyr
1265 1270 1275
Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val Arg
1280 1285 1290
Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu
1295 1300 1305
Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu

```
    1310                1315                1320
Pro Glu  Asp Gln Arg Leu Pro  Cys Val Glu Asp Tyr  Leu Ser Ala
    1325                1330                1335
Ile Leu  Asn Arg Val Cys Leu  Leu His Glu Lys Thr  Pro Val Ser
    1340                1345                1350
Glu His  Val Thr Lys Cys Cys  Ser Gly Ser Leu Val  Glu Arg Arg
    1355                1360                1365
Pro Cys  Phe Ser Ala Leu Thr  Val Asp Glu Thr Tyr  Val Pro Lys
    1370                1375                1380
Glu Phe  Lys Ala Glu Thr Phe  Thr Phe His Ser Asp  Ile Cys Thr
    1385                1390                1395
Leu Pro  Glu Lys Glu Lys Gln  Ile Lys Lys Gln Thr  Ala Leu Ala
    1400                1405                1410
Glu Leu  Val Lys His Lys Pro  Lys Ala Thr Ala Glu  Gln Leu Lys
    1415                1420                1425
Thr Val  Met Asp Asp Phe Ala  Gln Phe Leu Asp Thr  Cys Cys Lys
    1430                1435                1440
Ala Ala  Asp Lys Asp Thr Cys  Phe Ser Thr Glu Gly  Pro Asn Leu
    1445                1450                1455
Val Thr  Arg Cys Lys Asp Ala  Leu Ala
    1460                1465
```

Singly underlined:signal peptide sequence; double-underlined: beginning and end of NPP3; ** = cleavage position at the signal peptide sequence; bold residues indicate albumin sequence

SEQ. ID NO: 25 - ENPP7-ENPP3-Albumin

```
Met Arg Gly Pro Ala Val Leu Leu Thr Val Ala Leu Ala Thr Leu Leu
1               5                  10                  15
Ala Pro Gly Ala**Lys Gln Gly Ser Cys Arg Lys Lys Cys Phe Asp Ala
            20                  25                  30
Ser Phe Arg Gly Leu Glu Asn Cys Arg Cys Asp Val Ala Cys Lys Asp
        35                  40                  45
Arg Gly Asp Cys Cys Trp Asp Phe Glu Asp Thr Cys Val Glu Ser Thr
    50                  55                  60
Arg Ile Trp Met Cys Asn Lys Phe Arg Cys Gly Glu Arg Leu Glu Ala
65                  70                  75                  80
Ser Leu Cys Ser Cys Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys Cys
                85                  90                  95
Ala Asp Tyr Lys Ser Val Cys Gln Gly Glu Thr Ser Trp Leu Glu Glu
            100                 105                 110
Asn Cys Asp Thr Ala Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp Leu
        115                 120                 125
Pro Pro Val Ile Leu Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr Leu
    130                 135                 140
Tyr Thr Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys Thr Cys
145                 150                 155                 160
Gly Ile His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr Phe
```

```
                 165                 170                 175
Pro Asn His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly
            180                 185                 190
Ile Ile Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser
        195                 200                 205
Leu Ser Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro
    210                 215                 220
Met Trp Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe
225                 230                 235                 240
Trp Pro Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr
                245                 250                 255
Met Pro Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu
            260                 265                 270
Leu Lys Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr
        275                 280                 285
Met Tyr Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val
    290                 295                 300
Ser Ala Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala Phe Gly
305                 310                 315                 320
Met Leu Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn
                325                 330                 335
Ile Ile Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys
            340                 345                 350
Met Glu Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr Met
        355                 360                 365
Tyr Glu Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro His Asp
    370                 375                 380
Phe Phe Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg
385                 390                 395                 400
Lys Pro Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys
                405                 410                 415
Arg Leu His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His Leu Phe
            420                 425                 430
Val Asp Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys
        435                 440                 445
Gly Gly Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala
    450                 455                 460
Ile Phe Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu
465                 470                 475                 480
Pro Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg
                485                 490                 495
Ile Gln Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His Leu
            500                 505                 510
Leu Lys Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys
        515                 520                 525
Phe Ser Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu Asp
    530                 535                 540
Cys Phe Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn
545                 550                 555                 560
Gln Met Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val
                565                 570                 575
Asn Leu Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val Asp His
```

580 585 590
Cys Leu Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala Met
595 600 605
Arg Met Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp Thr
610 615 620
Ser Pro Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp Val Arg
625 630 635 640
Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys
645 650 655
Asn Ile Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser
660 665 670
Asp Ser Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro Met Tyr
675 680 685
Glu Glu Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu Leu Ile
690 695 700
Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile
705 710 715 720
Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr
725 730 735
Lys His Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val
740 745 750
Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro
755 760 765
Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn
770 775 780
Val Glu Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu
785 790 795 800
Arg Phe Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr
805 810 815
Gly Leu Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu
820 825 830
Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile Asp Lys Thr
835 840 845
His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
850 855 860
Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
865 870 875 880
Thr Pro Glu Val Thr Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
885 890 895
Gly Gly Ser **Met Lys Trp Val Thr Phe Leu Leu Leu Leu Phe Val Ser**
900 905 910
Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg Glu Ala His Lys Ser
915 920 925
Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly
930 935 940
Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp
945 950 955 960
Glu His Ala Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys
965 970 975
Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu
980 985 990
Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly

995 1000 1005

Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu
1010 1015 1020
Cys Phe Leu Gln His Lys Asp Asp Asn Pro Ser Leu Pro Pro Phe
1025 1030 1035
Glu Arg Pro Glu Ala Glu Ala Met Cys Thr Ser Phe Lys Glu Asn
1040 1045 1050
Pro Thr Thr Phe Met Gly His Tyr Leu His Glu Val Ala Arg Arg
1055 1060 1065
His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Tyr Tyr Ala Glu Gln
1070 1075 1080
Tyr Asn Glu Ile Leu Thr Gln Cys Cys Ala Glu Ala Asp Lys Glu
1085 1090 1095
Ser Cys Leu Thr Pro Lys Leu Asp Gly Val Lys Glu Lys Ala Leu
1100 1105 1110
Val Ser Ser Val Arg Gln Arg Met Lys Cys Ser Ser Met Gln Lys
1115 1120 1125
Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser
1130 1135 1140
Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr Lys Leu Ala
1145 1150 1155
Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly Asp Leu
1160 1165 1170
Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met Cys
1175 1180 1185
Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys Cys Asp
1190 1195 1200
Lys Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val Glu His
1205 1210 1215
Asp Thr Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp Phe Val
1220 1225 1230
Glu Asp Gln Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val
1235 1240 1245
Phe Leu Gly Thr Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Asp
1250 1255 1260
Tyr Ser Val Ser Leu Leu Leu Arg Leu Ala Lys Lys Tyr Glu Ala
1265 1270 1275
Thr Leu Glu Lys Cys Cys Ala Glu Ala Asn Pro Pro Ala Cys Tyr
1280 1285 1290
Gly Thr Val Leu Ala Glu Phe Gln Pro Leu Val Glu Glu Pro Lys
1295 1300 1305
Asn Leu Val Lys Thr Asn Cys Asp Leu Tyr Glu Lys Leu Gly Glu
1310 1315 1320
Tyr Gly Phe Gln Asn Ala Ile Leu Val Arg Tyr Thr Gln Lys Ala
1325 1330 1335
Pro Gln Val Ser Thr Pro Thr Leu Val Glu Ala Ala Arg Asn Leu
1340 1345 1350
Gly Arg Val Gly Thr Lys Cys Cys Thr Leu Pro Glu Asp Gln Arg
1355 1360 1365
Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile Leu Asn Arg Val
1370 1375 1380
Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His Val Thr Lys

```
    1385                1390                1395
Cys Cys  Ser Gly Ser Leu Val  Glu Arg Arg Pro Cys  Phe Ser Ala
    1400                1405                1410
Leu Thr  Val Asp Glu Thr Tyr  Val Pro Lys Glu Phe  Lys Ala Glu
    1415                1420                1425
Thr Phe  Thr Phe His Ser Asp  Ile Cys Thr Leu Pro  Glu Lys Glu
    1430                1435                1440
Lys Gln  Ile Lys Lys Gln Thr  Ala Leu Ala Glu Leu  Val Lys His
    1445                1450                1455
Lys Pro  Lys Ala Thr Ala Glu  Gln Leu Lys Thr Val  Met Asp Asp
    1460                1465                1470
Phe Ala  Gln Phe Leu Asp Thr  Cys Cys Lys Ala Ala  Asp Lys Asp
    1475                1480                1485
Thr Cys  Phe Ser Thr Glu Gly  Pro Asn Leu Val Thr  Arg Cys Lys
    1490                1495                1500
Asp Ala  Leu Ala
    1505
```

Singly underlined:signal peptide sequence; double-underlined: beginning and end of NPP3; ** = cleavage position at the signal peptide sequence; bold residues indicate albumin sequence

SEQ. ID NO: 26 - ENPP71-GLK Amino Acid Sequence

```
Met Arg Gly Pro Ala Val Leu Leu Thr Val Ala Leu Ala Thr Leu Leu
1               5                  10                  15
Ala Pro Gly Ala Gly Ala**Gly Leu Lys Pro Ser Cys Ala Lys Glu Val
            20                  25                  30
Lys Ser Cys Lys Gly Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg
        35                  40                  45
Cys Asp Ala Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln
    50                  55                  60
Glu Thr Cys Ile Glu Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg
65                  70                  75                  80
Cys Gly Glu Lys Arg Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp
                85                  90                  95
Cys Lys Asp Lys Gly Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln
            100                 105                 110
Gly Glu Lys Ser Trp Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro
        115                 120                 125
Gln Cys Pro Ala Gly Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu
    130                 135                 140
Asp Gly Phe Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro
145                 150                 155                 160
Val Ile Ser Lys Leu Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg
                165                 170                 175
Pro Val Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr
            180                 185                 190
Gly Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp
```

```
        195                 200                 205
Pro Lys Met Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn
    210                 215                 220
Pro Glu Trp Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln
225                 230                 235                 240
Gly Leu Lys Ser Gly Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile
                245                 250                 255
Asn Gly Ile Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro
            260                 265                 270
Phe Glu Glu Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys
        275                 280                 285
Asp Glu Arg Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser
    290                 295                 300
Ser Gly His Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu
305                 310                 315                 320
Gln Arg Val Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu
                325                 330                 335
Leu Asn Leu His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly
            340                 345                 350
Met Glu Gln Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu
        355                 360                 365
Gly Asp Val Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu
    370                 375                 380
Arg Pro Ser Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly
385                 390                 395                 400
Ile Ala Arg Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro
                405                 410                 415
Tyr Leu Lys His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp
            420                 425                 430
Arg Ile Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala
        435                 440                 445
Leu Asn Pro Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser
    450                 455                 460
Asp Asn Val Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro
465                 470                 475                 480
Gly Phe Lys His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val
                485                 490                 495
Tyr Asn Leu Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn
            500                 505                 510
Gly Thr His Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr
        515                 520                 525
Pro Lys His Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr
    530                 535                 540
Arg Asn Pro Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu
545                 550                 555                 560
Pro Ile Glu Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu
                565                 570                 575
Lys Ile Ile Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu
            580                 585                 590
Gln Lys Glu Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser
        595                 600                 605
Gly Tyr Ser Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val
```

```
    610                 615                 620
Asp Arg Asn Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr
625                 630                 635                 640
Gln Asp Phe Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr
                645                 650                 655
Lys Asn Asn Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu
            660                 665                 670
Asn Lys Asn Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn
        675                 680                 685
Ile Val Pro Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His
    690                 695                 700
Asp Thr Leu Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val
705                 710                 715                 720
Val Ser Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser
                725                 730                 735
Leu Glu Asn Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile
            740                 745                 750
Leu Ile Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr
        755                 760                 765
Ser Gln Thr Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile
    770                 775                 780
Leu Pro His Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His
785                 790                 795                 800
Asp Ser Ser Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile
                805                 810                 815
Thr Asp Val Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys
            820                 825                 830
Glu Pro Val Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe
        835                 840                 845
Ser Gln Glu Asp
    850
```

Singly underlined:signal peptide sequence; double-underlined: beginning and end of NPP1; ** = cleavage position at the signal peptide sequence

SEQ. ID NO: 27 - ENPP121 Amino Acid Sequence

```
Met Glu Arg Asp Gly Cys Ala Gly Gly Gly Ser Arg Gly Gly Glu Gly
1               5                   10                  15
Gly Arg Ala Pro Arg Glu Gly Pro Ala Gly Asn Gly Arg Asp Arg Gly
            20                  25                  30
Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala Ser
        35                  40                  45
Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala
    50                  55                  60
Arg Ala Arg Thr Ala Lys Asp Pro Asn Thr Tyr Lys Ile Ile Ser Leu
65                  70                  75                  80
Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly**Phe Thr Ala Gly
```

```
                85                  90                  95
Leu Lys Pro Ser Cys Ala Lys Glu Val Lys Ser Cys Lys Gly Arg Cys
            100                 105                 110
Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala Ala Cys Val Glu
        115                 120                 125
Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys Ile Glu Pro Glu
    130                 135                 140
His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu Lys Arg Leu Thr
145                 150                 155                 160
Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp Lys Gly Asp Cys
                165                 170                 175
Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp Val Glu
            180                 185                 190
Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro Ala Gly Phe Glu
        195                 200                 205
Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe Arg Ala Glu Tyr
    210                 215                 220
Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser Lys Leu Lys Lys
225                 230                 235                 240
Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr Lys Thr
                245                 250                 255
Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu Ser His
            260                 265                 270
Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala Ser Phe
        275                 280                 285
Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys Gly Glu
    290                 295                 300
Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly Thr Phe
305                 310                 315                 320
Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro Asp Ile
                325                 330                 335
Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Leu Ala
            340                 345                 350
Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His Phe Tyr
        355                 360                 365
Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr Gly Pro
    370                 375                 380
Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly Met Val
385                 390                 395                 400
Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg Cys Leu
                405                 410                 415
Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser Cys Lys
            420                 425                 430
Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn Ile Lys
        435                 440                 445
Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val Pro Asp
    450                 455                 460
Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu Ser Cys
465                 470                 475                 480
Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe Leu Pro
                485                 490                 495
Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu Thr Phe
```

```
            500                 505                 510
Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu Arg Lys
        515                 520                 525
Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser Asn Met
    530                 535                 540
Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys His Gly Ile Glu
545                 550                 555                 560
Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu
                565                 570                 575
Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn
            580                 585                 590
His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His Pro Lys Glu Val
        595                 600                 605
His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp Asn Leu
    610                 615                 620
Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe Gln Thr
625                 630                 635                 640
Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His Glu Thr
                645                 650                 655
Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr Ile Cys
            660                 665                 670
Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp Ile Leu
        675                 680                 685
Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser Phe Ser
    690                 695                 700
Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile Pro Leu
705                 710                 715                 720
Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val Ser
                725                 730                 735
Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser Gly Ile
            740                 745                 750
Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln Ser
        755                 760                 765
Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys Tyr
    770                 775                 780
Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val Phe Asp
785                 790                 795                 800
Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln Lys
                805                 810                 815
Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe Phe
            820                 825                 830
Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His Cys
        835                 840                 845
Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp Asn
    850                 855                 860
Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu Glu
865                 870                 875                 880
Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile Thr
                885                 890                 895
Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile Leu
            900                 905                 910
Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp
```

915 920 925

Singly underlined:signal peptide sequence; double-underlined: beginning and end of NPP1; ** = cleavage position at the signal peptide sequence

SEQ. ID. NO: 28 - ENPP121-Fc Amino Acid Sequence

```
Met Glu Arg Asp Gly Cys Ala Gly Gly Gly Ser Arg Gly Gly Glu Gly
1               5                  10                  15
Gly Arg Ala Pro Arg Glu Gly Pro Ala Gly Asn Gly Arg Asp Arg Gly
            20                  25                  30
Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala Ser
        35                  40                  45
Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala
    50                  55                  60
Arg Ala Arg Thr Ala Lys Asp Pro Asn Thr Tyr Lys Ile Ile Ser Leu
65                  70                  75                  80
Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly**Phe Thr Ala Gly
                85                  90                  95
Leu Lys Pro Ser Cys Ala Lys Glu Val Lys Ser Cys Lys Gly Arg Cys
            100                 105                 110
Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala Ala Cys Val Glu
        115                 120                 125
Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys Ile Glu Pro Glu
    130                 135                 140
His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu Lys Arg Leu Thr
145                 150                 155                 160
Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp Lys Gly Asp Cys
                165                 170                 175
Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp Val Glu
            180                 185                 190
Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro Ala Gly Phe Glu
        195                 200                 205
Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe Arg Ala Glu Tyr
    210                 215                 220
Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser Lys Leu Lys Lys
225                 230                 235                 240
Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr Lys Thr
                245                 250                 255
Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu Ser His
            260                 265                 270
Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala Ser Phe
        275                 280                 285
Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys Gly Glu
    290                 295                 300
Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly Thr Phe
305                 310                 315                 320
Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro Asp Ile
```

```
                325                 330                 335
Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Leu Ala
            340                 345                 350
Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His Phe Tyr
        355                 360                 365
Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr Gly Pro
    370                 375                 380
Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly Met Val
385                 390                 395                 400
Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg Cys Leu
                405                 410                 415
Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser Cys Lys
            420                 425                 430
Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn Ile Lys
        435                 440                 445
Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val Pro Asp
    450                 455                 460
Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu Ser Cys
465                 470                 475                 480
Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe Leu Pro
                485                 490                 495
Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu Thr Phe
            500                 505                 510
Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu Arg Lys
        515                 520                 525
Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser Asn Met
    530                 535                 540
Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys His Gly Ile Glu
545                 550                 555                 560
Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu
                565                 570                 575
Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn
            580                 585                 590
His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His Pro Lys Glu Val
        595                 600                 605
His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp Asn Leu
    610                 615                 620
Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe Gln Thr
625                 630                 635                 640
Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His Glu Thr
                645                 650                 655
Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr Ile Cys
            660                 665                 670
Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp Ile Leu
        675                 680                 685
Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser Phe Ser
    690                 695                 700
Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile Pro Leu
705                 710                 715                 720
Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val Ser
                725                 730                 735
Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser Gly Ile
```

740 745 750
Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln Ser
755 760 765
Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys Tyr
770 775 780
Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val Phe Asp
785 790 795 800
Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln Lys
805 810 815
Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe Phe
820 825 830
Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His Cys
835 840 845
Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp Asn
850 855 860
Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu Glu
865 870 875 880
Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile Thr
885 890 895
Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile Leu
900 905 910
Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp Leu Ile Asn
915 920 925
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
930 935 940
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
945 950 955 960
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
965 970 975
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
980 985 990
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
995 1000 1005
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
1010 1015 1020
Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
1025 1030 1035
Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
1040 1045 1050
Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
1055 1060 1065
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
1070 1075 1080
Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
1085 1090 1095
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
1100 1105 1110
Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
1115 1120 1125
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
1130 1135 1140
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

1145 1150 1155

Singly underlined:signal peptide sequence; double-underlined: beginning and end of NPP1; ** = cleavage position at the signal peptide sequence; bold residues indicate Fc sequence

SEQ. ID NO: 29 - ENPP121-ALB Amino Acid Sequence:

```
Met Glu Arg Asp Gly Cys Ala Gly Gly Gly Ser Arg Gly Gly Glu Gly
1               5                  10                  15
Gly Arg Ala Pro Arg Glu Gly Pro Ala Gly Asn Gly Arg Asp Arg Gly
            20                  25                  30
Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala Ser
        35                  40                  45
Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala
    50                  55                  60
Arg Ala Arg Thr Ala Lys Asp Pro Asn Thr Tyr Lys Ile Ile Ser Leu
65                  70                  75                  80
Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly**Phe Thr Ala Gly
                85                  90                  95
Leu Lys Pro Ser Cys Ala Lys Glu Val Lys Ser Cys Lys Gly Arg Cys
            100                 105                 110
Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala Ala Cys Val Glu
        115                 120                 125
Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys Ile Glu Pro Glu
    130                 135                 140
His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu Lys Arg Leu Thr
145                 150                 155                 160
Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp Lys Gly Asp Cys
                165                 170                 175
Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp Val Glu
            180                 185                 190
Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro Ala Gly Phe Glu
        195                 200                 205
Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe Arg Ala Glu Tyr
    210                 215                 220
Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser Lys Leu Lys Lys
225                 230                 235                 240
Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr Lys Thr
                245                 250                 255
Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu Ser His
            260                 265                 270
Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala Ser Phe
        275                 280                 285
Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys Gly Glu
    290                 295                 300
Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly Thr Phe
305                 310                 315                 320
Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro Asp Ile
                325                 330                 335
Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Leu Ala
```

```
            340                 345                 350
Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His Phe Tyr
        355                 360                 365
Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr Gly Pro
    370                 375                 380
Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly Met Val
385                 390                 395                 400
Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg Cys Leu
                405                 410                 415
Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser Cys Lys
            420                 425                 430
Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn Ile Lys
        435                 440                 445
Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val Pro Asp
    450                 455                 460
Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu Ser Cys
465                 470                 475                 480
Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe Leu Pro
                485                 490                 495
Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu Thr Phe
            500                 505                 510
Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu Arg Lys
        515                 520                 525
Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser Asn Met
    530                 535                 540
Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys His Gly Ile Glu
545                 550                 555                 560
Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu
                565                 570                 575
Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn
            580                 585                 590
His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His Pro Lys Glu Val
        595                 600                 605
His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp Asn Leu
    610                 615                 620
Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe Gln Thr
625                 630                 635                 640
Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His Glu Thr
                645                 650                 655
Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr Ile Cys
            660                 665                 670
Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp Ile Leu
        675                 680                 685
Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser Phe Ser
    690                 695                 700
Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile Pro Leu
705                 710                 715                 720
Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val Ser
                725                 730                 735
Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser Gly Ile
            740                 745                 750
Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln Ser
```

```
        755                 760                 765
Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys Tyr
    770                 775                 780
Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val Phe Asp
785                 790                 795                 800
Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln Lys
                805                 810                 815
Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe Phe
            820                 825                 830
Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His Cys
        835                 840                 845
Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp Asn
    850                 855                 860
Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu Glu
865                 870                 875                 880
Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile Thr
                885                 890                 895
Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile Leu
            900                 905                 910
Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp Arg Ser Gly
        915                 920                 925
Ser Gly Gly Ser Met Lys Trp Val Thr Phe Leu Leu Leu Leu Phe Val
    930                 935                 940
Ser Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg Glu Ala His Lys
945                 950                 955                 960
Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys
                965                 970                 975
Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr
            980                 985                 990
Asp Glu His Ala Lys Leu Val Gln  Glu Val Thr Asp Phe  Ala Lys Thr
        995                 1000                1005
Cys Val  Ala Asp Glu Ser Ala  Ala Asn Cys Asp Lys  Ser Leu His
    1010                1015                1020
Thr Leu  Phe Gly Asp Lys Leu  Cys Ala Ile Pro Asn  Leu Arg Glu
    1025                1030                1035
Asn Tyr  Gly Glu Leu Ala Asp  Cys Cys Thr Lys Gln  Glu Pro Glu
    1040                1045                1050
Arg Asn  Glu Cys Phe Leu Gln  His Lys Asp Asp Asn  Pro Ser Leu
    1055                1060                1065
Pro Pro  Phe Glu Arg Pro Glu  Ala Glu Ala Met Cys  Thr Ser Phe
    1070                1075                1080
Lys Glu  Asn Pro Thr Thr Phe  Met Gly His Tyr Leu  His Glu Val
    1085                1090                1095
Ala Arg  Arg His Pro Tyr Phe  Tyr Ala Pro Glu Leu  Leu Tyr Tyr
    1100                1105                1110
Ala Glu  Gln Tyr Asn Glu Ile  Leu Thr Gln Cys Cys  Ala Glu Ala
    1115                1120                1125
Asp Lys  Glu Ser Cys Leu Thr  Pro Lys Leu Asp Gly  Val Lys Glu
    1130                1135                1140
Lys Ala  Leu Val Ser Ser Val  Arg Gln Arg Met Lys  Cys Ser Ser
    1145                1150                1155
Met Gln  Lys Phe Gly Glu Arg  Ala Phe Lys Ala Trp  Ala Val Ala
```

```
    1160                1165                1170
Arg Leu  Ser Gln Thr Phe Pro  Asn Ala Asp Phe Ala  Glu Ile Thr
    1175                1180                1185
Lys Leu  Ala Thr Asp Leu Thr  Lys Val Asn Lys Glu  Cys Cys His
    1190                1195                1200
Gly Asp  Leu Leu Glu Cys Ala  Asp Asp Arg Ala Glu  Leu Ala Lys
    1205                1210                1215
Tyr Met  Cys Glu Asn Gln Ala  Thr Ile Ser Ser Lys  Leu Gln Thr
    1220                1225                1230
Cys Cys  Asp Lys Pro Leu Leu  Lys Lys Ala His Cys  Leu Ser Glu
    1235                1240                1245
Val Glu  His Asp Thr Met Pro  Ala Asp Leu Pro Ala  Ile Ala Ala
    1250                1255                1260
Asp Phe  Val Glu Asp Gln Glu  Val Cys Lys Asn Tyr  Ala Glu Ala
    1265                1270                1275
Lys Asp  Val Phe Leu Gly Thr  Phe Leu Tyr Glu Tyr  Ser Arg Arg
    1280                1285                1290
His Pro  Asp Tyr Ser Val Ser  Leu Leu Leu Arg Leu  Ala Lys Lys
    1295                1300                1305
Tyr Glu  Ala Thr Leu Glu Lys  Cys Cys Ala Glu Ala  Asn Pro Pro
    1310                1315                1320
Ala Cys  Tyr Gly Thr Val Leu  Ala Glu Phe Gln Pro  Leu Val Glu
    1325                1330                1335
Glu Pro  Lys Asn Leu Val Lys  Thr Asn Cys Asp Leu  Tyr Glu Lys
    1340                1345                1350
Leu Gly  Glu Tyr Gly Phe Gln  Asn Ala Ile Leu Val  Arg Tyr Thr
    1355                1360                1365
Gln Lys  Ala Pro Gln Val Ser  Thr Pro Thr Leu Val  Glu Ala Ala
    1370                1375                1380
Arg Asn  Leu Gly Arg Val Gly  Thr Lys Cys Cys Thr  Leu Pro Glu
    1385                1390                1395
Asp Gln  Arg Leu Pro Cys Val  Glu Asp Tyr Leu Ser  Ala Ile Leu
    1400                1405                1410
Asn Arg  Val Cys Leu Leu His  Glu Lys Thr Pro Val  Ser Glu His
    1415                1420                1425
Val Thr  Lys Cys Cys Ser Gly  Ser Leu Val Glu Arg  Arg Pro Cys
    1430                1435                1440
Phe Ser  Ala Leu Thr Val Asp  Glu Thr Tyr Val Pro  Lys Glu Phe
    1445                1450                1455
Lys Ala  Glu Thr Phe Thr Phe  His Ser Asp Ile Cys  Thr Leu Pro
    1460                1465                1470
Glu Lys  Glu Lys Gln Ile Lys  Lys Gln Thr Ala Leu  Ala Glu Leu
    1475                1480                1485
Val Lys  His Lys Pro Lys Ala  Thr Ala Glu Gln Leu  Lys Thr Val
    1490                1495                1500
Met Asp  Asp Phe Ala Gln Phe  Leu Asp Thr Cys Cys  Lys Ala Ala
    1505                1510                1515
Asp Lys  Asp Thr Cys Phe Ser  Thr Glu Gly Pro Asn  Leu Val Thr
    1520                1525                1530
Arg Cys  Lys Asp Ala Leu Ala  Arg Ser Trp Ser His  Pro Gln Phe
    1535                1540                1545
Glu Lys
```

1550

Singly underlined:signal peptide sequence; double-underlined: beginning and end of NPP1; ** = cleavage position at the signal peptide sequence; bold residues indicate albumin sequence

SEQ. ID NO: 30 - ENPP121-NPP3-Fc sequence

```
Met Glu Arg Asp Gly Cys Ala Gly Gly Gly Ser Arg Gly Gly Glu Gly
1               5                  10                  15
Gly Arg Ala Pro Arg Glu Gly Pro Ala Gly Asn Gly Arg Asp Arg Gly
            20                  25                  30
Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala Ser
        35                  40                  45
Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala
    50                  55                  60
Arg Ala Arg Thr Ala Lys Asp Pro Asn Thr Tyr Lys Ile Ile Ser Leu
65                  70                  75                  80
Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly Phe Thr Ala**Lys
                85                  90                  95
Gln Gly Ser Cys Arg Lys Lys Cys Phe Asp Ala Ser Phe Arg Gly Leu
            100                 105                 110
Glu Asn Cys Arg Cys Asp Val Ala Cys Lys Asp Arg Gly Asp Cys Cys
        115                 120                 125
Trp Asp Phe Glu Asp Thr Cys Val Glu Ser Thr Arg Ile Trp Met Cys
    130                 135                 140
Asn Lys Phe Arg Cys Gly Glu Arg Leu Glu Ala Ser Leu Cys Ser Cys
145                 150                 155                 160
Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys Cys Ala Asp Tyr Lys Ser
                165                 170                 175
Val Cys Gln Gly Glu Thr Ser Trp Leu Glu Glu Asn Cys Asp Thr Ala
            180                 185                 190
Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp Leu Pro Pro Val Ile Leu
        195                 200                 205
Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr Leu Tyr Thr Trp Asp Thr
    210                 215                 220
Leu Met Pro Asn Ile Asn Lys Leu Lys Thr Cys Gly Ile His Ser Lys
225                 230                 235                 240
Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Thr
                245                 250                 255
Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Asn
            260                 265                 270
Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser Leu Ser Ser Lys Glu
        275                 280                 285
Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro Met Trp Leu Thr Ala
    290                 295                 300
Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe Trp Pro Gly Ser Glu
305                 310                 315                 320
Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr Met Pro Tyr Asn Gly
```

```
                325                 330                 335
Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu Leu Lys Trp Leu Asp
            340                 345                 350
Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr Met Tyr Phe Glu Glu
        355                 360                 365
Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val Ser Ala Arg Val Ile
    370                 375                 380
Lys Ala Leu Gln Val Val Asp His Ala Phe Gly Met Leu Met Glu Gly
385                 390                 395                 400
Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn Ile Ile Leu Leu Ala
                405                 410                 415
Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys Met Glu Tyr Met Thr
            420                 425                 430
Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr Met Tyr Glu Gly Pro Ala
        435                 440                 445
Pro Arg Ile Arg Ala His Asn Ile Pro His Asp Phe Phe Ser Phe Asn
    450                 455                 460
Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg Lys Pro Asp Gln His
465                 470                 475                 480
Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys Arg Leu His Tyr Ala
                485                 490                 495
Lys Asn Val Arg Ile Asp Lys Val His Leu Phe Val Asp Gln Gln Trp
            500                 505                 510
Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys Gly Gly Gly Asn His
        515                 520                 525
Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala Ile Phe Leu Ala His
    530                 535                 540
Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu Pro Phe Glu Asn Ile
545                 550                 555                 560
Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg Ile Gln Pro Ala Pro
                565                 570                 575
Asn Asn Gly Thr His Gly Ser Leu Asn His Leu Leu Lys Val Pro Phe
            580                 585                 590
Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys Phe Ser Val Cys Gly
        595                 600                 605
Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu Asp Cys Phe Cys Pro His
    610                 615                 620
Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn Gln Met Leu Asn Leu
625                 630                 635                 640
Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val Asn Leu Pro Phe Gly
                645                 650                 655
Arg Pro Arg Val Leu Gln Lys Asn Val Asp His Cys Leu Leu Tyr His
            660                 665                 670
Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala Met Arg Met Pro Met Trp
        675                 680                 685
Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp Thr Ser Pro Leu Pro Pro
    690                 695                 700
Thr Val Pro Asp Cys Leu Arg Ala Asp Val Arg Val Pro Pro Ser Glu
705                 710                 715                 720
Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys Asn Ile Thr His Gly
                725                 730                 735
Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser Asp Ser Gln Tyr Asp
```

```
            740                 745                 750
Ala Leu Ile Thr Ser Asn Leu Val Pro Met Tyr Glu Glu Phe Arg Lys
        755                 760                 765
Met Trp Asp Tyr Phe His Ser Val Leu Leu Ile Lys His Ala Thr Glu
    770                 775                 780
Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile Phe Asp Tyr Asn Tyr
785                 790                 795                 800
Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr Lys His Leu Ala Asn
                805                 810                 815
Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val Val Leu Thr Ser Cys
            820                 825                 830
Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro Gly Trp Leu Asp Val
        835                 840                 845
Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn Val Glu Ser Cys Pro
    850                 855                 860
Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu Arg Phe Thr Ala His
865                 870                 875                 880
Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr Gly Leu Asp Phe Tyr
                885                 890                 895
Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu Gln Leu Lys Thr Tyr
            900                 905                 910
Leu Pro Thr Phe Glu Thr Thr Ile Asp Lys Thr His Thr Cys Pro Pro
        915                 920                 925
Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
    930                 935                 940
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
945                 950                 955                 960
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
                965                 970                 975
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
            980                 985                 990
Glu Glu Gln Tyr Asn Ser Thr Tyr  Arg Val Val Ser Val  Leu Thr Val
        995                 1000                1005
Leu His  Gln Asp Trp Leu Asn  Gly Lys Glu Tyr Lys  Cys Lys Val
    1010                1015                1020
Ser Asn  Lys Ala Leu Pro Ala  Pro Ile Glu Lys Thr  Ile Ser Lys
    1025                1030                1035
Ala Lys  Gly Gln Pro Arg Glu  Pro Gln Val Tyr Thr  Leu Pro Pro
    1040                1045                1050
Ser Arg  Glu Glu Met Thr Lys  Asn Gln Val Ser Leu  Thr Cys Leu
    1055                1060                1065
Val Lys  Gly Phe Tyr Pro Ser  Asp Ile Ala Val Glu  Trp Glu Ser
    1070                1075                1080
Asn Gly  Gln Pro Glu Asn Asn  Tyr Lys Thr Thr Pro  Pro Val Leu
    1085                1090                1095
Asp Ser  Asp Gly Ser Phe Phe  Leu Tyr Ser Lys Leu  Thr Val Asp
    1100                1105                1110
Lys Ser  Arg Trp Gln Gln Gly  Asn Val Phe Ser Cys  Ser Val Met
    1115                1120                1125
His Glu  Ala Leu His Asn His  Tyr Thr Gln Lys Ser  Leu Ser Leu
    1130                1135                1140
Ser Pro  Gly Lys
```

1145

Singly underlined:signal peptide sequence; double-underlined: beginning and end of NPP1; ** = cleavage position at the signal peptide sequence; bold residues indicate Fc sequence

SEQ. ID NO: 31 - ENPP121-NPP3-Albumin sequence

```
Met Glu Arg Asp Gly Cys Ala Gly Gly Gly Ser Arg Gly Gly Glu Gly
1               5                  10                  15
Gly Arg Ala Pro Arg Glu Gly Pro Ala Gly Asn Gly Arg Asp Arg Gly
            20                  25                  30
Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala Ser
        35                  40                  45
Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala
    50                  55                  60
Arg Ala Arg Thr Ala Lys Asp Pro Asn Thr Tyr Lys Ile Ile Ser Leu
65                  70                  75                  80
Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly Phe Thr Ala**Lys
                85                  90                  95
Gln Gly Ser Cys Arg Lys Lys Cys Phe Asp Ala Ser Phe Arg Gly Leu
            100                 105                 110
Glu Asn Cys Arg Cys Asp Val Ala Cys Lys Asp Arg Gly Asp Cys Cys
        115                 120                 125
Trp Asp Phe Glu Asp Thr Cys Val Glu Ser Thr Arg Ile Trp Met Cys
    130                 135                 140
Asn Lys Phe Arg Cys Gly Glu Arg Leu Glu Ala Ser Leu Cys Ser Cys
145                 150                 155                 160
Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys Cys Ala Asp Tyr Lys Ser
                165                 170                 175
Val Cys Gln Gly Glu Thr Ser Trp Leu Glu Glu Asn Cys Asp Thr Ala
            180                 185                 190
Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp Leu Pro Pro Val Ile Leu
        195                 200                 205
Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr Leu Tyr Thr Trp Asp Thr
    210                 215                 220
Leu Met Pro Asn Ile Asn Lys Leu Lys Thr Cys Gly Ile His Ser Lys
225                 230                 235                 240
Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Thr
                245                 250                 255
Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Asn
            260                 265                 270
Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser Leu Ser Ser Lys Glu
        275                 280                 285
Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro Met Trp Leu Thr Ala
    290                 295                 300
Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe Trp Pro Gly Ser Glu
305                 310                 315                 320
Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr Met Pro Tyr Asn Gly
```

```
                325                 330                 335
Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu Leu Lys Trp Leu Asp
            340                 345                 350
Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr Met Tyr Phe Glu Glu
        355                 360                 365
Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val Ser Ala Arg Val Ile
    370                 375                 380
Lys Ala Leu Gln Val Val Asp His Ala Phe Gly Met Leu Met Glu Gly
385                 390                 395                 400
Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn Ile Ile Leu Leu Ala
                405                 410                 415
Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys Met Glu Tyr Met Thr
            420                 425                 430
Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr Met Tyr Glu Gly Pro Ala
        435                 440                 445
Pro Arg Ile Arg Ala His Asn Ile Pro His Asp Phe Phe Ser Phe Asn
    450                 455                 460
Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg Lys Pro Asp Gln His
465                 470                 475                 480
Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys Arg Leu His Tyr Ala
                485                 490                 495
Lys Asn Val Arg Ile Asp Lys Val His Leu Phe Val Asp Gln Gln Trp
            500                 505                 510
Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys Gly Gly Gly Asn His
        515                 520                 525
Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala Ile Phe Leu Ala His
    530                 535                 540
Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu Pro Phe Glu Asn Ile
545                 550                 555                 560
Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg Ile Gln Pro Ala Pro
                565                 570                 575
Asn Asn Gly Thr His Gly Ser Leu Asn His Leu Leu Lys Val Pro Phe
            580                 585                 590
Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys Phe Ser Val Cys Gly
        595                 600                 605
Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu Asp Cys Phe Cys Pro His
    610                 615                 620
Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn Gln Met Leu Asn Leu
625                 630                 635                 640
Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val Asn Leu Pro Phe Gly
                645                 650                 655
Arg Pro Arg Val Leu Gln Lys Asn Val Asp His Cys Leu Leu Tyr His
            660                 665                 670
Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala Met Arg Met Pro Met Trp
        675                 680                 685
Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp Thr Ser Pro Leu Pro Pro
    690                 695                 700
Thr Val Pro Asp Cys Leu Arg Ala Asp Val Arg Val Pro Pro Ser Glu
705                 710                 715                 720
Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys Asn Ile Thr His Gly
                725                 730                 735
Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser Asp Ser Gln Tyr Asp
```

740 745 750
Ala Leu Ile Thr Ser Asn Leu Val Pro Met Tyr Glu Glu Phe Arg Lys
755 760 765
Met Trp Asp Tyr Phe His Ser Val Leu Leu Ile Lys His Ala Thr Glu
770 775 780
Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile Phe Asp Tyr Asn Tyr
785 790 795 800
Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr Lys His Leu Ala Asn
805 810 815
Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val Val Leu Thr Ser Cys
820 825 830
Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro Gly Trp Leu Asp Val
835 840 845
Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn Val Glu Ser Cys Pro
850 855 860
Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu Arg Phe Thr Ala His
865 870 875 880
Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr Gly Leu Asp Phe Tyr
885 890 895
Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu Gln Leu Lys Thr Tyr
900 905 910
Leu Pro Thr Phe Glu Thr Thr Ile Gly Gly Gly Ser Gly Gly Gly Gly
915 920 925
Ser Gly Gly Gly Gly Ser **Met Lys Trp Val Thr Phe Leu Leu Leu Leu**
930 935 940
Phe Val Ser Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg Glu Ala
945 950 955 960
His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His
965 970 975
Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys
980 985 990
Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu Val Thr Asp Phe Ala
995 1000 1005
Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys Ser
1010 1015 1020
Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu
1025 1030 1035
Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu
1040 1045 1050
Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
1055 1060 1065
Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met Cys Thr
1070 1075 1080
Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly His Tyr Leu His
1085 1090 1095
Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
1100 1105 1110
Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys Ala
1115 1120 1125
Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val
1130 1135 1140
Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys

```
    1145                1150                1155
Ser Ser  Met Gln Lys Phe Gly  Glu Arg Ala Phe Lys  Ala Trp Ala
    1160                1165                1170
Val Ala  Arg Leu Ser Gln Thr  Phe Pro Asn Ala Asp  Phe Ala Glu
    1175                1180                1185
Ile Thr  Lys Leu Ala Thr Asp  Leu Thr Lys Val Asn  Lys Glu Cys
    1190                1195                1200
Cys His  Gly Asp Leu Leu Glu  Cys Ala Asp Asp Arg  Ala Glu Leu
    1205                1210                1215
Ala Lys  Tyr Met Cys Glu Asn  Gln Ala Thr Ile Ser  Ser Lys Leu
    1220                1225                1230
Gln Thr  Cys Cys Asp Lys Pro  Leu Leu Lys Lys Ala  His Cys Leu
    1235                1240                1245
Ser Glu  Val Glu His Asp Thr  Met Pro Ala Asp Leu  Pro Ala Ile
    1250                1255                1260
Ala Ala  Asp Phe Val Glu Asp  Gln Glu Val Cys Lys  Asn Tyr Ala
    1265                1270                1275
Glu Ala  Lys Asp Val Phe Leu  Gly Thr Phe Leu Tyr  Glu Tyr Ser
    1280                1285                1290
Arg Arg  His Pro Asp Tyr Ser  Val Ser Leu Leu Leu  Arg Leu Ala
    1295                1300                1305
Lys Lys  Tyr Glu Ala Thr Leu  Glu Lys Cys Cys Ala  Glu Ala Asn
    1310                1315                1320
Pro Pro  Ala Cys Tyr Gly Thr  Val Leu Ala Glu Phe  Gln Pro Leu
    1325                1330                1335
Val Glu  Glu Pro Lys Asn Leu  Val Lys Thr Asn Cys  Asp Leu Tyr
    1340                1345                1350
Glu Lys  Leu Gly Glu Tyr Gly  Phe Gln Asn Ala Ile  Leu Val Arg
    1355                1360                1365
Tyr Thr  Gln Lys Ala Pro Gln  Val Ser Thr Pro Thr  Leu Val Glu
    1370                1375                1380
Ala Ala  Arg Asn Leu Gly Arg  Val Gly Thr Lys Cys  Cys Thr Leu
    1385                1390                1395
Pro Glu  Asp Gln Arg Leu Pro  Cys Val Glu Asp Tyr  Leu Ser Ala
    1400                1405                1410
Ile Leu  Asn Arg Val Cys Leu  Leu His Glu Lys Thr  Pro Val Ser
    1415                1420                1425
Glu His  Val Thr Lys Cys Cys  Ser Gly Ser Leu Val  Glu Arg Arg
    1430                1435                1440
Pro Cys  Phe Ser Ala Leu Thr  Val Asp Glu Thr Tyr  Val Pro Lys
    1445                1450                1455
Glu Phe  Lys Ala Glu Thr Phe  Thr Phe His Ser Asp  Ile Cys Thr
    1460                1465                1470
Leu Pro  Glu Lys Glu Lys Gln  Ile Lys Lys Gln Thr  Ala Leu Ala
    1475                1480                1485
Glu Leu  Val Lys His Lys Pro  Lys Ala Thr Ala Glu  Gln Leu Lys
    1490                1495                1500
Thr Val  Met Asp Asp Phe Ala  Gln Phe Leu Asp Thr  Cys Cys Lys
    1505                1510                1515
Ala Ala  Asp Lys Asp Thr Cys  Phe Ser Thr Glu Gly  Pro Asn Leu
    1520                1525                1530
Val Thr  Arg Cys Lys Asp Ala  Leu Ala
```

1535 1540

Singly underlined:signal peptide sequence; double-underlined: beginning and end of NPP3; ** = cleavage position at the signal peptide sequence; bold residues indicate albumin sequence

SEQ. ID NO: 32 - ENPP121GLK Protein Export Signal Sequence

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

SEQ. ID NO: 33 - Albumin Sequence

```
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Met
1               5                  10                  15
Lys Trp Val Thr Phe Leu Leu Leu Leu Phe Val Ser Gly Ser Ala Phe
            20                  25                  30
Ser Arg Gly Val Phe Arg Arg Glu Ala His Lys Ser Glu Ile Ala His
        35                  40                  45
Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile
    50                  55                  60
Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys
65                  70                  75                  80
Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu
                85                  90                  95
Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys
            100                 105                 110
Leu Cys Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala Asp
        115                 120                 125
Cys Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His
    130                 135                 140
Lys Asp Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala Glu
145                 150                 155                 160
Ala Met Cys Thr Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly His
                165                 170                 175
```

```
Tyr Leu His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
            180                 185                 190
Leu Leu Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys
        195                 200                 205
Ala Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val
    210                 215                 220
Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys Ser
225                 230                 235                 240
Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala
                245                 250                 255
Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr Lys
            260                 265                 270
Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly Asp
        275                 280                 285
Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met Cys
    290                 295                 300
Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys Cys Asp Lys
305                 310                 315                 320
Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val Glu His Asp Thr
                325                 330                 335
Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp Phe Val Glu Asp Gln
            340                 345                 350
Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Thr
        355                 360                 365
Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Asp Tyr Ser Val Ser Leu
    370                 375                 380
Leu Leu Arg Leu Ala Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys Cys
385                 390                 395                 400
Ala Glu Ala Asn Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu Phe
                405                 410                 415
Gln Pro Leu Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys Asp
            420                 425                 430
Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val
        435                 440                 445
Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu
    450                 455                 460
Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu Pro
465                 470                 475                 480
Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile Leu
                485                 490                 495
Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His Val
            500                 505                 510
Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe Ser
        515                 520                 525
Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys Ala Glu
    530                 535                 540
Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu Lys Glu Lys
545                 550                 555                 560
Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val Lys His Lys Pro
                565                 570                 575
Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met Asp Asp Phe Ala Gln
            580                 585                 590
```

```
Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp Lys Asp Thr Cys Phe Ser
        595                 600                 605
Thr Glu Gly Pro Asn Leu Val Thr Arg Cys Lys Asp Ala Leu Ala
    610                 615                 620
```

SEQ. ID NO: 34 - Human IgG Fc domain, Fc

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1               5                  10                  15
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
    130                 135                 140
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220
Pro Gly Lys
225
```

SEQ. ID NO: 35 - Albumin Sequence

```
Met Lys Trp Val Thr Phe Leu Leu Leu Leu Phe Val Ser Gly Ser Ala
1               5                  10                  15
Phe Ser Arg Gly Val Phe Arg Arg Glu Ala His Lys Ser Glu Ile Ala
            20                  25                  30
His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu
        35                  40                  45
Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala
    50                  55                  60
Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80
```

```
Glu Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95
Lys Leu Cys Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala
            100                 105                 110
Asp Cys Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125
His Lys Asp Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala
    130                 135                 140
Glu Ala Met Cys Thr Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly
145                 150                 155                 160
His Tyr Leu His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175
Glu Leu Leu Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys
            180                 185                 190
Cys Ala Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly
        195                 200                 205
Val Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys
    210                 215                 220
Ser Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240
Ala Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr
                245                 250                 255
Lys Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly
            260                 265                 270
Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met
        275                 280                 285
Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys Cys Asp
    290                 295                 300
Lys Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val Glu His Asp
305                 310                 315                 320
Thr Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp Phe Val Glu Asp
                325                 330                 335
Gln Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350
Thr Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Asp Tyr Ser Val Ser
        355                 360                 365
Leu Leu Leu Arg Leu Ala Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys
    370                 375                 380
Cys Ala Glu Ala Asn Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu
385                 390                 395                 400
Phe Gln Pro Leu Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys
                405                 410                 415
Asp Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu
            420                 425                 430
Val Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445
Glu Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu
    450                 455                 460
Pro Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile
465                 470                 475                 480
Leu Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His
                485                 490                 495
```

```
Val Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe
            500                 505                 510
Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys Ala
        515                 520                 525
Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu Lys Glu
    530                 535                 540
Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val Lys His Lys
545                 550                 555                 560
Pro Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met Asp Asp Phe Ala
                565                 570                 575
Gln Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp Lys Asp Thr Cys Phe
            580                 585                 590
Ser Thr Glu Gly Pro Asn Leu Val Thr Arg Cys Lys Asp Ala Leu Ala
        595                 600                 605
Arg Ser Trp Ser His Pro Gln Phe Glu Lys
    610                 615
```

SEQ. ID NO: 36 - ENPP2 Signal Peptide

```
Leu Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly
1               5                   10                  15
Phe Thr Ala
```

SEQ. ID NO: 37 - Signal Sequence ENPP7

```
Met Arg Gly Pro Ala Val Leu Leu Thr Val Ala Leu Ala Thr Leu Leu
1               5                   10                  15
Ala Pro Gly Ala
            20
```

SEQ. ID NO: 38 - Signal sequence ENPP7

```
Met Arg Gly Pro Ala Val Leu Leu Thr Val Ala Leu Ala Thr Leu Leu
1               5                   10                  15
Ala Pro Gly Ala Gly Ala
            20
```

SEQ. ID NO: 39 - Signal Sequence ENPP1-2-1

```
Met Glu Arg Asp Gly Cys Ala Gly Gly Gly Ser Arg Gly Gly Glu Gly
1               5                   10                  15
Gly Arg Ala Pro Arg Glu Gly Pro Ala Gly Asn Gly Arg Asp Arg Gly
            20                  25                  30
Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala Ser
        35                  40                  45
Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala
    50                  55                  60
```

Arg Ala Arg Thr Ala Lys Asp Pro Asn Thr Tyr Lys Ile Ile Ser Leu
65 70 75 80
Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly Phe Thr Ala
85 90 95

SEQ. ID NO: 40 - exENPP3

Leu Leu Val Ile Met Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg

1 5 10 15

Lys

SEQ. ID NO: 41 - Signal Sequence ENPP5:

Met Thr Ser Lys Phe Leu Leu Val Ser Phe Ile Leu Ala Ala Leu Ser
1 5 10 15
Leu Ser Thr Thr Phe Ser
20

SEQ ID NO: 42 - Azurocidin-ENPP1-FC Nucleotide sequence

ggtaccgccacc**atg**acaagactgacagtgctggctctgctggccggactgttggcctcttctagagct**g**
ctccttcctgcgccaaagaagtgaagtcctgcaagggcagatgcttcgagcggaccttcggcaactgtag
atgtgacgccgcttgcgtggaactgggcaactgctgcctggactaccaagagacatgcatcgagcccgag
cacatctggacctgcaacaagttcagatgcggcgagaagcggctgaccagatctctgtgcgcctgctctg
acgactgcaaggacaagggcgactgctgcatcaactactcctctgtgtgccagggcgagaagtcctgggt
tgaagaaccctgcgagtccatcaacgagcctcagtgtcctgccggcttcgagacacctcctactctgctg
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tggcagcaaggcaatgtgttttcctgctctgtgatgcacgaggccctccacaatcactacacccagaagt
ccctgtctctgtcccctggcaaa**tgatag**ctcgag

Legend: blue = restriction site; **bold** = start/stop codon; green = Kozak sequence; underlined = nucleotide sequence of signal peptide.

SEQ ID NO: 43 - Azurocidin-ENPP1-Albumin Nucleotide sequence

atgacaagactgacagtgctggctctgctggccggactgttggcctcttctagagct**gct**ccttc
ctgcgccaaagaagtgaagtcctgcaagggcagatgcttcgagcggaccttcggcaactgtagatgtgac
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cacatcaccggcctgagcttctaccagcagcggaaagaacctgtgtccgatatcctgaagctgaaaaccc
atctgccaaccttcagccaagaggacctgatcaacatgaagtgggtgaccttcctgctgctgctgttcgt
gagcggcagcgccttcagcagaggcgtgttcagaagagaggcccacaagagcgagatcgcccacagatac
aacgacctgggcgagcagcacttcaagggcctggtgctgatcgccttcagccagtacctgcagaagtgca
gctacgacgagcacgccaagctggtgcaggaggtgaccgacttcgccaagacctgcgtggccgacgagag
cgccgccaactgcgacaagagcctgcacaccctgttcggcgacaagctgtgcgccatccccaacctgaga
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ggacgacttcgcccagttcctggacacctgctgcaaggccgccgacaaggacacctgcttcagcaccgag
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tggagccacccccagttcgagaag

SEQ ID NO: 44 - Azurocidin-ENPP1 Nucleotide sequence

atgacaagactgacagtgctggctctgctggccggactgttggcctcttctagagct**gct**ccttc
ctgcgccaaagaagtgaagtcctgcaagggcagatgcttcgagcggaccttcggcaactgtagatgtgac
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ccctgcgagtccatcaacgagcctcagtgtcctgccggcttcgagacacctcctactctgctgttctccc
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atctgccaaccttcagccaagaggac

SEQ ID NO: 45 - Azurocidin-ENPP3-FC Nucleotide sequence

atgaccagactgaccgtgctggccctgctggccggcctgctggccagcagcagagccgccaagca
gggcagctgcagaaagaagtgcttcgacgccagcttcagaggcctggagaactgcagatgcgacgtggcc
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caag

SEQ ID NO:46 – Azurocidin-ENPP3-Albumin Nucleotide sequence

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SEQ ID NO: 47 – Azurocidin-ENPP3-Nucleotide sequence

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SEQ. ID NO: 48 - ENPP7-1-Fc Nucleotide sequence

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SEQ. ID NO: 49 – ENPP7-NPP1 Albumin Nucleotide sequence:

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SEQ. ID NO: 50 -Nucleotide sequence of NPP121-NPP3-Fc

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SEQ. ID NO: 51 - Nucleotide sequence of NPP121-NPP3-Fc

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SEQ. ID NO: 52 - Nucleotide sequence of hNPP3-hFc-pcDNA3

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SEQ. ID NO: 53 -ENPP121-Fc-Nucleotide sequence

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SEQ. ID NO: 54 -ENPP121- Albumin Nucleotide sequence

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SEQ. ID NO: 55 - ENPP3 Nucleotide sequence

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tttcgttgtg gagagaccag attagaggcc agcctttgct cttgttcaga tgactgtttg 360

cagaggaaag attgctgtgc tgactataag agtgtttgcc aaggagaaac ctcatggctg 420

gaagaaaact gtgacacagc ccagcagtct cagtgcccag aagggtttga cctgccacca 480

gttatcttgt tttctatgga tggatttaga gctgaatatt tatacacatg ggatacttta 540

atgccaaata tcaataaact gaaaacatgt ggaattcatt caaaatacat gagagctatg 600

tatcctacca aaaccttccc aaatcattac accattgtca cgggcttgta tccagagtca 660

catggcatca ttgacaataa tatgtatgat gtaaatctca acaagaattt ttcactttct 720

tcaaaggaac aaaataatcc agcctggtgg catgggcaac caatgtggct gacagcaatg 780

tatcaaggtt taaaagccgc tacctacttt tggcccggat cagaagtggc tataaatggc 840

tcctttcctt ccatatacat gccttacaac ggaagtgtcc catttgaaga gaggatttct 900

acactgttaa aatggctgga cctgcccaaa gctgaaagac ccaggtttta taccatgtat 960

tttgaagaac ctgattcctc tggacatgca ggtggaccag tcagtgccag agtaattaaa 1020

gccttacagg tagtagatca tgcttttggg atgttgatgg aaggcctgaa gcagcggaat 1080

ttgcacaact gtgtcaatat catccttctg gctgaccatg gaatggacca gacttattgt 1140

aacaagatgg aatacatgac tgattatttt cccagaataa acttcttcta catgtacgaa 1200

gggcctgccc cccgcatccg agctcataat atacctcatg actttttag ttttaattct 1260

gaggaaattg ttagaaacct cagttgccga aaacctgatc agcatttcaa gccctatttg 1320

actcctgatt tgccaaagcg actgcactat gccaagaacg tcagaatcga caaagttcat 1380

ctctttgtgg atcaacagtg gctggctgtt aggagtaaat caaatacaaa ttgtggagga 1440

ggcaaccatg gttataacaa tgagtttagg agcatggagg ctatctttct ggcacatgga 1500

cccagtttta aagagaagac tgaagttgaa ccatttgaaa atattgaagt ctataaccta 1560

atgtgtgatc ttctacgcat tcaaccagca ccaaacaatg gaacccatgg tagtttaaac 1620

catcttctga aggtgccttt ttatgagcca tcccatgcag aggaggtgtc aaagttttct 1680

gtttgtggct ttgctaatcc attgcccaca gagtctcttg actgtttctg ccctcaccta 1740

caaaatagta ctcagctgga acaagtgaat cagatgctaa atctcaccca agaagaaata 1800

acagcaacag tgaaagtaaa tttgccattt gggaggccta gggtactgca gaagaacgtg 1860

gaccactgtc tcctttacca cagggaatat gtcagtggat ttggaaaagc tatgaggatg 1920

cccatgtgga gttcatacac agtcccccag ttgggagaca catcgcctct gcctcccact 1980

gtcccagact gtctgcgggc tgatgtcagg gttcctcctt ctgagagcca aaaatgttcc 2040

ttctatttag cagacaagaa tatcacccac ggcttcctct atcctcctgc cagcaataga 2100

acatcagata gccaatatga tgctttaatt actagcaatt tggtacctat gtatgaagaa 2160

ttcagaaaaa tgtgggacta cttccacagt gttcttctta taaaacatgc cacagaaaga 2220

aatggagtaa atgtggttag tggaccaata tttgattata attatgatgg ccattttgat 2280

gctccagatg aaattaccaa acatttagcc aacactgatg ttcccatccc aacacactac 2340

tttgtggtgc tgaccagttg taaaaacaag agccacacac cggaaaactg ccctgggtgg 2400

ctggatgtcc tacccttttat catccctcac cgacctacca acgtggagag ctgtcctgaa 2460

ggtaaaccag aagctctttg ggttgaagaa agatttacag ctcacattgc ccgggtccgt 2520

gatgtagaac ttctcactgg gcttgacttc tatcaggata aagtgcagcc tgtctctgaa 2580

attttgcaac taaagacata tttaccaaca tttgaaacca ctatt 2625

SEQ. ID NO: 56 – ENPP1 Nucleotide sequence:

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agagaaggac ctgccggcaa cggcagagac agaggcagat ctcatgccgc cgaagcccct 120

ggcgatcctc aggctgctgc ttctctgctg gcccccatgg atgtgggcga ggaacctctg 180

gaaaaggccg ccagagccag aaccgccaag gaccccaaca cctacaaggt gctgagcctg 240

gtgctgtccg tgtgcgtgct gaccaccatc ctgggctgca tcttcggcct gaagcccagc 300

tgcgccaaag aagtgaagtc ctgcaagggc cggtgcttcg agcggacctt cggcaactgc 360

agatgcgacg ccgcctgtgt ggaactgggc aactgctgcc tggactacca ggaaacctgc 420

atcgagcccg agcacatctg gacctgcaac aagttcagat gcggcgagaa gcggctgacc 480

agatccctgt gtgcctgcag cgacgactgc aaggacaagg gcgactgctg catcaactac 540

agcagcgtgt gccagggcga gaagtcctgg gtggaagaac cctgcgagag catcaacgag 600

ccccagtgcc ctgccggctt cgagacacct cctaccctgc tgttcagcct ggacggcttt 660

cgggccgagt acctgcacac atggggaggc ctgctgcccg tgatcagcaa gctgaagaag 720

tgcggcacct acaccaagaa catgcggccc gtgtacccca ccaagacctt ccccaaccac 780

tactccatcg tgaccggcct gtaccccgag agccacggca tcatcgacaa caagatgtac 840

gaccccaaga tgaacgccag cttcagcctg aagtccaaag agaagttcaa ccccgagtgg 900

tataagggcg agcccatctg ggtcaccgcc aagtaccagg gcctgaaaag cggcacattc 960

ttttggcccg gcagcgacgt ggaaatcaac ggcatcttcc ccgacatcta taagatgtac 1020

aacggcagcg tgcccttcga ggaacggatc ctggctgtgc tgcagtggct gcagctgccc 1080

aaggatgagc ggccccactt ctacaccctg tacctggaag aacctgacag cagcggccac 1140

agctacggcc ctgtgtccag cgaagtgatc aaggccctgc agcgggtgga cggcatggtg 1200

ggaatgctga tggacggcct gaaagagctg aacctgcaca gatgcctgaa cctgatcctg 1260

atcagcgacc acggcatgga acagggatcc tgcaagaagt acatctacct gaacaagtac 1320

ctgggcgacg tgaagaacat caaagtgatc tacggcccag ccgccagact gaggcctagc 1380

gacgtgcccg acaagtacta cagcttcaac tacgagggaa tcgcccggaa cctgagctgc 1440

agagagccca accagcactt caagccctac ctgaagcact tcctgcccaa gcggctgcac 1500

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gccctgaatc ccagcgagag aaagtactgc ggcagcggct tccacggctc cgacaacgtg 1620

ttcagcaaca tgcaggccct gttcgtgggc tacggacccg gctttaagca cggcatcgag 1680

gccgacacct tcgagaacat cgaggtgtac aatctgatgt gcgacctgct gaatctgacc 1740

cctgccccca acaatggcac ccacggcagc ctgaaccatc tgctgaagaa ccccgtgtac 1800

acccctaagc accccaaaga ggtgcacccc ctggtgcagt gccccttcac cagaaacccc 1860

agagacaacc tgggctgtag ctgcaacccc agcatcctgc ccatcgagga cttccagacc 1920

```
cagttcaacc tgaccgtggc cgaggaaaag atcatcaagc acgagacact gccctacggc     1980
agaccccggg tgctgcagaa agagaacacc atctgcctgc tgagccagca ccagttcatg     2040
agcggctact cccaggacat cctgatgccc ctgtggacca gctacaccgt ggaccggaac     2100
gacagcttct ccaccgagga tttcagcaac tgcctgtacc aggatttccg gatccccctg     2160
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agccctcccc agctgaacaa gaacagctcc ggcatctaca gcgaggccct gctgactacc     2280
aacatcgtgc ccatgtacca gagcttccaa gtgatctggc ggtacttcca cgacaccctg     2340
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ttcgactacg acggcagatg tgacagcctg gaaaatctgc ggcagaaaag aagagtgatc     2460
cggaaccagg aaattctgat ccctacccac ttctttatcg tgctgacaag ctgcaaggat     2520
accagccaga ccccccctgca ctgcgagaac ctggataccc tggccttcat cctgcctcac     2580
cggaccgaca acagcgagag ctgtgtgcac ggcaagcacg acagctcttg ggtggaagaa     2640
ctgctgatgc tgcaccgggc cagaatcacc gatgtggaac acatcaccgg cctgagcttt     2700
taccagcagc ggaaagaacc cgtgtccgat atcctgaagc tgaaaaccca tctgcccacc     2760
ttcagccagg aagat                                                      2775
```

SEQ. ID NO: 57 - Linker

Asp Ser Ser

SEQ. ID NO: 58 - Linker

Glu Ser Ser

SEQ. ID NO: 59 - Linker

Arg Gln Gln

SEQ. ID NO: 60 - Linker

Lys Arg

SEQ. ID NO: 61 - Linker

$(Arg)_m$; m=0-15

SEQ. ID NO: 62 - Linker

Asp Ser Ser Ser Glu Glu Lys Phe Leu Arg Arg Ile Gly Arg Phe Gly

SEQ. ID NO: 63 - Linker

Glu Glu Glu Glu Glu Glu Glu Pro Arg Gly Asp Thr

1 5 10

SEQ. ID NO: 64 – Linker

Ala Pro Trp His Leu Ser Ser Gln Tyr Ser Arg Thr

1 5 10

SEQ. ID NO: 65 - Linker

Ser Thr Leu Pro Ile Pro His Glu Phe Ser Arg Glu

1 5 10

SEQ. ID NO: 66 - Linker

Val Thr Lys His Leu Asn Gln Ile Ser Gln Ser Tyr

1 5 10

SEQ. ID NO: 67 - Linker

$(Glu)_m$; m=1-15

SEQ. ID NO: 68 - Linker

Leu Ile Asn

SEQ. ID NO: 69 - Linker

Gly Gly Ser Gly Gly Ser

1 5

SEQ. ID NO: 70 - Linker

Arg Ser Gly Ser Gly Gly Ser

1 5

SEQ. ID NO: 71 - Linker

$(Asp)_m$; m=1-15

1

SEQ. ID NO: 72 - Linker

Leu Val Ile Met Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys

1 5 10 15

SEQ. ID NO: 73 - Linker

Val Ile Met Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys

1 5 10 15

SEQ. ID NO: 74 - Linker

Ile Met Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys

1 5 10

SEQ. ID NO: 75 - Linker

Met Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys

1 5 10

SEQ. ID NO: 76 - Linker

Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys

1 5 10

SEQ. ID NO:77 - Linker

Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys

1 5 10

SEQ. ID NO: 78 - Linker

Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys

1 5 10

SEQ. ID NO: 79 - Linker

Leu Gly Leu Gly Leu Gly Leu Arg Lys

1 5

SEQ. ID NO: 80 - Linker

Gly Leu Gly Leu Gly Leu Arg Lys

1 5

SEQ. ID NO: 81 - Linker

Leu Gly Leu Gly Leu Arg Lys

1 5

SEQ. ID NO: 82 - Linker

Gly Leu Gly Leu Arg Lys

1 5

SEQ. ID NO: 83 - Linker

Leu Gly Leu Arg Lys

1 5

SEQ. ID NO: 84 - Linker

Gly Leu Arg Lys

1

SEQ. ID NO: 85 - Linker

Leu Arg Lys

1

SEQ. ID NO: 86 - Linker

Arg Lys

1

SEQ. ID NO: 87 - Linker

$(Lys)_m$; m=0-15

1

SEQ. ID NO: 88 -Linker

D_m; m=1-15

1

SEQ ID NO: 89- Soluble NPP1-Fc fusion protein sequence

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

Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His
Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser
Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val
Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val
Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu
Asp Leu Ile Asn **Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro**
Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
Leu Ser Leu Ser Pro Gly Lys

double-underlined: beginning and end of NPP1; bold residues indicate Fc sequence

SEQ ID NO: 90 – Nucleotide sequence of solube NPP1-Fc

ttca ccgccggact gaagcccagc

tgcgccaaag aagtgaagtc ctgcaagggc cggtgcttcg agcggacctt cggcaactgc

agatgcgacg ccgcctgtgt ggaactgggc aactgctgcc tggactacca ggaaacctgc

atcgagcccg agcacatctg gacctgcaac aagttcagat gcggcgagaa gcggctgacc

agatccctgt gtgcctgcag cgacgactgc aaggacaagg gcgactgctg catcaactac

agcagcgtgt gccagggcga gaagtcctgg gtggaagaac cctgcgagag catcaacgag

ccccagtgcc ctgccggctt cgagacacct cctaccctgc tgttcagcct ggacggcttt

cgggccgagt acctgcacac atggggaggc ctgctgcccg tgatcagcaa gctgaagaag

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gaccccaaga tgaacgccag cttcagcctg aagtccaaag agaagttcaa ccccgagtgg

tataagggcg agcccatctg ggtcaccgcc aagtaccagg gcctgaaaag cggcacattc

ttttggcccg gcagcgacgt ggaaatcaac ggcatcttcc ccgacatcta taagatgtac

aacggcagcg tgcccttcga ggaacggatc ctggctgtgc tgcagtggct gcagctgccc

aaggatgagc ggccccactt ctacaccctg tacctggaag aacctgacag cagcggccac

agctacggcc ctgtgtccag cgaagtgatc aaggccctgc agcgggtgga cggcatggtg

ggaatgctga tggacggcct gaaagagctg aacctgcaca gatgcctgaa cctgatcctg

atcagcgacc acggcatgga acagggatcc tgcaagaagt acatctacct gaacaagtac

ctgggcgacg tgaagaacat caaagtgatc tacggcccag ccgccagact gaggcctagc

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cctgccccca acaatggcac ccacggcagc ctgaaccatc tgctgaagaa ccccgtgtac

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accagccaga ccccccctgca ctgcgagaac ctggataccc tggccttcat cctgcctcac

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aactggtacg tcgacggtgt cgaagtccac aacgccaaga ccaagcccag ggaagaacag

tacaactcta cctaccgcgt cgtcagcgtc ctgaccgtcc tgcaccagga ctggctgaac

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gaagaaatga ccaagaacca ggtgtccctg acctgcctgg tcaagggatt ctacccctct

gacatcgccg tcgaatggga atctaacgga cagcccgaaa acaactacaa gaccaccccc

cctgtcctgg actctgacgg atcattcttc ctgtactcta agctgactgt cgacaagtct

aggtggcagc agggaaacgt gttctcttgc tctgtcatgc acgaagccct gcacaaccac

tacacccaga agtctctgtc tctgtccccc ggaaag

SEQ ID NO: 91- Soluble NPP1-(GLK)-Fc fusion protein sequence

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

Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr Ile
Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp Ile
Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser Phe
Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile Pro
Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val
Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser Gly
Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln
Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys
Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val Phe
Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln
Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe
Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His
Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp
Asn Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu
Glu Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile
Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile
Leu Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp Leu Ile
Asn **Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu**
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
Ser Pro Gly Lys

double-underlined: beginning and end of NPP1; bold residues indicate Fc sequence

SEQ ID NO: 92- Soluble NPP1-Fc fusion protein sequence

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

Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys Gly Glu Pro Ile
Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly Thr Phe Phe Trp
Pro Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro Asp Ile Tyr Lys
Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Leu Ala Val Leu
Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His Phe Tyr Thr Leu
Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr Gly Pro Val Ser
Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly Met Val Gly Met
Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg Cys Leu Asn Leu
Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser Cys Lys Lys Tyr
Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn Ile Lys Val Ile
Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val Pro Asp Lys Tyr
Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu Ser Cys Arg Glu
Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe Leu Pro Lys Arg
Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu Thr Phe Tyr Leu
Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu Arg Lys Tyr Cys
Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser Asn Met Gln Ala
Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys His Gly Ile Glu Ala Asp
Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Asn
Leu Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His Leu
Leu Lys Asn Pro Val Tyr Thr Pro Lys His Pro Lys Glu Val His Pro
Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp Asn Leu Gly Cys
Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe Gln Thr Gln Phe
Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His Glu Thr Leu Pro
Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr Ile Cys Leu Leu
Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp Ile Leu Met Pro
Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser Phe Ser Thr Glu
Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile Pro Leu Ser Pro
Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val Ser Tyr Gly
Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser Gly Ile Tyr Ser
Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln Ser Phe Gln
Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys Tyr Ala Glu
Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val Phe Asp Phe Asp
Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln Lys Arg Arg
Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe Phe Ile Val
Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His Cys Glu Asn
Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp Asn Ser Glu
Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu Glu Leu Leu
Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile Thr Gly Leu
Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile Leu Lys Leu
Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp Leu Ile Asn **Asp Lys**
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

double-underlined: beginning and end of NPP1; bold residues indicate Fc sequence

SEQ ID NO: 93- Soluble NPP1-Fc fusion protein sequence

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

Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln Ser Phe
Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys Tyr Ala
Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val Phe Asp Phe
Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln Lys Arg
Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe Phe Ile
Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His Cys Glu
Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp Asn Ser
Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu Glu Leu
Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile Thr Gly
Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile Leu Lys
Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp Leu Ile Asn **Asp**
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
Gly Lys

double-underlined: beginning and end of NPP1; bold residues indicate Fc sequence

SEQ ID NO: 94- Linker

Gly Gly Gly Gly Ser

Pharmaceutical Compositions according to the invention

The AAV vector according to the invention can be administered to the human or animal body by conventional methods, which require the formulation of said vectors in a pharmaceutical composition. In one embodiment, the invention relates to a pharmaceutical composition (hereinafter referred to as "pharmaceutical composition according to the invention") comprising an AAV vector comprises a recombinant viral genome wherein said recombinant viral genome comprises an expression cassette comprising a transcriptional regulatory region operatively linked to a nucleotide sequence encoding ENPP1 or ENPP3 or a functionally equivalent variant thereof.

All the embodiments disclosed in the context of the adeno-associated viral vectors, Herpes simplex vectors, Adenoviral vectors, Alphaviral vectors and Lentiviral vectors according to the invention are also applicable to the pharmaceutical compositions according to the invention.

In some embodiments the pharmaceutical composition may include a therapeutically effective quantity of the AAV vector according to the invention and a pharmaceutically acceptable carrier. In some embodiments the pharmaceutical composition may include a therapeutically effective quantity of the adenoviral vector according to the invention and a pharmaceutically acceptable carrier.

In some embodiments the pharmaceutical composition may include a therapeutically effective quantity of the lentiviral vector according to the invention and a pharmaceutically acceptable carrier.

In some embodiments the pharmaceutical composition may include a therapeutically effective quantity of the alphaviral vector according to the invention and a pharmaceutically acceptable carrier.

In some embodiments the pharmaceutical composition may include a therapeutically effective quantity of the Herpes simplex viral vector according to the invention and a pharmaceutically acceptable carrier.

The term "therapeutically effective quantity" refers to the quantity of the AAV vector according to the invention calculated to produce the desired effect and will generally be determined, among other reasons, by the own features of the viral vector according to the invention and the therapeutic effect to be obtained. The quantity of the viral vector according to

the invention that will be effective in the treatment of a disease can be determined by standard clinical techniques described herein or otherwise known in the art. Furthermore, in vitro tests can also be optionally used to help identify optimum dosage ranges. The precise dose to use in the formulation will depend on the administration route, and the severity of the condition, and it should be decided at the doctor's judgment and depending on each patient's circumstances.

Promoters

Vectors used in gene therapy require an expression cassette. The expression cassette consists of three important components: promoter, therapeutic gene and polyadenylation signal. The promoter is essential to control expression of the therapeutic gene. A tissue-specific promoter is a promoter that has activity in only certain cell types. Use of a tissue-specific promoter in the expression cassette can restrict unwanted transgene expression as well as facilitate persistent transgene expression. Commonly used promoters for gene therapy include cytomegalovirus immediate early (CMV-IE) promoter, Rous sarcoma virus long terminal repeat (RSV-LTR), Moloney murine leukaemia virus (MoMLV) LTR, and other retroviral LTR promoters. Eukaryotic promoters can be used for gene therapy, common examples for Eukaryotic promoters include human a1-antitrypsin (hAAT) and murine RNA polymerase II (large subunit) promoters. Non Tissue specific promoters such as small nuclear RNA U1b promoter, EF1α promoter, and PGK1 promoter are also available for use in gene therapy. Tissue specific promoters such as Apo A-I, ApoE and a1-antitrypsin (hAAT) enable tissue specific expression of protein of interest in gene therapy. Table I of Papadakis et al.*(Promoters and Control Elements: Designing Expression Cassettes for Gene Therapy, Current Gene Therapy, 2004, 4, 89-113*) lists examples of transcriptional targeting using eukaryotic promoters in gene therapy, all of which are incorporated by reference in their entirety herein.

Dosage and Mode of Administration

AAV titers are given as a "physical" titer in vector or viral genomes per ml (vg/ml) or (vg/kg) vector or viral genomes per kilogram dosage. QPCR of purified vector particles can be used to determine the titer. One method for performing AAV VG number titration is as follows: purified AAV vector samples are first treated with DNase to eliminate un-encapsidated AAV genome DNA or contaminating plasmid DNA from the production process. The DNase resistant

particles are then subjected to heat treatment to release the genome from the capsid. The released genomes are quantitated by real-time PCR using primer/probe sets targeting specific region of the viral genome.

A viral composition can be formulated in a dosage unit to contain an amount of a viral vector that is in the range of about 1.0×10^{9} vg/kg to about 1.0×10^{15} vg/kg and preferably 1.0×10^{12} vg/kg to 1.0×10^{14} vg/kg for a human patient. Preferably, the dose of virus in the formulation is 1.0×10^{9} vg/kg, 5.0×10^{9} vg/kg, 1.0×10^{10} vg/kg, 5.0×10^{10} vg/kg, 1.0×10^{11} vg/kg, 5.0×10^{11} vg/kg, 1.0×10^{12} vg/kg, 5.0×10^{12} vg/kg, or 1.0×10^{13} vg/kg, 5.0×10^{13} vg/kg, 1.0×10^{14} vg/kg, 5.0×10^{14} vg/kg, or 1.0×10^{15} vg/kg or 5.0×10^{15} vg/kg

In some embodiments, the dose administered to a mammal, particularly a human, in the context according to the invention varies with the particular viral vector, the composition containing the vector and the carrier therefor (as discussed above), and the mode of administration. The dose is sufficient to effect a desirable response, e.g., therapeutic or prophylactic response, within a desirable time frame. In terms of viral vector, the dose can be up to a maximum of 1×10^{15} vg/kg.

The vectors of the present invention permit long term gene expression, resulting in long term effects of a therapeutic protein. The phrases “long term expression”, “sustained expression” and “persistent expression” are used interchangeably. Long term expression according to the present invention means expression of a therapeutic gene and/or protein, preferably at therapeutic levels, for at least 45 days, at least 60 days, at least 90 days, at least 120 days, at least 180 days, at least 250 days, at least 360 days, at least 450 days, at least 730 days or more. Preferably, long term expression means expression for at least 90 days, at least 120 days, at least 180 days, at least 250 days, at least 360 days, at least 450 days, at least 720 days or more, more preferably, at least 360 days, at least 450 days, at least 720 days or more. This long-term expression may be achieved by repeated doses (if possible) or by a single dose

Repeated doses may be administered twice-daily, daily, twice-weekly, weekly, monthly, every two months, every three months, every four months, every six months, yearly, every two years, or more. Dosing may be continued for as long as required, for example, for at least six months, at least one year, two years, three years, four years, five years, ten years, fifteen years, twenty years, or more, up to for the lifetime of the patient to be treated.

A pharmaceutical composition according to the invention may be administered locally or systemically, intramuscularly, intravenously and parenterally. Delivery of therapeutic compositions according to the invention can be directed to central nervous system, cardiac system, and pulmonary system. A common delivery strategy is direct intramuscular injections. As a non-limiting example, Skeletal muscle has been shown to be a target tissue type that is efficiently transduced. Once transduced, the muscle cells serve as a production site for protein products that can act locally or systemically by many AAV variants.

In an embodiment, the pharmaceutical composition is administered near the tissue or organ whose cells are to be transduced. In a particular embodiment, the pharmaceutical composition according to the invention is administered locally in liver by injection into the liver parenchyma. In another embodiment, the pharmaceutical composition according to the invention is administered systemically.

As a non-limiting example, Systemic administration includes a systemic injection of the AAV vectors according to the invention, such as intramuscular (im), intravascular (ie), intra-arterial (ia), intravenous (iv), intraperitoneal (ip), or sub-cutaneous injections. Preferably, the systemic administration is via im, ip, is or iv injection. In some embodiments, the AAV vectors according to the invention are administered via intravenous injection.

In another embodiment the pharmaceutical compositions according to the invention are delivered to the liver of the subject. Administration to the liver is achieved using methods known in the art, including, but not limited to intravenous administration, intraportal administration, intrabiliary administration, intra-arterial administration, and direct injection into the liver parenchyma. In another embodiment, the pharmaceutical composition is administered intravenously.

A pharmaceutical composition according to the invention may be administered in a single dose or, in particular embodiments according to the invention, multiple doses (e.g. two, three, four, or more administrations) may be employed to achieve a therapeutic effect. Preferably, the AAV vector comprised in the pharmaceutical composition according to the invention are from different serotypes when multiple doses are required to obviate the effects of neutralizing antibodies.

Formulations

The preparations may also contain buffer salts. Alternatively, the compositions may be in powder form for constitution with a suitable vehicle (e.g. sterile pyrogen-free water) before use. When necessary, the composition may also include a local anaesthetic such as lidocaine to relieve pain at the injection site. When the composition is going to be administered by infiltration, it can be dispensed with an infiltration bottle which contains water or saline solution of pharmaceutical quality. When the composition is administered by injection, a water vial can be provided for injection or sterile saline solution, so that the ingredients can be mixed before administration. Preferably, the pharmaceutically acceptable carrier is saline solution and a detergent such as Pluronic®.

Compositions according to the invention may be formulated for delivery to animals for veterinary purposes (e.g. livestock (cattle, pigs, others)), and other non-human mammalian subjects, as well as to human subjects. The AAV vector can be formulated with a physiologically acceptable carrier for use in gene transfer and gene therapy applications. As a non-limiting example, also encompassed is the use of adjuvants in combination with or in admixture with the AAV vector according to the invention. Adjuvants contemplated include, but are not limited to, mineral salt adjuvants or mineral salt gel adjuvants, particulate adjuvants, microparticulate adjuvants, mucosal adjuvants. Adjuvants can be administered to a subject as a mixture with the AAV vector according to the invention or used in combination said AAV vector.

The terms “pharmaceutically acceptable carrier,” “pharmaceutically acceptable diluent,” “pharmaceutically acceptable excipient”, or “pharmaceutically acceptable vehicle”, used interchangeably herein, refer to a non-toxic solid, semisolid, or liquid filler, diluent, encapsulating material, or formulation auxiliary of any conventional type. A pharmaceutically acceptable carrier is essentially non-toxic to recipients at the employed dosages and concentrations and is compatible with other ingredients of the formulation. The number and the nature of the pharmaceutically acceptable carriers depend on the desired administration form. The pharmaceutically acceptable carriers are known and may be prepared by methods well known in the art (*Fauli i Trillo C, “Tratado de Farmacia Galénica”. Ed. Luzán 5, S. A., Madrid, ES, 1993; Gennaro A, Ed., “Remington: The Science and Practice of Pharmacy” 20th ed. Lippincott Williams & Wilkins, Philadelphia, Pa., US, 2003*).

As a non-limiting example, the AAV vector may be formulated for parenteral administration by injection (e.g. by bolus injection or continuous infusion). Formulations for

injection may be presented in unit dosage form (e.g. in ampoules or in multi-dose containers) with an added preservative. The viral compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing, or dispersing agents. Liquid preparations of the AAV formulations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats), emulsifying agents (e.g. lecithin or acacia), non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils), and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid).

Formulations suitable for parenteral administration include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. The formulations can be presented in unit-dose or multi-dose sealed containers, such as ampules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of a sterile liquid excipient, for example, water, for injections, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

In addition, the composition can comprise additional therapeutic or biologically-active agents. For example, therapeutic factors useful in the treatment of a particular indication can be present. Factors that control inflammation, such as ibuprofen or steroids, can be part of the composition to reduce swelling and inflammation associated with in vivo administration of the vector and physiological distress. Immune system suppressors can be administered with the composition method to reduce any immune response to the vector itself or associated with a disorder. Administration of immunosuppressive medications or immunosuppressants is the main method of deliberately induced immunosuppression, in optimal circumstances, immunosuppressive drugs are targeted only at any hyperactive component of the immune system.

Immunosuppressive drugs or immunosuppressive agents or antirejection medications are drugs that inhibit or prevent activity of the immune system. Such drugs include glucocorticoids, cytostatics, antibodies, drugs acting on immunophilins. In pharmacologic (supraphysiologic)

doses, glucocorticoids, such as prednisone, dexamethasone, and hydrocortisone are used to suppress various allergic and inflammatory responses. Cytostatics, such as purine analogs, alkylating agents, such as nitrogen mustards (cyclophosphamide), nitrosoureas, platinum compounds, and others. Cyclophosphamide (Baxter's Cytoxan) is probably the most potent immunosuppressive compound. Antimetabolites, for example, folic acid analogues, such as methotrexate, purine analogues, such as azathioprine and mercaptopurine, pyrimidine analogues, such as fluorouracil, and protein synthesis inhibitors. Cytotoxic antibiotics Among these, dactinomycin is the most important. It is used in kidney transplantations. Other cytotoxic antibiotics are anthracyclines, mitomycin C, bleomycin, mithramycin. Antibodies are sometimes used as a quick and potent immunosuppressive therapy to prevent the acute rejection reactions (e.g., anti-CD20 monoclonals).

Alternatively, immune enhancers can be included in the composition to upregulate the body's natural defenses against disease.

Antibiotics, i.e., microbicides and fungicides, can be present to reduce the risk of infection associated with gene transfer procedures and other disorders.

The pharmaceutical composition can be formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous, subcutaneous, or intramuscular administration to human beings.

Therapeutic Methods according to the invention

As a non-limiting example, a viral vector encoding human ENPP1 or ENPP3 is administered to a mammal, resulting in delivery of DNA encoding ENPP1 or ENPP3 and expression of the protein in the mammal, thereby restoring a level of ENPP1 or ENPP3 required to reduce calcification or ossification in soft tissues.

In one aspect, the invention relates to an adeno-associated viral vector comprising a recombinant viral genome wherein said recombinant viral genome comprises an expression cassette comprising a transcriptional regulatory region operatively linked to a nucleotide sequence encoding ENPP1 or ENPP3 or a functionally equivalent variant thereof or a pharmaceutical composition comprising said viral vector for use in the treatment and/or prevention of a disease of pathological calcification or ossification.

In another aspect, the invention relates to the use of an adeno-associated viral vector comprising a recombinant viral genome wherein said recombinant viral genome comprises an

expression cassette comprising a transcriptional regulatory region operatively linked to a nucleotide sequence encoding ENPP1or ENPP3 or a functionally equivalent variant thereof or a pharmaceutical composition comprising said viral vector for the manufacture of a medicament for the treatment and/or prevention of a disease a disease of pathological calcification or ossification.

In another aspect, the invention provides a method for the treatment and/or prevention of a disease of pathological calcification or ossification in a subject in need thereof which comprises the administration to said subject of an adeno-associated viral vector comprising a recombinant viral genome wherein said recombinant viral genome comprises an expression cassette comprising a transcriptional regulatory region operatively linked to a nucleotide sequence encoding ENPP1 or ENPP3 or a functionally equivalent variant thereof or a pharmaceutical composition comprising said viral vector.

In another aspect, the disease of pathological calcification or ossification being treated by the compositions and methods of this invention, are selected from the group consisting of X-linked hypophosphatemia (XLH), Chronic kidney disease (CKD), Mineral bone disorders (MBD), vascular calcification, pathological calcification of soft tissue, pathological ossification of soft tissue, Generalized arterial calcification of infants (GACI), Ossification of posterior longitudinal ligament (OPLL).

Polynucleotides, Vectors and Plasmids according to the invention

The invention also relates to polynucleotides which are useful for producing the viral vectors, for example, AAV vectors according to the invention. In one embodiment, the invention relates to a polynucleotide ("polynucleotide according to the invention") comprising an expression cassette flanked by adeno-associated virus ITRs wherein said expression cassette comprises a transcriptional regulatory region operatively linked to a nucleotide sequence encoding ENPP1 or ENPP3 or a functionally equivalent variant thereof.

In one embodiment the polynucleotide according to the invention comprises a transcriptional regulatory region that comprises a promoter; preferably a constitutive promoter; more preferably a liver-specific promoter; more preferably a liver-specific promoter selected from the group consisting of albumin promoter, phosphoenol pyruvate carboxykinase (PEPCK) promoter and alpha 1-antitrypsin promoter; the most preferred being the human alpha 1-

antitrypsin promoter. In another embodiment, the transcriptional regulatory region of the polynucleotide according to the invention further comprises an enhancer operatively linked to the promoter, preferably a liver-specific enhancer, more preferably a hepatic control region enhancer (HCR).

In another embodiment, the expression cassette of the polynucleotide according to the invention further comprises a polyadenylation signal, more preferably the SV40polyA. In another embodiment the ENPP1 encoded by the polynucleotide according to the invention is selected from the group consisting of human ENPP1 and human ENPP3.

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The polynucleotide according to the invention could be incorporated into a vector such as, for example, a plasmid. Thus, in another aspect, the invention relates to a vector or plasmid comprising the polynucleotide according to the invention. In a particular embodiment, the polynucleotide according to the invention is incorporated into an adeno-associated viral vector or plasmid.

Preferably, all other structural and non-structural coding sequences necessary for the production of adeno-associated virus are not present in the viral vector since they can be provided *in trans* by another vector, such as a plasmid, or by stably integrating the sequences into a packaging cell line.

Methods for Obtaining AAV according to the invention

The invention also relates to a method for obtaining the viral vectors according to the invention, as a non-limiting example, AAV vector. Said AAV vectors can be obtained by introducing the polynucleotides according to the invention into cells that express the Rep and Cap proteins constitutively or wherein the Rep and Cap coding sequences are provided in plasmids or vectors. Thus, in another aspect, the invention relates to a method for obtaining an adeno-associated viral vector comprising the steps of:

(i) providing a cell comprising a polynucleotide according to the invention, AAV Cap proteins, AAV Rep proteins and, optionally, viral proteins upon which AAV is dependent for replication,

(ii) maintaining the cell under conditions adequate for assembly of the AAV and

(iii) purifying the adeno-associated viral vector produced by the cell.

The production of recombinant AAV (rAAV) for vectorizing transgenes have been described previously (*Ayuso E, et al., Curr. Gene Ther. 2010, 10:423-436; Okada T, et al., Hum. Gene Ther. 2009, 20:1013-1021; Zhang H, et al., Hum. Gene Ther. 2009, 20:922-929; and Virag T, et al., Hum. Gene Ther. 2009, 20:807-817*). These protocols can be used or adapted to generate the AAV according to the invention. Any cell capable of producing adeno-associated viral vectors can be used in the present invention including mammalian and insect cells.

In one embodiment, the producer cell line is transfected transiently with the polynucleotide according to the invention (comprising the expression cassette flanked by ITRs) and with construct(s) that encodes Rep and Cap proteins and provides helper functions. In another embodiment, the cell line supplies stably the helper functions and is transfected transiently with the polynucleotide according to the invention (comprising the expression cassette flanked by ITRs) and with construct(s) that encodes Rep and Cap proteins.

In another embodiment, the cell line supplies stably the Rep and Cap proteins and the helper functions and is transiently transfected with the polynucleotide according to the invention. In another embodiment, the cell line supplies stably the Rep and Cap proteins and is transfected transiently with the polynucleotide according to the invention and a polynucleotide encoding the helper functions. In yet another embodiment, the cell line supplies stably the polynucleotide according to the invention, the Rep and Cap proteins and the helper functions. Methods of making and using these and other AAV production systems have been described in the art.

In another embodiment, the producer cell line is an insect cell line (typically Sf9 cells) that is infected with baculovirus expression vectors that provide Rep and Cap proteins. This system does not require adenovirus helper genes (*Ayuso E, et al., Curr. Gene Ther. 2010, 10:423-436*).

In another embodiment, the transgene delivery capacity of AAV can be increased by providing AAV ITRs of two genomes that can anneal to form head to tail concatamers. Generally, upon entry of the AAV into the host cell, the single-stranded DNA containing the transgene is converted by the host cell DNA polymerase complexes into double-stranded DNA, after which the ITRs aid in concatamer formation in the nucleus. As an alternative, the AAV may be engineered to be a self-complementary (sc) AAV, which enables the viral vector to bypass the

step of second-strand synthesis upon entry into a target cell, providing an scAAV viral vector with faster and, potentially, higher (e.g. up to 100-fold) transgene expression.

For example, the AAV may be engineered to have a genome comprising two connected single-stranded DNAs that encode, respectively, a transgene unit and its complement, which can snap together following delivery into a target cell, yielding a double-stranded DNA encoding the transgene unit of interest. Self-complementary AAV have been described in the art (*Carter B, U.S. Pat. No. 6,596,535, Carter B, U.S. Pat. No. 7,125,717, and Takano H, et al., U.S. Pat. No. 7,456,683*).

Preferably, all the structural and non-structural coding sequences (Cap proteins and Rep proteins) are not present in the AAV vector since they can be provided in trans by a vector, such as a plasmid. Cap proteins have been reported to have effects on host tropism, cell, tissue, or organ specificity, receptor use, infection efficiency, and immunogenicity of AAV viruses. Accordingly, an AAV Cap for use in an rAAV may be selected taking into consideration, for example, the subject's species (e.g. human or non-human), the subject's immunological state, the subject's suitability for long or short-term treatment, or a particular therapeutic application (e.g. treatment of a particular disease or disorder, or delivery to particular cells, tissues, or organs).

In another embodiment, the Cap protein is derived from the AAV of the group consisting of AAV2, AAV5, AAV7, AAV8, AAV9, AAV10 and AAVrh10 serotypes. In another embodiment, the Cap protein is derived from AAV8.

In some embodiments, an AAV Cap for use in the method according to the invention can be generated by mutagenesis (i.e. by insertions, deletions, or substitutions) of one of the aforementioned AAV Caps or its encoding nucleic acid. In some embodiments, the AAV Cap is at least 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% or more similar to one or more of the aforementioned AAV Caps.

In some embodiments, the AAV Cap is chimeric, comprising domains from two, three, four, or more of the aforementioned AAV Caps. In some embodiments, the AAV Cap is a mosaic of VP1, VP2, and VP3 monomers originating from two or three different AAV or a recombinant AAV. In some embodiments, a rAAV composition comprises more than one of the aforementioned Caps.

In some embodiments, an AAV Cap for use in a rAAV composition is engineered to contain a heterologous sequence or other modification. For example, a peptide or protein

sequence that confers selective targeting or immune evasion may be engineered into a Cap protein. Alternatively, or in addition, the Cap may be chemically modified so that the surface of the rAAV is polyethylene glycolated (i.e. pegylated), which may facilitate immune evasion. The Cap protein may also be mutagenized (e.g. to remove its natural receptor binding, or to mask an immunogenic epitope).

In some embodiments, an AAV Rep protein for use in the method according to the invention can be generated by mutagenesis (i.e. by insertions, deletions, or substitutions) of one of the aforementioned AAV Reps or its encoding nucleic acid. In some embodiments, the AAV Rep is at least 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% or more similar to one or more of the aforementioned AAV Reps.

In another embodiment, the AAV Rep and Cap proteins derive from an AAV serotype selected from the group consisting of AAV2, AAV5, AAV7, AAV8, AAV9, AAV10 and AAVrh10.

In some embodiments, a viral protein upon which AAV is dependent for replication for use in the method according to the invention can be generated by mutagenesis (i.e. by insertions, deletions, or substitutions) of one of the aforementioned viral proteins or its encoding nucleic acid. In some embodiments, the viral protein is at least 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% or more similar to one or more of the aforementioned viral proteins.

Methods for assaying the functions of Cap proteins, Rep proteins and viral proteins upon which AAV is dependent for replication are well known in the art. The genes AAV rep, AAV cap and genes providing helper functions can be introduced into the cell by incorporating said genes into a vector such as, for example, a plasmid, and introducing said vector into the cell. The genes can be incorporated into the same plasmid or into different plasmids. In another embodiment, the AAV rep and cap genes are incorporated into one plasmid and the genes providing helper functions are incorporated into another plasmid. Examples of plasmids comprising the AAV rep and cap genes suitable for use with the methods according to the invention include the pHLP19 and pRep6cap6 vectors (*Colisi P, U.S. Pat. No. 6,001,650 and Russell D, et al., U.S. Pat. No. 6,156,303).*

The polynucleotide according to the invention and the polynucleotides comprising AAV rep and cap genes or genes providing helper functions can be introduced into the cell by using any suitable method well known in the art. Examples of transfection methods include, but are not

limited to, co-precipitation with calcium phosphate, DEAE-dextran, polybrene, electroporation, microinjection, liposome-mediated fusion, lipofection, retrovirus infection and biolistic transfection. In a particular embodiment, the transfection is carried out by means of co-precipitation with calcium phosphate. When the cell lacks the expression of any of the AAV rep and cap genes and genes providing adenoviral helper functions, said genes can be introduced into the cell simultaneously with the polynucleotide according to the invention.

Alternatively, said genes can be introduced in the cell before or after the introduction of the polynucleotide according to the invention. In a particular embodiment, the cells are transfected simultaneously with three plasmids:

1) a plasmid comprising the polynucleotide according to the invention

2) a plasmid comprising the AAV rep and cap genes

3) a plasmid comprising the genes providing the helper functions.

Alternatively, the AAV rep and cap genes and genes providing helper functions may be carried by the packaging cell, either episomally and/or integrated into the genome of the packaging cell.

The invention encompasses methods that involve maintaining the cell under conditions adequate for assembly of the AAV. Methods of culturing packaging cells and exemplary conditions which promote the release of AAV vector particles, such as the producing of a cell lysate, may be carried out as described in examples herein. Producer cells are grown for a suitable period of time in order to promote the assembly of the AAV and the release of viral vectors into the media. Generally, cells may be grown for about 24 hours, about 36 hours, about 48 hours, about 72 hours, about 4 days, about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, up to about 10 days. After about 10 days (or sooner, depending on the culture conditions and the particular producer cell used), the level of production generally decreases significantly. Generally, time of culture is measured from the point of viral production. For example, in the case of AAV, viral production generally begins upon supplying helper virus function in an appropriate producer cell as described herein. Generally, cells are harvested about 48 to about 100, preferably about 48 to about 96, preferably about 72 to about 96, preferably about 68 to about 72 hours after helper virus infection (or after viral production begins).

The invention encompasses methods of purifying the adeno-associated viral vector produced by the cell. The AAV according to the invention can be obtained from both: i) the cells

transfected with the polynucleotides according to the invention and ii) the culture medium of said cells after a period of time post-transfection, preferably 72 hours. Any method for the purification of the AAV from said cells or said culture medium can be used for obtaining the AAV according to the invention. In a particular embodiment, the AAV according to the invention are purified following an optimized method based on a polyethylene glycol precipitation step and two consecutive cesium chloride (CsCl) gradients. Purified AAV according to the invention can be dialyzed against PBS, filtered and stored at −80° C. Titers of viral genomes can be determined by quantitative PCR following the protocol described for the AAV2 reference standard material using linearized plasmid DNA as standard curve (*Lock M, et al., Hum. Gene Ther. 2010; 21:1273-1285*).

In another embodiment, the purification is further carried out by a polyethylene glycol precipitation step or a cesium chloride gradient fractionation. In some embodiments, the methods further comprise purification steps, such as treatment of the cell lysate with benzonase, purification of the cell lysate over a CsCl gradient, or purification of the cell lysate with the use of heparin sulphate chromatography (*Halbert C, et al., Methods Mol. Biol. 2004; 246:201-212*).

Various naturally occurring and recombinant AAV, their encoding nucleic acids, AAV Cap and Rep proteins and their sequences, as well as methods for isolating or generating, propagating, and purifying such AAV, and in particular, their capsids, suitable for use in producing AAV are known in the art.

Animal Models

The following are non-limiting animal models that can be used to test the efficacy of administering ENPP1 or ENPP3 to prevent or reduce the progression of pathological ossification or calcification.

1. *Enpp1* $^{asj/asj}$ model of Generalized Arterial Calcification of Infancy (GACI) ; *Li, et al. , 2013, Disease Models & Mech. 6(5): 1227-35.*

2. *Enpp1*$^{asj/asj}$ model of Generalized Arterial Calcification of Infancy (GACI); *Li, et al, 2014, PloS one 9(12):el 13542.*

3. *ABCC6*$^{-/-}$ mouse model of Pseudoxanthoma Elasticum (PXE); *Jiang, et al. , 2007, J. Invest. Derm. 127(6): 1392-4102.*

4. *HYP* mouse model of X-linked hypophosphatasia (XLH); *Liang, et al., 2009, Calcif. Tissue Int. 85(3):235-46.*

5. *LmnaG609G/+* mouse model of Hutchison-Gilford Progeria Syndrome; *Villa-Bellosta, etal, 2013, Circulation 127(24):2442-51.*

6. Tip toe walking *(ttw)* mouse model of Ossification of the Posterior Longitudinal Ligament (OPLL) (*Okawa, et al, 1998, Nature Genetics 19(3):271-3*; *Nakamura, et al, 1999, Human Genetics l04(6):492-7*) and osteoarthritis (*Bertrand, et al, 2012, Annals Rheum. Diseases 71(7): 1249-53*).

7. Rat model of chronic kidney disease (*CKD*) on the adenine diet; *Schibler, et al. , 1968, Clin. Sci. 35(2):363-72*; *O'Neill, etal, 2011, Kidney Int. 79(5):512-7.*

8. Mouse model of chronic kidney disease (*CKD*) on the adenine diet; *Jia, et al., 2013, BMC Nephrol. 14:116.*

9. *5/6th nephrectomy rat model* of CKD; Morrison, 1962, *Lab Invest. 11:321-32; Shimamura & Morrison, 1975, Am. J. Pathol. 79(1):95-106.*

10. ENPP1 knockout mouse model of GACI and osteopenia; Mackenzie, et al, *2012, PloS one 7(2):e32177.*

Animal models, such as the above, are used to test for changes in soft tissue calcification and ossification upon administration of a vector encoding ENPP1 or ENPP3, according to the invention. For example, the following mouse models: (a)*Npt2a$^{-/-}$* (b) the double mutant *Npt2a$^{-/-}$/Enpp1 $^{asj/asj}$* , and (c) a C57BL/6 mouse (Jackson Labs) that has been subject to diet-induced formation of renal stones, the diet being a high calcium, low magnesium diet (*such as Teklad Labs diet TD.00042, Harlan Labs, Madison, WI*).

Npt2a$^{-/-}$ mice show kidney stone formation when fed using normal chow starting at weaning age and persist at least until 10 weeks of age. Conversely double mutant *Npt2a$^{-/-}$/Enpp1 $^{asj/asj}$* mice present twice the levels of kidney stone formation when compared with Npt2a-/- mice when fed a normal chow. *Npt2a$^{-/-}$* mice, and *Npt2a$^{-/-}$/Enpp1 $^{asj/asj}$* mice are commercially obtained from Jackson laboratory, ME. Double mutant mice (*Npt2a$^{-/-}$/Enpp1 $^{asj/asj}$*) are created by cross breeding *Npt2a$^{-/-}$* mice and *Enpp 1 $^{asj/asj}$* mice following standard protocols known in the art (*Jackson Laboratory Recourse Manual, (2007, 1-29)*). The *Npt2a$^{-/-}$* or *Npt2a$^{-/-}$/Enpp1 $^{asj/asj}$*

double mutant mouse models for renal stone related disease can be used to test the efficacy of treatment according to the invention (*Khan & Canales, 2011, J. Urol. 186(3):1107-13; Wu, 2015, Urolithiasis 43(Suppl 1):65-76*). Oxalate stone-forming rodent models, i.e., ethylene glycol, hydroxyl purine-fed mice or rats, or intraperitoneal injection of sodium oxalate of mice and rats (*Khan & Glenton, J. Urology 184:1189-1196*), urate stone forming (*Wu, et al., 1994, Proc. Natl. Acad. Sci. U S A 91(2):742-6*) and cystinuria mouse models (*Zee, et al., 2017, Nat. Med. 23(3):288-290; Sahota, et al., 2014, Urology 84(5):1249 e9-15*) can also be tested.

In certain embodiments, there is no rodent model that recapitulates the adult form of the human disease GACI, also referred to in the literature as Autosomal Recessive Hypohposphatemic Rickets type 2 (ARHR2) (*Levy-Litan, et al, 2010, Am. J. Human Gen. 86(2):273-8.*)

Experimental details on enzymatic activity of ENPP1, enzymatic activity of ENPP3, quantification of plasma PPi, micro-CT scans, quantification of plasma PPi uptake, are described in detail in the patent application and publications of *PCT/US2016/33236-Braddock et al., WO 2014/126965- Braddock et al., WO 2017/087936- Braddock et al., and US 2015/0359858-Braddock et al.*, all of which are herein incorporated in their entirety.

The present invention is further illustrated by the following examples which in no way should be construed as being further limiting. The contents of all cited references (including literature references, issued patents, published patent applications, and co-pending patent applications) cited throughout this application are hereby expressly incorporated by reference.

Examples

Example:1 – Cloning of NPP1 sequences into AAV system, generating constructs for AAV infection, AAV production and purification

An AAV plasmid used in this example contains an expression cassette flanked by two ITRs from AAV2. The genome of AAV2 may be pseudo typed with AAV8. An expression cassette may have the following elements in the 5′ to 3′ direction: a liver-specific enhancer hepatic control region (HCR), a liver-specific promoter human alpha anti-trypsin (hAAT), an intron, a polynucleotide comprising N terminal Azurocidin signal sequence, the NPP1 cDNA, C terminal Fc sequence, and an SV40 polyadenylation signal. The expression cassette is flanked by

the 5′ ITR and the 3′ ITR from AAV2. The construct generated is shown in the schematic of FIG. 1..

ENPP1 protein is a transmembrane protein localized to the cell surface with distinct intramembrane domains. ENPP1 protein was made soluble by omitting the transmembrane domain. Human NPP1 (NCBI accession NP_006199) was modified to express a soluble, recombinant protein by replacing its transmembrane region (e.g., residues 77-98 of ENPP1, NCBI accession NP_006199) with a suitable signal peptide sequence selected from the group consisting of (a). residues 12-30 of human NPP2 (NCBI accession NP_001 124335) or (b). residues 1-22 of ENPP7 or (c), residues 1-24 of ENPP5 or (d), human serum albumin or (e), human Azurocidin

SEQ IDS (1-4, 6-15, 17-31 and 42-56) indicate several ENPP1-Fc and ENPP3-Fc constructs, all of which can be used for Cloning of ENPP1 or ENPP3 sequences into AAV system, generating constructs for AAV infection.

The modified NPP1 sequence was cloned using standard molecular biology protocols into a plasmid. A non-coding plasmid carrying the same components of the construct, but without the NPP1 cDNA and having a multi-cloning site was used to produce null particles as a control.

Infectious AAV vector particles are generated in HEK293 cells cultured in roller bottles, by co-transfecting each roller bottle with 125 μg of vector plasmid (containing the ITRs and the expression cassette) together with 125 μg of the rep/cap plasmid (expressing capsid proteins of the AAV particle and proteins necessary for virus replication), and 150 μg of the helper plasmid expressing adenovirus helper functions by calcium phosphate co-precipitation. A total of 10 roller bottles are used for each vector preparation. Approximately three days after transfection, cells are harvested and centrifuged at 2500 g for 10 min. Cell pellet and medium are then processed separately. Cell pellet is thoroughly reconstituted in TBS (50 mM TrisHCl, 150 mM NaCl, 2 mM MgCl2, pH 8.0).

After 3 freeze/thaw cycles the lysate is centrifuged at 2500 g for 30 min. Supernatant from this centrifugation is added to the medium and vector particles are precipitated by incubation with 8% of PEG 8000 (Sigma) for 15 h and pelleted at 2500 g for 30 min. The pellet, containing vectors from cells and medium, is thoroughly reconstituted in TBS, treated with benzonase (Merck) for 30 min at 37° C. and centrifuged at 10,000 g for 10 min. The supernatant

is loaded into 37.5 ml ultra-clear tubes (Beckman) containing 1.3-1.5 g/ml CsCl density step gradient and centrifuged for 17 hours at 28,000 rpm in a SW28 rotor (Beckman). Viral bands are collected using a 10 ml syringe and 18-gauge needle and transferred to a new 12.5 ml ultra-clear tube, which is filled up with 1.379 g/ml CsCl solution to generate a continuous gradient. Tubes are centrifuged at 38,000 rpm in SW40Ti rotor (Beckman) for 48 hours. Finally, the band of full particles is collected and dialyzed in PBS using 10 KDa membrane (Slide-A-Lyzer Dialysis Products, Pierce) and filtered with 0.45 μm Millipore filters. This PEG and CsCl-based purification protocol dramatically reduces empty AAV capsids and DNA and protein impurities from the viral stock thus increasing AAV purity, which ultimately results in higher transduction *in vivo*. The same protocol is used for generating infectious AAV particles carrying the "null" vector which does not encode any ENPP protein.

Example -2 – Expression of ENPP1 using different signal sequences

ENPP1 is produced by establishing stable transfections in either CHO or HEK293 mammalian cells. To establish stable cell lines, a nucleic acid sequence encoding ENPP1 fusion proteins (such as sequences disclosed elsewhere herein) is placed in an appropriate vector for large scale protein production. There are a variety of such vectors available from commercial sources.

For example, FIG. 3 shows plasmid maps of NPP2^{signal}-NPP1-Fc cloned into the pcDNA3 plasmid, NPP7^{signal}-NPP1-Fc cloned into the pcDNA3 plasmid and Azurocidin ^{signal}-NPP1-Fc cloned into the pcDNA3 plasmid with appropriate endonuclease restriction sites. The pcDNA3 plasmids containing the desired protein constructs are stably transfected into expression plasmid using established techniques such as electroporation or lipofectamine, and the cells are grown under antibiotic selection to enhance for stably transfected cells.

Clones of single, stably transfected cells are then established and screened for high expressing clones of the desired fusion protein. Screening of the single cell clones for ENPP1 protein expression are accomplished in a high-throughput manner in 96 well plates using the synthetic enzymatic substrate pNP-TMP as previously described for ENPP1 *(Saunders, et al., 2008, Mol. Cancer Ther. 7(10):3352-62; Albright, et al., 2015, Nat Commun. 6:10006)*.

Upon identification of high expressing clones through screening, protein production is accomplished in shaking flasks or using bio-reactors as previously described for ENPP1 (*Albright,*

et al., 2015, Nat Commun. 6:10006). Purification of ENPP1 is accomplished using a combination of standard purification techniques known in the art.

As demonstrated in FIG. 2, the construct comprising Azurocidin signal sequence produces the highest amount of NPP1 protein. The amount ENPP1 protein produced using Azurocidin signal sequence (731 mg/Liter) is surprisingly five-fold higher than when compared to the ENPP1 protein produced using NPP2 (127 mg/Liter) or using NPP7 (136 mg/Liter) signal sequence. The ENPP1 protein thus produced is further purified using additional techniques and/or chromatographic steps as described above, to reach substantially higher purity such as ~99% purity.

Enzymatic activity of the ENPP1 thus produced is measured by determining the steady state hydrolysis of ATP by human NPP1 using HPLC. Briefly, enzyme reactions are started by addition of 10 nM ENPP1 to varying concentrations of ATP in the reaction buffer containing 20mM Tris, pH 7.4, 150 mM NaCl, 4.5 nM KCl, 14μM $ZnCl_2$, 1mM $MgCl_2$ and 1mM $CaCl_2$. At various time points, 50 μl reaction solution is removed and quenched with an equal volume of 3M formic acid. The quenched reaction solution is loaded on a C-18 (5 μm, 250 X 4.6 mm) column (Higgins Analytical) equilibrated in 5 mM ammonium acetate (pH 6.0) solution and eluted with a 0% to 20% methanol gradient. Substrate and products were monitored by UV absorbance at 259 nm and quantified according to the integration of their correspondent peaks and standard curves. The ENPP1 protein is thus characterized following the protocols discussed herein and elsewhere in PCT/2014/015945- *Braddock et al.*; PCT/2016/033236-*Braddock et al.* and PCT/2016/063034-*Braddock et al.*

Example -3- Injection of AAV viral particles encoding ENPP1-Fc to mice and measuring weight gain, bone density, bone strength and bone volume.

The efficacy of delivery of a vector encoding and capable of expressing NPP1 or NPP3 is tested using a mouse model such as Enpp1 $^{asj/asj}$ mouse model , *ABCC6*$^{-/-}$ mouse model, *HYP* mouse model, *ttw* mouse model, mouse model of chronic kidney disease (*CKD*) or 5/6th nephrectomy rat model of CKD. As a non-limiting example, the following experiment uses Enpp1 $^{asj/asj}$ mouse as the mouse model, Azurocidin-NPP1-Fc construct as the polynucleotide being delivered to the mouse model, and the delivery is accomplished by using AAV particles (prepared as shown in Example 1) which encodes ENPP1-Fc protein in vivo.

A person of ordinary skill would recognize the same experiment can be repeated by using alternate mouse models, alternate polynucleotide constructs comprising alternate signal sequences (NPP2, NPP5, NPP7. Albumin or Azurocidin etc.) encoding different ENPP1 fusions proteins (ENPP1-Albumin or ENPP1-Fc or ENPP1 functional equivalents or ENPP1 lacking Fc or Albumin domains etc.) or different ENPP3 fusion proteins (ENPP3-Fc or ENPP3- Albumin or ENPP3- lacking Fc or Albumin domain or ENPP3 functional equivalents etc.) disclosed in the invention for testing the efficacy of gene therapy for treating diseases of pathological calcification or ossification. The Azurocidin-NPP1-Fc construct utilized in the experiment encodes human ENPP1-Fc protein as a proof of concept and the same experiment can be repeated with an Azurocidin-NPP3-Fc construct that encodes human ENPP3-Fc.

Four sets of mice are used in this experiment, each set has at least five mice (6-8 weeks old), before injection of AAV particles, all sets of mice are tolerized by intraperitoneal injection of Titer GK1.5CD4 antibody at a concentration of 1000µg/ml (final dose of 25-40 µg/ animal) to reduce immune responses in mouse to human proteins produced by AAV constructs, a first cohort of ENPP1 ^{wt} mice that serve as control group are injected with AAV particles that comprise a null vector, a second cohort of ENPP1 $^{asj/asj}$ mice that serve as a control group are injected with AAV particles that comprise a null vector, a third cohort of ENPP1 ^{wt} mice that serve as study group are injected with AAV particles comprising polynucleotide that encodes ENPP1-Fc protein, and a fourth cohort of ENPP1 $^{asj/asj}$ that serve as test group are injected with AAV particles comprising polynucleotide that encodes ENPP1-Fc protein .Tolerization injections are repeated weekly(i.e. at Days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 91, 98 and 105 days post AAV administration) after the AAV injection to each cohort.

The mice of the experiment are fed with either an acceleration diet ((*Harlan Teklad, Rodent diet TD.00442, Madison, WI), which is enriched in phosphorus and has reduced magnesium content*) or regular chow (*Laboratory Autoclavable Rodent Diet 5010; PMI Nutritional International, Brentwood, MO*) and after 6-8 weeks of age, all mice receive a retro-orbital injection or tail vein injection of approx. 1×10^{12} to 1×10^{15} $^{vg/kg}$, preferably 1×10^{13} to 1×10^{14} $^{vg/kg}$ in PBS pH 7.4. The injected vectors are either empty "null" (control group) or carry the NPP1 gene (study group). Weight measurements are made daily to record any increases or decreases in body weight post AAV injection. Blood, urine , bone and tissue samples from the mice are collected and analyzed as follows. The experimental protocols are listed in detail in

Albright et al., Nat Commun. 2015 Dec 1;6:10006, and *Caballero et al., PLoS One. 2017; 12(7): e0180098*, the contents of all of which are hereby incorporated by reference in their entirety. At the end of the study (at 7, 28 and 112 days, all mice are euthanized following orbital exsanguination in deep anesthesia with isoflurane and vital organs are removed as described in art. (*Impaired urinary osteopontin excretion in Npt2a-/- mice., Caballero et al., Am J Physiol Renal Physiol. 2017 Jan 1; 312(1):F77-F83; Response of Npt2a knockout mice to dietary calcium and phosphorus ,Li Y et al., PLoS One. 2017; 12(4):e0176232.*).

Quantification of plasma PPi

Animals are bled retro-orbitally using heparinized, micropipets, and the blood is dispensed into heparin-treated eppendorf tubes and placed on wet ice. The samples are spun in a 4 °C pre-cooled microcentrifuge at 4,000 r.p.m. for 5 min, and plasma is collected and diluted in one volume of 50 mM Tris-Acetate pH=8.0. The collected plasma is filtered through a 300 KDa membrane via ultracentrifugation (*NanoSep 300 K, Pall Corp., Ann Arbour, MI*) and frozen at −80 °C. Pyrophosphate is quantitated using standard three-step enzymatic assays using uridine 5' diphospho[^{14}C] glucose to record the reaction product, uridine 5' diphospho[^{14}C]gluconic acid.(*Analysis of inorganic pyrophosphate at the picomole level. Cheung CP, Suhadolnik RJ, Anal Biochem. 1977 Nov; 83(1):61-3*). Briefly, a reaction mixture (100 µl) containing 5 mM MgCl2, 90 mM KCL, 63 mM Tris-HCL (pH 7.6), 1 nmol NADP+, 2 nmol glucose 1,6-diphosphate, 400 pmol uridine 5'-diphosphoglucose, 0.02 µCi uridine 5' diphospho[^{14}C]glucose, 0.25 units of uridine 5'-diphosphoglucose pyrophosphorylase, 0.25 units of phosphoglucose mutase, 0.5 units of glucose 6-phosphate dehydrogenase, and inorganic pyrophosphate (50–200 pmol) is incubated for 30 min at 37 °C. The reaction is terminated by the addition of 200 µl of 2% charcoal well suspended in water. An aliquote of 200 µl of supernatant is then counted in scintillation solution.

In vivo^{99m}PYP imaging

If desired, bone imaging may be performed. The bone imaging agent 99mTc-pyrophosphate (Pharmalucence, Inc) is evaluated in cohorts of animals using a preclinical microSPECT/CT hybrid imaging system with dual 1 mm pinhole collimators (X-SPECT, Gamma Medica-Ideas)38. Each animal is injected intraperitoneally with 2–5 mCi of the

radiolabelled tracer and imaged 1–1.5 h after injection. A CT scan (512 projections at 50 kVp, 800 uA and a magnification factor of 1.25) is acquired for anatomical co-localization with the SPECT image. The SPECT imaging is acquired with 180° per collimator head in a counter-clockwise rotation, 32 projections, 60 s per projection with an ROR of 7.0 cm, FOV of 8.95 cm and an energy window of 140 keV±20. CT images shall be reconstructed with the FLEX X-O CT software (Gamma Medica-Ideas) using a filtered back-projection algorithm. SPECT images shall be reconstructed using the FLEX SPECT software (5 iterations, 4 subsets) and subsequently fused with the CT images and will be analyzed using the AMIRA software.

Quantification of ^{99}mPYP uptake

For the ^{99}mPYP murine scans, the animals are imaged within 7 days of injection. The resulting SPECT scans is imported into NIH's ImageJ image processing software and regions of interest are drawn around each animal's head (target organ) and whole body. Per cent injected activity (PIA), often referred to as 'per cent injected dose' is calculated by comparing the ratio of counts in the head to the counts in the whole body and expressed as per cent injected dose to give a measure as of the affinity with which the radiotracer is taken up by the region of interest (head). The total counts in each scan is taken as the whole-body measure of injected dose.

Blood and urine parameters

Biochemical analyses also may be performed using blood samples (taken by orbital exsanguination) and spot urines collected following an overnight fast at the same time of day between 10 AM and 2 PM. Following deproteinization of heparinized plasma by filtration (*NanoSep 300 K, Pall Corp., Ann Arbor, MI*), plasma and urinary total pyrophosphate (PPi) concentrations are determined using a fluorometric probe (AB112155, ABCAM, Cambridge, MA). Urine PPi is corrected for urine creatinine, which is measured by LC-MS/MS or by ELISA using appropriate controls to adjust for inter-assay variability.

Kidney histology

Left kidneys are fixed in 4% formalin/PBS at 4°C for 12 hrs and then dehydrated with increasing concentration of ethanol and xylene, followed by paraffin embedding. Mineral deposits are determined on 10 um von Kossa stained sections counterstained with 1% methyl

green. Hematoxyline/eosin is used as counterstain for morphological evaluation. Histomorphometric evaluation of sagittal kidney sections that includes cortex, medulla and pelvis are performed blinded by two independent observers using an Osteomeasure System (*Osteometrics, Atlanta, GA*). Percent calcified area is determined by using the formula: % calc. area = 100*calcified area/total area (including cortex, medulla and pelvic lumen), and is dependent on number of observed areas per section. Mineralization size is determined by using the formula: calc. size = calcified area/number of observed calcified areas per section.

For transmission electron microscopy, a 1 mm^3 block of the left kidney is fixed in 2.5% glutaraldehyde and 2% paraformaldehyde in phosphate buffered saline for 2 hrs., followed by post-fixation in 1% osmium liquid for 2 hours. Dehydration will be carried out using a series of ethanol concentrations (50% to 100%). Renal tissue will be embedded in epoxy resin, and polymerization will be carried out overnight at 60°C. After preparing a thin section (50 nm), the tissues will be double stained with uranium and lead and observed using a Tecnai Biotwin (LaB6, 80 kV) (FEI, Thermo Fisher, Hillsboro, OR).

Histology, Histomorphometry, and Micro-CT

Tibiae and femora of mice are stripped of soft tissue, fixed in 70% ethanol, dehydrated, and embedded in methyl methacrylate before being sectioned and stained with toluidine blue (*C. B. Ware et al., Targeted disruption of the low-affinity leukemia inhibitory factor receptor gene causes placental, skeletal, neural and metabolic defects and results in perinatal death. Development 121, 1283-1299 (1995)*). Histomorphometric measurements are performed on a fixed region just below the growth plate corresponding to the primary spongiosa (*A. M. Parfitt et al., Bone histomorphometry: standardization of nomenclature, symbols, and units. Report of the ASBMR Histomorphometry Nomenclature Committee. J Bone Miner Res 2, 595-610 (1987)*) and analyzed by Osteomeasure software (Osteometrics, Atlanta, GA). The bones are scanned using a Scanco μCT-35 (Scanco, Brutissellen, Switzerland) and analyzed for numerous structural parameters at both the proximal tibia and distal femur just below the growth plate (trabecular bone) and at the tibial or femoral midshaft (cortical bone).

Bone biomechanical testing

Femurs from mice on the acceleration diet are loaded to failure with three-point bending; femurs from mice on regular chow are loaded to failure with four-point bending. All whole bone tests are conducted by loading the femur in the posterior to anterior direction, such that the anterior quadrant is subjected to tensile loads. The widths of the lower and upper supports of the four-point bending apparatus are 7mm and 3mm, respectively. Tests are conducted with a deflection rate of 0.05 mm/sec using a servohydraulic testing machine (*Instron model 8874; Instron Corp., Norwood, MA, USA*). The load and mid-span deflection is acquired directly at a sampling frequency of 200Hz. Load-deflection curves are analyzed for stiffness, maximum load, and work to fracture. Yield is defined as a 10% reduction in the secant stiffness (load range normalized for deflection range) relative to the initial tangent stiffness. Femurs are tested at room temperature and kept moist with phosphate-buffered saline (PBS). Post-yield deflection, which is defined as the deflection at failure minus the deflection at yield are measured as well.

Example 4 – Treatment of chronic kidney disease using viral vectors expressing ENPP1 or ENPP3.

The following example provides AAV expressing ENPP1 or ENPP3 which are expected to be effective in treating vascular calcification and symptoms associated with CKD. ENPP1-Fc and ENPP3-Fc are used in the examples for illustrative purposes and similar results can be obtained by using other ENPP1 or ENPP3 fusions of the invention.

AAV virions expressing ENPP1-Fc and ENPP3-Fc protein are made according to example 1 and administered to a CKD mouse (which is a model of chronic kidney disease (CKD) (*BMC Nephrology, 2013, 14:116*). Six sets of mice are used for treatment with ENPP1 and ENPP3.

Control cohorts: in this experiment, a first cohort of ENPP1 wt mice that serve as control group are injected with AAV particles that comprise a null vector and, a second cohort of CKD mice that serve as a control group are injected with AAV particles that comprise a null vector.

ENPP1-treated mice cohorts: a third cohort of ENPP1 ^{wt} mice are injected with AAV particles engineered to express ENPP1-Fc protein, and a fourth cohort of CKD mice are injected with AAV particles engineered to express ENPP1-Fc protein.

ENPP3-treated mice cohorts: a fifth cohort of ENPP1 ^{wt} mice are injected with AAV particles engineered to express ENPP3-Fc protein, and a sixth cohort of CKD mice are injected with AAV particles engineered to express ENPP3-Fc protein.

Adenine Diet: The CKD mice are maintained on adenine diet and whereas wildtype mice are maintained on regular chow (*Laboratory Autoclavable Rodent Diet 5010; PMI Nutritional International, Brentwood, MO)*. To provide an adenine-containing chow consumed by the CKD mice, adenine is mixed with a casein-based diet that blunted the smell and taste. Adenine is purchased from Sigma Aldrich (MO, USA) and the powdered casein-based diet is purchased from Special Diets Services (SDS, UK) (reference number 824522). Other ingredients of the diet are maize starch (39.3%), casein (20.0%), maltodextrin (14.0%), sucrose (9.2%), maize/corn oil (5%), cellulose (5%), vitamin mix (1.0%), DL-methionine (0.3%) and choline bitartrate (0.2%).

Vector Injection: After two weeks of age, all mice receive a retro-orbital injection or tail vein injection of approx. 1×10^{12} to 1×10^{15} vg/kg, preferably. 1×10^{13} to 1×10^{14} vg/kg in PBS pH 7.4 per mouse. The injected vectors are either empty "null" (control group) or carried the NPP1or NPP3 gene (study group).

Assays: Kidney histology, PPi levels, and blood urine parameters such as FGF-23 levels, vitamin D, Parathyroid hormone (PTH) levels, serum/blood urea levels, blood urea nitrogen (BUN) levels, serum/blood creatine levels and plasma pyrophosphate (PPi) are analyzed for each cohort as described in Example 3. Urine is collected as spot urine samples after spontaneous urination. Serum and urine calcium, phosphorous, creatinine and urea levels are measured on a Konelab 20XTi (*Thermo Scientific, Finland*). Creatinine concentrations are validated with a colorimetric assay (*BioChain, CA USA*). PTH is measured by a mouse intact PTH ELISA kit (*Immutopics, CA, USA*), FGF23 levels are measured with an intact FGF23 ELISA (*Kainos, Japan*) and Vitamin D is measured with EIA kits (*Immunodiagnostic Systems, UK*). Experimental details are listed in *BMC Nephrology, 2013, 14:116,* and *PLoS One. 2017 Jul 13;12(7).*

Results: Untreated CKD mice generally exhibit reduced body weight and signs of declining kidney function such as decreased ratios between urine urea/serum urea and urine creatinine/serum creatinine. In contrast, CKD mice treated with AAV expressing ENPP1 or

ENPP3 proteins are expected to show an increase in body weight approaching the body weight ranges of normal WT mice. Generally, serum urea levels ranging from 80–100 mg/dL is considered optimal. Urea levels of above 100 mg/dL are associated with increased morbidity along with weight loss and reduced physical activity. Treated (AAV with ENPP1 or ENPP3) CKD mice are expected to exhibit improved kidney functions manifested by a decrease in serum urea levels and increase in urine urea levels leading to higher urine urea/serum urea ratios.

Renal histology analysis of kidney tissues of CKD mice are expected to show deposition of crystalline structures in regions such as tubular lumen, micro abscesses and dilated tubules, Periodic acid–Schiff (PAS) staining showing dilated Bowman's space, presence of atrophic tubules with protein casts ("thyroidization") and tubular atrophy with thickening of the tubular basement membrane, presence of mild interstitial fibrosis seen through Ladewig staining and occurrence of extensive calcification of tubular structures seen through von Kossa staining. In contrast, CKD mice treated according to the invention with ENPP1 or ENPP3 are expected to show a reduction or lack of renal mineral deposits in the tubular lumen and soft tissue vasculature with histology similar to that of healthy wildtype mice.

Untreated CKD mice are expected to show a significant increase in serum inorganic phosphorous (pi), increase in PTH and FGF23 levels but a decrease in $1,25(OH)_2$-Vitamin D levels and lower PPi levels (~ 0.5 μM) when compared with that of healthy wild type mice (*Normal levels of PPi are about 2-4 μM ; about 10-65 ng/L for PTH; median FGF23 level is 13 RU/ml and normal FGF23 level ranges from 5 to 210 RU/ml*; *normal Vitamin D levels are 20 ng/mL to 50 ng/mL*). In contrast, treated CKD mice are expected to show elevated levels of PPi (*~4-5 μM*) which are expected to be higher than the PPi levels found in untreated CKD mice *(~0.5 μM)*. Thus a person of ordinary skill can determine the therapeutic efficacy of vector based ENPP1 or ENPP3 in treating chronic kidney diseases by observing one or more factors like reduction (*25%, or 50%, or 70%, or 90% or 100% reduction*) of calcification of soft tissues in kidneys and coronary arteries visualized through histological analysis , increase in serum PPi levels, normalization of vitamin D levels, reduction in FGF23 levels to normal ranges, normalization of PTH levels from blood analysis, increased survival, improved kidney function observed by increase in urine urea and creatine along with increased weight gain.

Treatment of human subjects:

A human patient suffering from CKD is treated by providing an intravenal injection containing approximately 5×10^{11} -$5x10^{15}$ vg/kg in 1X PBS at pH 7.4, in some embodiments approximately $1x10^{12}$-$1X10^{15}$ vg/kg in 1X PBS at pH 7.4 per subject capable of delivering and expressing ENPP1 or ENPP3. Successful treatment of CKD is observed by monitoring the one or more aforesaid parameters through periodic blood and urine tests as discussed for mouse models. Instead of histological analysis which requires staining of kidney slices or arterial tissues which is not feasible to perform in living patients, instead one uses noninvasive visualization techniques commonly known in art such as CT scan, ultrasound, or intravenous pyelography to visualize the presence of calcifications and the reduction of calcifications in response to vector-based delivery and expression of ENPP1 or ENPP3 in patients suffering from CKD. Intravenous pyelography is an X-ray exam that uses a contrast medium, which functions as a dye, to help visualize the urinary tract and detect the presence of renal calcifications. Computed tomography is a noninvasive imaging technique that uses X-ray technology to depict internal structures of the body such as the urinary tract. Renal calcifications are visible on CT scans. CT scans collect X-ray images from different angles around the body to generate detailed cross-sectional images as well as three-dimensional images of the body's internal structures and organs. CT scan can also be used in arteries to detect the presence and subsequent reduction of calcification following treatment. A computer analyzes the radiation transmitted through the body to reconstruct the images of the internal structures and organs.

A medical doctor having skill in visualizing soft tissue calcification, cardiac calcification, myocardial infarction undertakes treatment of a subject afflicted with CKD by administering AAV virions expressing human ENPP1 or human ENPP3. The physician administers viral particles that deliver constructs of hENPP1 or hENPP3 and express the corresponding proteins under the control of an inducible promoter. The physician thus has the option to control the dosage (amount of hENPP1 or hENPP3 expressed) based on the rate and extent of improvement of symptoms. Successful treatment is observed by a medical professional of skill in art by observing one or more positive symptoms such as improved kidney function, improved urine creatine levels (*normal creatine levels in urine for men are 40 – 278 mg/dL and 29 – 226 mg/dL for women*), and improved urine-urea levels (*normal urea levels in urine for adults are 26 – 43 g*

/ 24 h) , normal serum-creatine levels (*normal serum creatinine range is 0.6–1.1 mg/dL in women and 0.7–1.3 mg/dL in men*), normal vitamin D levels (*20ng/ml to 50 ng/mL is considered adequate for healthy people. A level less than 12 ng/mL indicates vitamin D deficiency*), normal blood urea nitrogen levels (*BUN level for healthy adults is 7–20 mg/dL*), weight gain, increase in serum PPi levels (*at least about 4-5 μm*), reduction in calcification (*25%, or 50%, or 70%, or 90% or 100% reduction*) of arterial tissues and or reduction of calcification in kidney tubules visualized by noninvasive techniques such as CT or ultrasound scans.

Example 5– Treatment of GACI using viral vectors expressing ENPP1 or ENPP3.

The following example provides AAV expressing ENPP1 or ENPP3 which are expected to be effective in treating vascular calcification and symptoms associated with GACI. ENPP1-Fc and ENPP3-Fc are used in the examples for illustrative purposes and similar results can be obtained by using other ENPP1 or ENPP3 fusions of the invention.

AAV virions expressing ENPP1-Fc and ENPP3-Fc protein are made according to example 1, and administered to a *Enpp1* $^{asj/asj}$ mouse (which is a model for Generalized Arterial Calcification of Infancy (*Li, et al. , 2013, Disease Models & Mech. 6(5): 1227-35*). Six sets of mice are used for treatment with ENPP1 and ENPP3.

Control cohorts: in this experiment, a first cohort of ENPP1 wt mice that serve as control group are injected with AAV particles that comprise a null vector and, a second cohort of *Enpp1* $^{asj/asj}$ mice that serve as a control group are injected with AAV particles that comprise a null vector.

ENPP1-treated mice cohorts: a third cohort of ENPP1 ^{wt} mice are injected with AAV particles engineered to express ENPP1-Fc protein, and a fourth cohort of *Enpp1* $^{asj/asj}$ mice are injected with AAV particles engineered to express ENPP1-Fc protein.

ENPP3-treated mice cohorts: a fifth cohort of ENPP1 ^{wt} mice are injected with AAV particles engineered to express ENPP3-Fc protein, and a sixth cohort of *Enpp1* $^{asj/asj}$ mice are injected with AAV particles engineered to express ENPP3-Fc protein. The wildtype mice are maintained on regular chow diet and the *Enpp1* $^{asj/asj}$ mice are fed high phosphate Teklad diet.

Vector Injection: After two weeks of age, all mice receive a retro-orbital injection or tail vein injection of approx. 1×10^{12} to 1×10^{15} vg/kg, preferably 1×10^{13} to 1×10^{14} vg/kg in PBS pH 7.4 per mouse. The injected vectors are either empty "null" (control group) or carried the NPP1 or NPP3 gene (study group).

Assay: Kidney histology, PPi levels, and blood urine parameters such as FGF-23 levels, vitamin D, Parathyroid hormone (PTH) levels, serum/blood urea levels, blood urea nitrogen (BUN) levels, serum/blood creatine levels and plasma pyrophosphate (PPi) are analyzed for each cohort as described in Example 3 and 4.

Results: Untreated *Enpp1* $^{asj/asj}$ mice generally exhibit reduced body weight and increased mortality. In contrast, *Enpp1* $^{asj/asj}$ mice treated with AAV expressing ENPP1 proteins or ENPP3 proteins are expected to show an increase in body weight approaching the body weight ranges of normal WT mice.

Enpp1 $^{asj/asj}$ mice treated with null vector are expected to display calcifications in their hearts, aortas and coronary arteries, and histologic evidence of myocardial infarctions in the free wall of right ventricle, calcifications of coronary arteries, heart, ascending and descending aorta, myocardial cell necrosis, and myocardial fibrosis in the myocardial tissue adjacent to regions of coronary artery calcification. In contrast, *Enpp1* $^{asj/asj}$ animals treated with AAV expressing ENPP1-Fc or ENPP3-Fc are expected to display an absence of cardiac, arterial, or aortic calcification on histology or post-mortem micro-CT. *Enpp1* $^{asj/asj}$ mice treated with null vector also show calcifications centered in the renal medulla along with heavy, extensive calcifications, centered in the outer medulla, with extension into the renal cortex. In contrast, *Enpp1* $^{asj/asj}$ mice treated with according to the invention with ENPP1 or ENPP3 are expected to show a reduction or lack of renal mineral deposits in the tubular lumen and soft tissue vasculature with histology similar to that of healthy wildtype mice.

In addition to survival, daily animal weights, and terminal histology, treatment response is assessed via post-mortem high-resolution micro-CT scans to image vascular calcifications, plasma PPi concentrations, and 99mTc PPi (99mPYP) uptake. None of the WT or treated (*vector expressing ENPP1or ENPP3*) Enpp1 $^{asj/asj}$ are expected to possess any vascular calcifications via micro-CT, in contrast to the dramatic calcifications are expected in the aortas, coronary arteries,

and hearts of the untreated (*null vector*) Enpp1 $^{asj/asj}$ cohort. In addition, serum PPi concentrations of treated (*vector expressing ENPP1 or ENPP3*) Enpp1 $^{asj/asj}$ animals (5.2 μM) are expected to be elevated to WT levels (4.4 μM) and significantly above untreated enpp1asj/asj levels (0.5μM).

99mPYP is an imaging agent typically employed in cardiac imaging and bone remodeling. It is sensitive to areas of unusually high-bone rebuilding activity since it localizes to the surface of hydroxyapatite and then may be taken up by osteoclasts. Weekly serial imaging of untreated Enpp1 $^{asj/asj}$ animals are expected to show greater uptake of 99mPYP in the heads compared with that of treated Enpp1 $^{asj/asj}$ animals. Measurements are made on days 30–35 and at days 50–65 post administration of viral particles containing null vector or vector expressing ENPP1. Comparison of these experimental groups are expected to show that ENPP1-Fc or ENPP3-Fc treatment returned 99mPYP uptake in GACI mice to WT levels suggesting that ENPP1-Fc or ENPP3-Fc treatment is able to abrogate unregulated tissue, vibrissae and skull mineralization in Enpp1 $^{asj/asj}$ mice by raising the extracellular PPi concentrations. These observations are expected to show that the Enpp1 $^{asj/asj}$ mice dosed viral particles containing vector expressing ENPP1-Fc or ENPP3-Fc are free of vascular calcifications and have normal plasma PPi concentrations.

Untreated Enpp1 $^{asj/asj}$ mice are also expected to show a significant increase in serum inorganic phosphorous (pi), increase in PTH and FGF23 levels but a decrease in 1,25$(OH)_2$-Vitamin D levels and lower PPi levels (~ 0.5 μM) when compared with that of healthy wild type mice (*Normal levels of PP are about 2-4 μM ; about 10-65 ng/L for PTH; median FGF23 level is 13 RU/ml and normal FGF23 level ranges from 5 to 210 RU/ml; normal Vitamin D levels are 20 ng/mL to 50 ng/mL*). In contrast, treated Enpp1 $^{asj/asj}$ mice are expected to show elevated levels of PPi (*~4-5 μM*) which are expected to be higher than the PPi levels found in untreated CKD mice *(~0.5 μM)*. Thus a person of ordinary skill can determine the therapeutic efficacy of vector based ENPP1 or ENPP3 in treating GACI by observing one or more factors like reduction (*25%, or 50%, or 70%, or 90% or 100% reduction*) of calcification of soft tissues in kidneys and coronary arteries visualized through histological analysis , increase in serum PPi levels, normalization of vitamin D levels, reduction in FGF23 levels to normal ranges and

normalization of PTH levels from blood analysis, increased survival, improved kidney function observed by increase in urine urea and creatine along with increased weight gain.

Treatment of human subjects

A human patient suffering from GACI is treated by providing an injection containing approximately. 5×10^{11} -$5x10^{15}$ vg/kg in 1X PBS at pH 7.4, in some embodiments approximately $1x10^{12}$-$1X10^{15}$ vg/kg in 1X PBS at pH 7.4 per subject capable of delivering and expressing hENPP1 or hENPP3. Successful treatment of GACI is observed by monitoring one or more aforesaid parameters through periodic blood and urine tests as discussed for mouse models. Instead of histological analysis which requires staining of kidney slices or arterial tissues which is not feasible to perform in living patients, one instead uses noninvasive visualization techniques as discussed in example 4.

A medical doctor having skill in visualizing soft tissue calcification, cardiac calcification, myocardial infarction undertakes treatment of a subject afflicted with GACI by administering AAV virions expressing hENPP1 or hENPP3. The physician administers viral particles that deliver a construct encoding hENPP1 or hENPP3, the vector expresses the ENPP protein under the control of an inducible promoter. The physician can control the dosage (amount of hENPP1 or hENPP3 expressed) based on the rate and extent of improvement of symptoms. A successful treatment is observed by a medical professional of skill in art by observing one or more positive symptoms such as normal vitamin D levels (*20ng/ml to 50 ng/mL is considered adequate for healthy people. A level less than 12 ng/mL indicates vitamin D deficiency*), normal blood urea nitrogen levels (*BUN level for healthy adults is 7–20 mg/dL*), weight gain, increase in serum PPi levels (*at least about 4-5 μm*), reduction in calcification (*25%, or 50%, or 70%, or 90% or 100% reduction*) of arterial tissues and/or reduction of calcification in kidney tubules visualized by noninvasive techniques such as CT or ultrasound scans.

Example 6– Treatment of PXE using viral vectors expressing ENPP1 or ENPP3.

The following example provides AAV expressing ENPP1 or ENPP3 which are expected to be effective in treating vascular calcification and symptoms associated with PXE. ENPP1-Fc

and ENPP3-Fc are used in the examples for illustrative purposes and similar results can be obtained by using other ENPP1 or ENPP3 fusions of the invention.

AAV virions expressing ENPP1-Fc protein and ENPP3-Fc protein are made according to example 1, and administered to a *ABCC6*$^{-/-}$ mouse (which is a model for Pseudoxanthoma Elasticum; *Jiang, et al., 2007, J. Invest. Derm. 127(6): 1392-4102).* Six sets of mice are used for treatment with ENPP1 and ENPP3.

Control cohorts: in this experiment, a first cohort of ENPP1 wt mice that serve as control group are injected with AAV particles that comprise a null vector and, a second cohort of *ABCC6*$^{-/-}$ mice that serve as a control group are injected with AAV particles that comprise a null vector.

ENPP1-treated mice cohorts: a third cohort of ENPP1 ^{wt} mice are injected with AAV particles engineered to express ENPP1-Fc protein, and a fourth cohort of *ABCC6*$^{-/-}$ mice are injected with AAV particles engineered to express ENPP1-Fc protein.

ENPP3-treated mice cohorts: a fifth cohort of ENPP1 ^{wt} mice are injected with AAV particles engineered to express ENPP3-Fc protein, and a sixth cohort of *ABCC6*$^{-/-}$ mice are injected with AAV particles engineered to express ENPP3-Fc protein. The wildtype mice are maintained on regular chow diet and the *ABCC6*$^{-/-}$ mice are fed high phosphate Teklad diet.

Vector Injection: After two weeks of age, all mice receive a retro-orbital injection or tail vein injection of approx.. 1×10^{12} to 1×10^{15} $^{vg/kg}$, preferably 1×10^{13} to 1×10^{14} $^{vg/kg}$ in PBS pH 7.4 per mouse. The injected vectors are either empty "null" (control group) or carried the NPP1 or NPP3 gene (study group).

Assays: Kidney histology, PPi levels, and blood urine parameters such as FGF-23 levels, vitamin D, Parathyroid hormone (PTH) levels, serum/blood urea levels, blood urea nitrogen (BUN) levels, serum/blood creatine levels and plasma pyrophosphate (PPi) are analyzed for each cohort as described in Example 3 and 4.

Results: Untreated *ABCC6-/-* mice generally exhibit reduced body weight and increased mortality. In contrast, *ABCC6-/-* mice treated with AAV expressing ENPP1 or ENPP3 proteins

are expected to show an increase in body weight approaching the body weight ranges of normal WT mice. *ABCC6-/-* mice treated with null vector are expected to display calcifications in their hearts, aortas and coronary arteries, and histologic evidence of myocardial infarctions in the free wall of right ventricle, calcifications of coronary arteries, heart, ascending and descending aorta, myocardial cell necrosis, and myocardial fibrosis in the myocardial tissue adjacent to regions of coronary artery calcification. In contrast, *ABCC6-/-* animals treated with vector expressing ENPP1-Fc or ENPP3-Fc are expected to display an absence of cardiac, arterial, or aortic calcification on histology or post-mortem micro-CT. *Enpp1* $^{asj/asj}$ mice treated with null vector also show calcifications centered in the renal medulla along with heavy, extensive calcifications, centered in the outer medulla, with extension into the renal cortex. In contrast, *Enpp1* $^{asj/asj}$ mice treated with viral vector-based expression of ENPP1 or ENPP3 are expected to show a reduction or a lack of renal mineral deposits in the tubular lumen and soft tissue vasculature with histology similar to that of healthy wildtype mice.

In addition to survival, daily animal weights, and terminal histology, treatment response is assessed via post-mortem high-resolution micro-CT scans to image vascular calcifications, and plasma PPi concentrations. None of the WT or treated (*vector expressing ENPP1*) *ABCC6*$^{-/-}$ are expected to possess any vascular calcifications via micro-CT, in contrast to the dramatic calcifications that are expected to be seen in the aortas, coronary arteries, and hearts of the untreated (*null vector*) *ABCC6*$^{-/-}$ cohort. In addition, serum PPi concentrations of treated (*vector expressing ENPP1*) *ABCC6*$^{-/-}$ animals (5.2 μM) are expected to be elevated to WT levels (4.4 μM) and significantly above untreated *ABCC6*$^{-/-}$ levels (0.5μM).

Untreated *ABCC6*$^{-/-}$ mice are also expected to show a significant increase in serum inorganic phosphorous (pi), increase in PTH and FGF23 levels but a decrease in $1,25(OH)_2$-Vitamin D levels and lower PPi levels (~ 0.5 μM) when compared with that of healthy wild type mice (*Normal levels of PP are about 2-4 μM ; about 10-65 ng/L for PTH; median FGF23 level is 13 RU/ml and normal FGF23 level ranges from 5 to 210 RU/ml; normal Vitamin D levels are 20 ng/mL to 50 ng/mL*). In contrast, treated *ABCC6*$^{-/-}$ mice are expected to show elevated levels of PPi (*~4-5 μM*) which are expected to be higher than the PPi levels found in untreated *ABCC6*$^{-/-}$ mice *(~0.5 μM)*. Thus a person of ordinary skill can determine the therapeutic efficacy of vector based ENPP1 or ENPP3 in treating PXE by observing one or more factors like reduction

(*25%, or 50%, or 70%, or 90% or 100% reduction*) of calcification of soft tissues in kidneys and coronary arteries visualized through histological analysis , increase in serum PPi levels, normalization of vitamin D levels, reduction in FGF23 levels to normal ranges and normalization of PTH levels from blood analysis, increased survival and improved kidney function observed by increase in urine urea and creatine along with increased weight gain.

Treatment of human subjects:

A human patient suffering from PXE is treated by providing an intravenal injection containing approximately. 5×10^{11} -$5x10^{15}$ vg/kg in 1X PBS at pH 7.4, in some embodiments approximately $1x10^{12}$-$1X10^{15}$ vg/kg in 1X PBS at pH 7.4 per subject capable of delivering and expressing ENPP1 or ENPP3. Successful treatment of PXE is observed by monitoring one or more aforesaid parameters through periodic blood and urine tests as discussed for mouse models. Instead of histological analysis which requires staining of kidney slices or arterial tissues which is not feasible to perform in living patients, one instead uses noninvasive visualization techniques as discussed in example 4.

A medical doctor having skill in visualizing soft tissue calcification, cardiac calcification, myocardial infarction can undertake the treatment of a subject afflicted with PXE by administering AAV virions expressing ENPP1 or ENPP3. The physician can also use viral particles that deliver constructs of ENPP1 or ENPP3 and express the corresponding proteins under the control of an inducible promoter. The physician thus has the option to control the dosage (amount of ENPP1 or ENPP3 expressed) based on the rate and extent of improvement of symptoms. A successful treatment and suitable dosage is readily inferred by a medical professional of skill in art by observing one or more positive symptoms such as normal vitamin D levels (*20ng/ml to 50 ng/mL is considered adequate for healthy people. A level less than 12 ng/mL indicates vitamin D deficiency*), disappearance or reduction of size and or number of angioid streaks, reduction or lack of retinal bleeding, normal blood urea nitrogen levels (*BUN level for healthy adults is 7–20 mg/dL*), weight gain, increase in serum PPi levels (*at least about 4-5 μm*), reduction in calcification (*25%, or 50%, or 70%, or 90% or 100% reduction*) of arterial tissues, connective tissues and or reduction of calcification in kidney tubules visualized by noninvasive techniques such as CT or ultrasound scans.

Example 7– Treatment of OPLL using viral vectors expressing human ENPP1 or ENPP3.

The following example provides AAV expressing human ENPP1 or ENPP3 which are expected to be effective in treating vascular calcification and symptoms associated with PXE. ENPP1-Fc and ENPP3-Fc fusions are used in the examples for illustrative purposes and similar results can be obtained by using other ENPP1 or ENPP3 fusions of the invention.

AAV virions expressing ENPP1-Fc protein or ENPP3-Fc protein are made according to example 1, and administered to a Tip toe walking *(ttw)* mouse (which is a model for Ossification of the Posterior Longitudinal Ligament; (*Okawa, et al, 1998, Nature Genetics 19(3):271-3*; *Nakamura, et al, 1999, Human Genetics l04(6):492-7*). Six sets of mice are used for treatment with ENPP1 and ENPP3.

Control cohorts: in this experiment, a first cohort of ENPP1 wt mice that serve as control group are injected with AAV particles that comprise a null vector and, a second cohort of *ttw* mice that serve as a control group are injected with AAV particles that comprise a null vector.

ENPP1-treated mice cohorts: a third cohort of ENPP1 ^{wt} mice are injected with AAV particles engineered to express ENPP1-Fc protein, and a fourth cohort of *ttw* mice are injected with AAV particles engineered to express ENPP1-Fc protein.

ENPP3-treated mice cohorts: a fifth cohort of ENPP1 ^{wt} mice are injected with AAV particles engineered to express ENPP3-Fc protein, and a sixth cohort of *ttw* mice are injected with AAV particles engineered to express ENPP3-Fc protein. The wildtype mice are maintained on regular chow diet and the *ttw* mice are fed high phosphate Teklad diet.

Vector injection: After two weeks of age, all mice receive a retro-orbital injection or tail vein injection of approx. 1×10^{12} to 1×10^{15} $^{vg/kg}$, preferably 1×10^{13} to 1×10^{14} $^{vg/kg}$ in PBS pH 7.4 per mouse. The injected vectors are either empty "null" (control group) or carried the NPP1 or NPP3 gene (study group).

Assays: Kidney histology, PPi levels, and blood urine parameters such as FGF-23 levels, vitamin D, Parathyroid hormone (PTH) levels, serum/blood urea levels, blood urea nitrogen

(BUN) levels, serum/blood creatine levels and plasma pyrophosphate (PPi) are analyzed for each cohort as described in Example 3 and 4.

Results: Untreated *ttw* mice generally exhibit reduced body weight, thickening of spine, lethargy and increased mortality. In contrast, *ttw* mice treated with AAV expressing ENPP1 proteins or ENPP3 proteins are expected to show an increase in body weight approaching the body weight ranges of normal WT mice, normal alertness, and reduction in spine thickness approaching the thickness of wild type mouse. *ttw* mice treated with null vector are expected to display calcifications in their hearts, aortas and coronary arteries, and histologic evidence of myocardial infarctions in the free wall of right ventricle, calcifications of coronary arteries, heart, ascending and descending aorta, myocardial cell necrosis, and myocardial fibrosis in the myocardial tissue adjacent to regions of coronary artery calcification. In contrast, *ttw* animals treated with vector expressing ENPP1-Fc or ENPP3-Fc are expected to display an absence of cardiac, arterial, or aortic calcification on histology or post-mortem micro-CT. *ttw* mice treated with null vector also show calcifications centered in the renal medulla along with heavy, extensive calcifications, centered in the outer medulla, with extension into the renal cortex. In contrast, *ttw* mice treated with viral vector-based expression of ENPP1 or ENPP3 are expected to show a reduction or lack of renal mineral deposits in the tubular lumen, reduction of calcification of spine, and soft tissue vasculature with histology similar to that of healthy wildtype mice.

In addition to survival, daily animal weights, and terminal histology, treatment response is assessed via post-mortem high-resolution micro-CT scans to image vascular calcifications, and plasma PPi concentrations. None of the WT or treated (*vector expressing ENPP1*) *ttw* are expected to possess any vascular calcifications via micro-CT, in contrast to the dramatic calcifications that are expected to be seen in the aortas, coronary arteries, and hearts of the untreated (*null vector*) *ttw* cohort. In addition, serum PPi concentrations of treated (*vector expressing ENPP1*) *ttw*$^{-}$ animals (5.2 μM) are expected to be elevated to WT levels (4.4 μM) and significantly above untreated *ttw* levels (0.5μM).

Untreated *ttw* mice are also expected to show a significant increase in serum inorganic phosphorous (pi), increase in PTH and FGF23 levels but a decrease in $1,25(OH)_2$-Vitamin D levels and lower PPi levels (~ 0.5 μM) when compared with that of healthy wild type mice

(*Normal levels of PP are about 2-4 μM ; about 10-65 ng/L for PTH; median FGF23 level is 13 RU/ml and normal FGF23 level ranges from 5 to 210 RU/ml*; *normal Vitamin D levels are 20 ng/mL to 50 ng/mL*). In contrast, treated *ttw* mice are expected to show elevated levels of PPi (*~4-5 μM*) which are expected to be higher than the PPi levels found in untreated *ttw* mice *(~0.5 μM*). Thus a person of ordinary skill can determine the therapeutic efficacy of vector based ENPP1 or ENPP3 in treating OPLL by observing one or more factors like reduction (*25%, or 50%, or 70%, or 90% or 100% reduction*) of calcification of soft tissues in kidneys and coronary arteries visualized through histological analysis , increase in serum PPi levels, normalization of vitamin D levels, reduction in FGF23 levels to normal ranges and normalization of PTH levels from blood analysis, increased survival and improved kidney function observed by increase in urine urea and creatine along with increased weight gain.

Treatment of human subjects:

A human patient suffering from OPLL is treated by providing an intravenal injection containing approximately. 5×10^{11} -$5x10^{15}$ vg/kg in 1X PBS at pH 7.4, in some embodiments approximately $1x10^{12}$-$1X10^{15}$ vg/kg in 1X PBS at pH 7.4 per subject capable of delivering and expressing hENPP1 or hENPP3. Successful treatment of OPLL is observed by monitoring one or more aforesaid parameters through periodic blood and urine tests as discussed for mouse models. Instead of histological analysis which requires staining of kidney slices or arterial tissues which is not feasible to perform in living patients, one instead uses noninvasive visualization techniques as discussed in example 4.

A medical doctor having skill in visualizing soft tissue calcification, cardiac calcification, myocardial infarction can undertake the treatment of a subject afflicted with OPLL upon administration of AAV virions expressing hENPP1 or hENPP3. In some embodiments, the physician uses viral particles that deliver constructs of hENPP1 or hENPP3 and express the corresponding proteins under the control of an inducible promoter. The physician thus has the option to control the dosage (amount of hENPP1 or hENPP3 expressed) based on the rate and extent of improvement of symptoms. A successful treatment and suitable dosage is readily inferred by a medical professional of skill in art by observing one or more positive symptoms such as normal vitamin D levels (*20ng/ml to 50 ng/mL is considered adequate for healthy*

people. A level less than 12 ng/mL indicates vitamin D deficiency), normal blood urea nitrogen levels (*BUN level for healthy adults is 7–20 mg/dL*), weight gain, increase in serum PPi levels (*at least about 4-5 μm*), reduction in calcification (*25%, or 50%, or 70%, or 90% or 100% reduction*) of arterial tissues, reduction in thickness of spine and pain senstation, reduction of spinal stenosis visualized by noninvasive techniques such as CT, magnetic resonance imaging (MRI) or ultrasound scans.

Example 8– Treatment of Osteopenia and or Osteomalacia using viral vectors expressing ENPP1 or ENPP3.

The following example provides AAV expressing ENPP1 or ENPP3 which are expected to be effective in treating symptoms associated with Osteopenia and/or Osteomalacia. ENPP1-Fc and ENPP3-Fc are used in the examples for illustrative purposes and similar results can be obtained by using other ENPP1 or ENPP3 fusions of the invention.

AAV virions expressing ENPP1-Fc protein or ENPP3-Fc protein are made according to example 1 and administered to a Tip toe walking *(ttw)* mouse (which is a mouse model for osteoarthritis (*Bertrand, et al, 2012, Annals Rheum. Diseases 71(7): 1249-53*)). Six sets of mice are used for treatment with ENPP1 and ENPP3. Similar experiment is repeated using ENPP1 knockout mice ($ENPP1^{KO}$) which also serves as a model for osteopenia. (*Mackenzie, et al, 2012, PloS one 7(2):e32177*) in addition to GACI.

Control cohorts: in this experiment, a first cohort of ENPP1 wt mice that serve as control group are injected with AAV particles that comprise a null vector and, a second cohort of *ttw* (or $ENPP1^{KO}$) mice that serve as a control group are injected with AAV particles that comprise a null vector.

ENPP1-treated mice cohorts: a third cohort of ENPP1 ^{wt} mice are injected with AAV particles engineered to express ENPP1-Fc protein, and a fourth cohort of *ttw* mice (or $ENPP1^{KO}$) are injected with AAV particles engineered to express ENPP1-Fc protein.

ENPP3-treated mice cohorts: a fifth cohort of ENPP1 ^{wt} mice are injected with AAV particles engineered to express ENPP3-Fc protein, and a sixth cohort of *ttw* (or $ENPP1^{KO}$)mice are injected with AAV particles engineered to express ENPP3-Fc protein. The wildtype mice are

maintained on regular chow diet and the *ttw* mice (or *ENPP1*^{KO}) are fed high phosphate Teklad diet.

Vector injection: After two weeks of age, all mice receive a retro-orbital injection or tail vein injection of approx. 1×10^{12} to 1×10^{15} vg/kg, preferably. 1×10^{13} to 1×10^{14} vg/kg in PBS pH 7.4 per mouse. The injected vectors are either empty "null" (control group) or carried the NPP1or NPP3 gene (study group).

Assays: Kidney histology, PPi levels, and blood urine parameters such as FGF-23 levels, vitamin D, Parathyroid hormone (PTH) levels, serum/blood urea levels, blood urea nitrogen (BUN) levels, serum/blood creatine levels and plasma pyrophosphate (PPi) are analyzed for each cohort as described in Example 3 and 4.

Histology, Histomorphometry, and Micro-CT: Bone analysis is conducted following the protocols as described in Example 3.

Bone biomechanical testing: Bone analysis is conducted following the protocols as described in Example 3.

Results: Untreated *ttw* (or *ENPP1*^{KO}) mice generally exhibit reduced body weight, lethargy, diminished cortical bone thickness and trabecular bone volume , calcification of cartilage and ligaments, reduced bone density in the long bones such as Femur and Tibia, and increased mortality compared to wild type. In contrast, *ttw* (or *ENPP1*^{KO}) mice treated with AAV expressing ENPP1 proteins or ENPP3 proteins are expected to show an increase in body weight approaching the body weight ranges of normal WT mice, normal alertness, increases bone mineral density, improved cortical bone thickness and trabecular bone volume, increased bone strength and bone ductility. The *ttw* (or *ENPP1*^{KO}) mice treated with null vector are expected to display calcifications in their hearts, aortas and coronary arteries, and histologic evidence of myocardial infarctions in the free wall of right ventricle, calcifications of coronary arteries, heart, ascending and descending aorta, myocardial cell necrosis, and myocardial fibrosis in the myocardial tissue adjacent to regions of coronary artery calcification. In contrast, *ttw* (or *ENPP1*^{KO}) animals treated with vector expressing ENPP1-Fc or ENPP3-Fc are expected to display an absence of cardiac, arterial, or aortic calcification on histology or post-mortem micro-

CT. The *ttw* (or *ENPP1^{KO}*) mice treated with null vector also show calcifications centered in the renal medulla along with heavy, extensive calcifications, centered in the outer medulla, with extension into the renal cortex. In contrast, *ttw* (or *ENPP1^{KO}*) mice treated with viral vector based expression of ENPP1 or ENPP3 are expected to show a reduction or lack of renal mineral deposits in the tubular lumen, reduction of calcification of spine, and soft tissue vasculature with histology similar to that of healthy wildtype mice.

In addition to survival, daily animal weights, and terminal histology, treatment response is assessed via post-mortem high-resolution micro-CT scans to image vascular calcifications, and plasma PPi concentrations. None of the WT or treated (*vector expressing ENPP1*) *ttw* (or *ENPP1^{KO}*) are expected to possess any vascular calcifications via micro-CT, in contrast to the dramatic calcifications that are expected to be seen in the aortas, coronary arteries, and hearts of the untreated (*null vector*) *ttw* (or *ENPP1^{KO}*) cohort. In addition, serum PPi concentrations of treated (*vector expressing ENPP1*) *ttw* (or *ENPP1^{KO}*) animals (5.2 μM) are expected to be elevated to WT levels (4.4 μM) and significantly above untreated *ttw* (or *ENPP1^{KO}*) levels (0.5μM).

Untreated *ttw* (or *ENPP1^{KO}*) mice are also expected to show a significant increase in serum inorganic phosphorous (pi), increase in PTH and FGF23 levels but a decrease in 1,25$(OH)_2$-Vitamin D levels and lower PPi levels (~ 0.5 μM) when compared with that of healthy wild type mice (*Normal levels of PP are about 2-4 μM ; about 10-65 ng/L for PTH; median FGF23 level is 13 RU/ml and normal FGF23 level ranges from 5 to 210 RU/ml*; *normal Vitamin D levels are 20 ng/mL to 50 ng/mL*). In contrast, treated *ttw* (or *ENPP1^{KO}*) mice are expected to show elevated levels of PPi (*~4-5 μM*) which are expected to be higher than the PPi levels found in untreated *ttw* (or *ENPP1^{KO}*) mice *(~0.5 μM)*. Thus a person of ordinary skill can determine the therapeutic efficacy of vector based ENPP1 or ENPP3 in treating Osteopenia or Osteomalcia or Osteoarthritis by observing one or more factors like reduction (*25%, or 50%, or 70%, or 90% or 100% reduction*) of calcification of soft tissues in kidneys and coronary arteries visualized through histological analysis , increase in serum PPi levels, normalization of vitamin D levels, reduction in FGF23 levels to normal ranges and normalization of PTH levels from blood analysis, improved long bone strength, increased bone density, improved corticular bone

thickness and trabecular bone volume, increased survival and improved kidney function observed by increase in urine urea and creatine along with increased weight gain.

Treatment of human subjects:

A human patient suffering from Osteopenia or Osteomalacia or Osteoarthritis is treated by providing an intravenal injection containing approximately. 5×10^{11} -$5x10^{15}$ vg/kg in 1X PBS at pH 7.4, in some embodiments approximately $1x10^{12}$-$1x10^{15}$ vg/kg in 1X PBS at pH 7.4 per subject capable of delivering and expressing hENPP1 or hENPP3. Successful treatment of Osteopenia or Osteomalacia or Osteoarthritis is observed by monitoring one or more aforesaid parameters through periodic bone strength, bone density blood and urine tests as discussed for mouse models. Instead of histological analysis which requires staining of kidney slices or arterial tissues which is not feasible to perform in living patients, one instead uses noninvasive visualization techniques as discussed in example 4.

Similarly, patients are subjected to periodic bone density measurements using dual energy x-ray absorptiometry (DXA) or peripheral dual energy x-ray absorptiometry (pDXA) or quantitative ultrasound (QUS) or peripheral quantitative computed tomography (pQCT). Bone density scores obtained from one of these methods provides indication of the condition and progress obtained after the treatment. A T-score of -1.0 or above is considered as normal bone density, a T-score between -1.0 and -2.5 indicates the presence of Osteopenia and whereas a T-score of -2.5 or below indicates the presence of Osteoporosis. A gradual improvement of T-score is expected in patients treated with ENPP1 or ENPP3 of the invention.

A medical doctor having skill in visualizing soft tissue calcification, cardiac calcification, bone density visualization undertakes the treatment of a subject afflicted with Osteopenia or Osteoarthiritis by administration of AAV virions expressing hENPP1 or hENPP3. In some embodiments, the physician uses viral particles that deliver constructs of hENPP1 or hENPP3 and express the corresponding proteins under the control of an inducible promoter. The physician thus has the option to control the dosage (amount of hENPP1 or hENPP3 expressed) based on the rate and extent of improvement of symptoms. A successful treatment and suitable dosage is readily inferred by a medical professional of skill in art by observing one or more positive symptoms such as normal vitamin D levels (*20ng/ml to 50 ng/mL is considered adequate for*

healthy people. A level less than 12 ng/mL indicates vitamin D deficiency), normal bone density (T score of ≥ -1) normal blood urea nitrogen levels (*BUN level for healthy adults is 7–20 mg/dL*), weight gain, increase in serum PPi levels (*at least about 4-5 μm*), reduction in calcification (*25%, or 50%, or 70%, or 90% or 100% reduction*) of arterial tissues, improved bone strength visualized by noninvasive techniques such as CT, magnetic resonance imaging (MRI) or ultrasound scans.

Example 9– Treatment of ADHR-2 orARHR-2 and or XLH using viral vectors expressing ENPP1 or ENPP3.

The following example provides AAV expressing ENPP1 or ENPP3 which are expected to be effective in treating symptoms associated with ADHR-2 orARHR-2 or XLH. ENPP1-Fc and ENPP3-Fc are used in the examples for illustrative purposes and similar results can be obtained by using other ENPP1 or ENPP3 fusions of the invention.

AAV virions expressing ENPP1-Fc protein or ENPP3-Fc protein are made according to example 1, and administered to a *HYP* mouse model of X-linked hypophosphatasia (XLH); (*Liang, et al. , 2009, Calcif. Tissue Int. 85(3):235-46*). Six sets of mice are used for treatment with ENPP1 and ENPP3. Similar experiment is repeated using ENPP1 age stiffened joint mouse (*ENPP1$^{asj/asj}$*) which also serves as a model for ARHR-2. (*Am J Hum Genet. 2010 Feb 12; 86(2): 273–278.*) in addition to GACI.

Control cohorts: In this experiment, a first cohort of ENPP1 wt mice that serve as control group are injected with AAV particles that comprise a null vector and, a second cohort of *HYP* (or *ENPP1$^{asj/asj}$*) mice that serve as a control group are injected with AAV particles that comprise a null vector.

ENPP1-treated mice cohorts: a third cohort of ENPP1 ^{wt} mice are injected with AAV particles engineered to express ENPP1-Fc protein, and a fourth cohort of *HYP* (or *ENPP1$^{asj/asj}$*) mice are injected with AAV particles engineered to express ENPP1-Fc protein.

ENPP3-treated mice cohorts: a fifth cohort of ENPP1 ^{wt} mice are injected with AAV particles engineered to express ENPP3-Fc protein, and a sixth cohort of *HYP* (or *ENPP1$^{asj/asj}$*) mice are injected with AAV particles engineered to express ENPP3-Fc protein. The wildtype

mice are maintained on regular chow diet and the *HYP* (or *ENPP1*$^{asj/asj}$) mice are fed high phosphate Teklad diet.

Vector injection: After two weeks of age, all mice receive a retro-orbital injection or tail vein injection of approx. . 1×10^{12} to 1×10^{15} vg/kg, preferably 1×10^{13} to 1×10^{14} vg/kg in PBS pH 7.4 per mouse. The injected vectors are either empty "null" (control group) or carried the NPP1or NPP3 gene (study group).

Assays: Kidney histology, PPi levels, and blood urine parameters such as FGF-23 levels, vitamin D, Parathyroid hormone (PTH) levels, serum/blood urea levels, blood urea nitrogen (BUN) levels, serum/blood creatine levels and plasma pyrophosphate (PPi) are analyzed for each cohort as described in Example 3 and 4.

Histology, Histomorphometry, and Micro-CT: Bone analysis is conducted following the protocols as described in Example 3.

Bone biomechanical testing: Bone analysis is conducted following the protocols as described in Example 3.

Results: Untreated *HYP* (or *ENPP1*$^{asj/asj}$) mice generally exhibit reduced body weight, lethargy, diminished cortical bone thickness and trabecular bone volume , calcification of cartilage and ligaments, reduced bone density in the long bones such as Femur and Tibia, and increased mortality compared to wild type. In contrast, *HYP* (or *ENPP1*$^{asj/asj}$) mice treated with AAV expressing ENPP1 proteins or ENPP3 proteins are expected to show an increase in body weight approaching the body weight ranges of normal WT mice, normal alertness, increases bone mineral density, improved cortical bone thickness and trabecular bone volume, increased bone strength and bone ductility. The *HYP* (or *ENPP1*$^{asj/asj}$) mice treated with null vector are expected to display calcifications in their hearts, aortas and coronary arteries, and histologic evidence of myocardial infarctions in the free wall of right ventricle, calcifications of coronary arteries, heart, ascending and descending aorta, myocardial cell necrosis, and myocardial fibrosis in the myocardial tissue adjacent to regions of coronary artery calcification. In contrast, *HYP* (or *ENPP1*$^{asj/asj}$) mice treated with vector expressing ENPP1-Fc or ENPP3-Fc are expected to display an absence of cardiac, arterial, or aortic calcification on histology or post-mortem micro-

CT. The *HYP* (or *ENPP1*$^{asj/asj}$) mice treated with null vector also show calcifications centered in the renal medulla along with heavy, extensive calcifications, centered in the outer medulla, with extension into the renal cortex. In contrast *HYP* (or *ENPP1*$^{asj/asj}$) mice treated with viral vector based expression of ENPP1 or ENPP3 are expected to show a reduction or lack of renal mineral deposits in the tubular lumen, reduction of calcification of spine, and soft tissue vasculature with histology similar to that of healthy wildtype mice.

In addition to survival, daily animal weights, and terminal histology, treatment response is assessed via post-mortem high-resolution micro-CT scans to image vascular calcifications, and plasma PPi concentrations. None of the WT or treated (*vector expressing ENPP1*) *HYP* (or *ENPP1*$^{asj/asj}$) mice are expected to possess any vascular calcifications via micro-CT, in contrast to the dramatic calcifications that are expected to be seen in the aortas, coronary arteries, and hearts of the untreated (*null vector*) *HYP* (or *ENPP1*$^{asj/asj}$) cohort. In addition, serum PPi concentrations of treated (*vector expressing ENPP1*) *HYP* (or *ENPP1*$^{asj/asj}$) mice (5.2 μM) are expected to be elevated to WT levels (4.4 μM) and significantly above untreated *HYP* (or *ENPP1*$^{asj/asj}$) levels (0.5μM).

Untreated *HYP* (or *ENPP1*$^{asj/asj}$) mice are also expected to show a significant increase in serum inorganic phosphorous (pi), increase in PTH and FGF23 levels but a decrease in 1,25$(OH)_2$-Vitamin D levels and lower PPi levels (~ 0.5 μM) when compared with that of healthy wild type mice (*Normal levels of PP are about 2-4 μM ; about 10-65 ng/L for PTH; median FGF23 level is 13 RU/ml and normal FGF23 level ranges from 5 to 210 RU/ml*; *normal Vitamin D levels are 20 ng/mL to 50 ng/mL*). In contrast, treated *HYP* (or *ENPP1*$^{asj/asj}$) mice are expected to show elevated levels of PPi (*~4-5 μM*) which are expected to be higher than the PPi levels found in untreated *HYP* (or *ENPP1*$^{asj/asj}$) mice *(~0.5 μM)*. Thus a person of ordinary skill can determine the therapeutic efficacy of vector based ENPP1 or ENPP3 in treating ADHR-2 or ARHR-2 or XLH by observing one or more factors like reduction (*25%, or 50%, or 70%, or 90% or 100% reduction*) of calcification of soft tissues in kidneys and coronary arteries visualized through histological analysis , increase in serum PPi levels, normalization of vitamin D levels, reduction in FGF23 levels to normal ranges and normalization of PTH levels from blood analysis, improved long bone strength, increased bone density, improved corticular bone

thickness and trabecular bone volume, increased survival and improved kidney function observed by increase in urine urea and creatine along with increased weight gain.

Treatment of human subjects:

A human patient suffering from ADHR-2 or ARHR-2 or XLH is treated by providing an intravenal injection containing approximately. 5×10^{11} -$5x10^{15}$ vg/kg in 1X PBS at pH 7.4, in some embodiments approximately $1x10^{12}$-$1X10^{15}$ vg/kg in 1X PBS at pH 7.4 per subject capable of delivering and expressing hENPP1 or hENPP3. Successful treatment of ADHR-2 orARHR-2 or XLH is observed by monitoring one or more aforesaid parameters through periodic bone strength, bone density blood and urine tests as discussed for mouse models. Instead of histological analysis which requires staining of kidney slices or arterial tissues which is not feasible to perform in living patients, one instead uses noninvasive visualization techniques as discussed in example 4.

Similarly, patients are subjected to periodic bone density measurements using dual energy x-ray absorptiometry (DXA) or peripheral dual energy x-ray absorptiometry (pDXA) or quantitative ultrasound (QUS) or peripheral quantitative computed tomography (pQCT). Bone density scores obtained from one of these methods provides indication of the condition and progress obtained after the treatment. A T-score of -1.0 or above is considered as normal bone density, a T-score between -1.0 and -2.5 indicates the presence of Osteopenia and whereas a T-score of -2.5 or below indicates the presence of Osteoporosis. A gradual improvement of T-score is expected in patients treated with ENPP1 or ENPP3 of the invention.

A medical doctor having skill in visualizing soft tissue calcification, cardiac calcification, bone density visualization undertakes the treatment of a subject afflicted with ADHR-2 orARHR-2 or XLH by administering AAV virions expressing hENPP1 or hENPP3. In some embodiments, the physician uses viral particles that deliver constructs of hENPP1 or hENPP3 and express the corresponding proteins under the control of an inducible promoter. The physician thus has the option to control the dosage (amount of hENPP1 or hENPP3 expressed) based on the rate and extent of improvement of symptoms. A successful treatment and suitable dosage is readily inferred by a medical professional of skill in art by observing one or more positive symptoms such as normal vitamin D levels (*20ng/ml to 50 ng/mL is considered adequate for*

healthy people. A level less than 12 ng/mL indicates vitamin D deficiency), normal bone density (T score of ≥ -1) normal blood urea nitrogen levels (*BUN level for healthy adults is 7–20 mg/dL*), weight gain, increase in serum PPi levels (*at least about 4-5 μm*), reduction in calcification (*25%, or 50%, or 70%, or 90% or 100% reduction*) of arterial tissues, improved bone strength visualized by noninvasive techniques such as CT, magnetic resonance imaging (MRI) or ultrasound scans.

Example 10– Analysis of Plasma PPi levels, ENPP1 concentration and activity levels in model mice post viral adminstration.

Three cohorts of Normal mice were used for this experiment. Each cohort contains five adult mice. The first cohort was used as a "Control group" and saline solution was injected to the control group. The second cohort was used as the "Low dose group" and AAV vector at $1e^{13}$ vg/kg concentration was injected to the low dose group. The Third cohort was used a "High dose group" and AAV vector at $1e^{14}$ vg/kg concentration was injected to the high dose group. The process of generating viral particles from AAVconstruct and injecting the recombinant AAV viral paritcles comprising ENPP1 fusion proteins into normal mice is schematically shown in Figure 4. Mice from all cohorts were bled at 7th, 28th and 56th day post injection to collect blood plasma and serum.

Blood was collected into heparin-treated tubes. Plasma was isolated, and platelets were removed by filtering through a Nanosep 30 kDa Omega centrifugal filter (Pall, OD030C35). The samples were centrifuged at top speed (~20kg) at 4°C for 20min. The flow-through was collected and placed on dry ice to flash freeze the samples. The samples were stored at -80°C for later use in assay.

The samples collected were first assayed to determine the activity levels of ENPP1 using the colorimetric substrate, p-nitrophenyl thymidine 5′-monophosphate (Sigma). Plasma samples were incubated with 1 mg/ml p-nitrophenyl thymidine 5′-monophosphate for 1 hr in 1% Triton,

$$\text{Specific Activity (pmol/min/μg)} = \frac{\text{Adjusted } V_{max}\text{* (OD/min) x Conversion Factor** (pmol/OD)}}{\text{amount of enzyme (μg)}}$$

*Adjusted for Substrate Blank

**Derived using calibration standard 4-Nitrophenol (Sigma-Aldrich, Catalog # 241326).

200 mM Tris, pH 8.0 buffer. 100 mM NaOH was added after 1 hr to stop the reaction, and absorbance was measured at 405 nm. Specific activity was determined by following assay proto cols disclosed by R& D Systems for recombinant human ENPP-1; Catalog No: 6136-WN.

The results of the ENPP1 activity assay are in Figure 5 and they show that there is a dose dependent increase in ENPP1 activity post injection. Normal mouse plasma was used as a reference standard to normalize the ENPP1 activity levels and One-way ANOVA was used for statistical analysis. Figure 5 shows that the ENPP1 activity levels were higher in the low dose group when compared with that of the control group. Similarly, the ENPP1 activity levels were higher in the high dose group when compared with that of the low dose group and the control group. Amongst the low dose and high dose cohorts, ENPP1 activity was stable in the plasma samples from day 7 to day 56 in the high-dose group, but there was a slight decrease in the ENPP1 activity from day 28 to day 56 in the low-dose group.

The samples were then assayed to determine the concentration of ENPP1 using sandwich ELISA assay with ENPP1 polyclonal antibody derived from Sigma (SAB1400199). 96 Well Clear Flat Bottom Polystyrene High Bind Microplate (Corning Cat#9018), BSA (Sigma # 7906), 10X Dulbecco's Phosphate Buffered Saline (DPBS) (Quality Biological Cat#119-068-101) , Tween-20 (Sigma Cat#P2287) , Anti-ENPP1, Antibody Produced in Mouse(Sigma-Aldrich Cat# SAB1400199), Sure Blue TMB Microwell Peroxidase Substrate (1-component) (KPL Prod # 52-00-01), 2N Sulphuric acid(BDH Product# BDH7500-1), MilliQ Water, C57BL/6 Mouse Plasma NaHep Pooled Gender (BioIVT cat# MSE01PLNHPNN), Mouse Serum (BIO IVT elevating Science cat# MSE01SRMPNN) were used for the ELISA assay.

A standard curve for ENPP1-Fc protein is generated by following standard procedures known in art. Briefly serial dilutions of ENPP1-Fc protein ranging from 2mg/ml to 30 ng.ml were made. The 96 well plate was first coated with 1 µg/1 mL of overnight coat solution comprising the ENPP1 capture antibody in 1XPBS. The wells were then incubated with 5% BSA in PBS for 1 hr and were then washed with post block solution. The ENPP1 dilution samples were added to the coated 96 well plates and incubated for 1.5 hrs. After incubation, the wells were washed four times with 300 µl of 0.05T% PBST. The washed wells were then treated with 100 µL/well of the detection HRP antibody conjugate and were incubated for 1 hour. After incubation with HRP antibody conjugate, the wells were washed four times with 300 µl of

0.05T% PBST. The washed wells were then treated with 100µl of TMB Microwell Peroxidase Substrate per well and incubated in dark for 30 minutes. The wells were then washed four times with 300 µl of 0.05T% PBST and the reaction was stopped using 2N Sulphuric Acid. The absorbance of the well was read using Microplate Reader at a wavelength of 450nm. A standard curve was generated using the absorbance read and the corresponding concentration of the ENPP1 serial dilution samples.

The assay was then repeated using plasma samples obtained from control, low dose and high dose cohorts on 7, 28 and 56 days post viral injection. The absorbance generated in each plasma sample was correlated with the standard curve of ENPP1-Fc to determine concentration of ENPP1-Fc in the plasma samples. The results of ENPP1 concentration assay are shown in Figure 6 and they show a dose dependent increase in ENPP1 concentration post viral vector injection. Normal mouse plasma was used as a reference standard to normalize the ENPP1 concentration levels and One-way ANOVA was used for statistical analysis. Figure 6 shows that the ENPP1 concentration was higher in the low dose group when compared with that of the control group. Similarly, the ENPP1 activity levels were higher in the high dose group when compared with that of the low dose group and the control group. Amongst the low dose and high dose cohorts, ENPP1 level was stable in the samples from day 7 to day 56 in the high-dose group, but there was a slight decrease in the ENPP1 level from day 28 to day 56 in the low-dose group

The samples were also assayed to determine the concentration of Plasma PPi using Sulfurylase assay. ATP sulfurylase (NEB-M0394L, Lot#:10028529), Adenosine 5'-phosphosulfate (APS; Santa Cruz, sc-214506)), PPi: 100uM stock, HEPES pH 7.4 buffer (Boston Bioproducts BB2076), Magnesium sulfate (MgSO4) solution at 1M, Calcium chloride (CaCl2) solution at 1M, BactiterGlo (Promega G8231), Plates (Costar 3915, black flat bottom) and Plate reader (Molecular Devices Spectramax I3x) were used for the PPi-Sulfurylase assay. PPi standards (0.125-4µM) were prepared in water using serial dilution. PPi standards and PPi in filtered plasma samples were converted into ATP by ATP sulfurylase in the presence of excess adenosine 5' phosphosulfate (APS). The sample (15 µl) was treated with 5 µl of a mixture containing 8mM $CaCl_2$, 2mM MgSO4, 40mM HEPES pH7.4, 80uM APS (Santa Cruz, sc-214506), and 0.1U/ml ATP sulfurylase (NEB-M0394L). The mixture was incubated for 40 min

at 37 °C, after which ATP sulfurylase was inactivated by incubation at 90 °C for 10 min. The generated ATP was determined using BactiterGlo (Promega G8231) by mixing 20 µl of treated sample or standard with 20 µl of BactiterGlo reagent. Bioluminescence was subsequently determined in a microplate reader and from the standard curve, the amount of PPi generated in each sample was subsequently determined.

The results of Plasma PPi assay are shown in Figure 7. Results show a dose dependent increase in Plasma PPi post viral vector injection. Normal mouse plasma was used as a reference standard to normalize the Plasma PPi concentraion levels and One-way ANOVA was used for statistical analysis. Figure 7 shows that the Plasma PPi concentration was slightly higher in the low dose group when compared with that of the control group. Similarly, the Plasma PPi concentration were higher in the high dose group when compared with that of the low dose group and the control group. Amongst the low dose and high dose cohorts, ENPP1 level was stable in the plasma samples from day 7 to day 56 in the high-dose group, but a slight decrease in the ENPP1 level from day 28 to day 56 in the low-dose group was observed.

In a related experiment, C57/Bl male mice 5-6 weeks old were administered intravenously a single dose of an AAV viral vector at 1e14 vg/kg, or a vehicle control (containing no AAV vector). Animals were administered GK1.5 (40 µg/ mouse one day prior to administration of the viral vector or vehicle, and then 25 µg/mouse every seven days thereafter until completion of the study). The AAV viral vector was engineered to express a fusion protein of ENPP1 and an IgG Fc similar to the polypeptide described in Example 10 except the ENPP1 portion and the IgG Fc portion of the fusion protein were joined by the following linker amino acid sequence: GGGGS. Mice administered the AAV viral vector demonstrated a higher level of ENPP1 enzyme activity than the vehicle only control as measured over an approximately 40 day period.

Example 11– Analysis of ENPP1 concentration and activity levels in model mice 112 days post viral adminstration.

Three cohorts of Normal mice were used for this experiment. Each cohort contains five adult mice. The first cohort was used as a "Control group" and saline solution was injected to the control group. The second cohort was used as the "Low dose group" and AAV vector at $1e^{13}$

vg/kg concentration was injected to the low dose group. The Third cohort was used a "High dose group" and AAV vector at $1e^{14}$ vg/kg concentration was injected to the high dose group. The process of generating viral particles from AAVconstruct and injecting the recombinant AAV viral paritcles comprising ENPP1 fusion proteins into normal mice is schematically shown in Figure 4. Mice from all cohorts were bled at 7^{th}, 28^{th}, 56^{th} and 112^{th} day post injection to collect blood plasma and serum.

Blood was collected into heparin-treated tubes. The samples were centrifuged at top speed (~20kg) at 4°C for 20min. The flow-through was collected and placed on dry ice to flash freeze the samples. The samples were stored at -80°C for later use in assay.

The samples collected were first assayed to determine the activity levels of ENPP1 using the colorimetric substrate, p-nitrophenyl thymidine 5′-monophosphate (Sigma) as described in Example 10. The results of the ENPP1 activity assay are in Figure 9 and they show that there is a dose dependent increase in ENPP1 activity post injection. Normal mouse plasma was used as a reference standard to normalize the ENPP1 activity levels and One-way ANOVA was used for statistical analysis. Figure 9 shows that the ENPP1 activity levels were higher in the low dose group when compared with that of the control group. Similarly, the ENPP1 activity levels were higher in the high dose group when compared with that of the low dose group and the control group.

The samples were then assayed to determine the concentration of ENPP1 using sandwich ELISA assay with ENPP1 polyclonal antibody derived from Sigma (SAB1400199) following the protocols taught in Example 10. The assay was then repeated using plasma samples obtained from control, low dose and high dose cohorts on 7, 28 ,56 and 112 days post viral injection. The absorbance generated in each plasma sample was correlated with the standard curve of ENPP1-Fc to determine concentration of ENPP1-Fc in the plasma samples.

The results of ENPP1 concentration assay are shown in Figure 8 and they show a dose dependent increase in ENPP1 concentration post viral vector injection. Normal mouse plasma was used as a reference standard to normalize the ENPP1 concentration levels and One-way ANOVA was used for statistical analysis. Figure 8 shows that the ENPP1 concentration was higher in the low dose group when compared with that of the control group. Similarly, the ENPP1 levels were higher in the high dose group when compared with that of the low dose group and the control group.

Other Embodiments

From the foregoing description, it will be apparent that variations and modifications may be made to the invention described herein to adopt it to various usages and conditions, including the use of different signal sequences to express functional variants of ENPP1 or ENPP3 or combinations thereof in different viral vectors having different promoters or enhancers or different cell types known in art to treat any diseases characterized by the presence of pathological calcification or ossification are within the scope according to the invention. Other embodiments according to the invention are within the following claims.

Recitation of a listing of elements in any definition of a variable herein includes definitions of that variable as any single element or combination (or sub combination) of listed elements. Recitation of an embodiment herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

All publications and patent applications mentioned in the specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

Other embodiments are within the following claims.

CLAIMS

1. A recombinant polynucleotide encoding a precursor polypeptide comprising an Azurocidin signal peptide fused to ectonucleotide pyrophosphatase/phosphodiesterase-1 (ENPP1) or to ectonucleotide pyrophosphatase/phosphodiesterase-3 (ENPP3), wherein upon expression of said polynucleotide in mammalian cells, said precursor polypeptide is proteolytically cleaved to produce soluble ENPP1 or soluble ENPP3 which is active to reduce ectopic calcification of soft tissue.

2. The recombinant polynucleotide of claim 1, wherein said polynucleotide comprises a vector or a plasmid.

3. The recombinant polynucleotide of claim 1, wherein said vector or said plasmid is capable of expressing said encoded polypeptide.

4. The recombinant polynucleotide of claim 3, wherein said vector is a viral vector.

5. The recombinant polynucleotide of claim 4, wherein the viral vector is an Adeno-associated viral (AAV) vector.

6. The recombinant polynucleotide of any one of claims 1-5, wherein said polynucleotide encodes said Azurocidin signal peptide fused to said ENPP1 or said Azurocidin signal peptide fused to said ENPP3 and said ENPP1 or said ENPP3 fused to an Fc polypeptide to form in amino to carboxy terminal order Azurocidin signal peptide-ENPP1-Fc or Azurocidin signal peptide-ENPP3-Fc, respectively.

7. The recombinant polynucleotide of any one of claims 1-5, wherein said polynucleotide encodes said Azurocidin signal peptide fused to said ENPP1 or said Azurocidin signal peptide fused to said ENPP3 and said ENPP1 or said ENPP3 fused to human serum albumin to form in amino to carboxy terminal order Azurocidin signal peptide-ENPP1-albumin or Azurocidin signal peptide-ENPP3-albumin, respectively.

8. A viral vector comprising and capable of expressing a nucleic acid sequence encoding a signal peptide fused to the N-terminus of ENPP1 or ENPP3.

9. The viral vector of claim 8, wherein the vector comprises a promoter.

10. The viral vector of claim 9, wherein said promoter is a liver specific promoter.

11. The viral vector of claim 10, wherein the liver specific promoter is selected from the group consisting of: albumin promoter, phosphoenol pyruvate carboxykinase (PEPCK) promoter and alpha-1-antitrypsin promoter.

12. The viral vector of any one of claims 8-11, wherein the vector comprises a sequence encoding a polyadenylation signal.

13. The viral vector of any one of claim 8-12, wherein the signal peptide is an Azurocidin signal peptide.

14. The viral vector of any one of claims 8-13, wherein the viral vector is an Adeno-associated viral (AAV) vector.

15. The viral vector of claim 14, said AAV vector having a serotype selected from the group consisting of: AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, and AAV-rh74.

16. The viral vector of any one of claims 13-15, wherein said polynucleotide encodes said Azurocidin signal peptide fused to said ENPP1 or said Azurocidin signal peptide fused to said ENPP3, and said ENPP1 or said ENPP3 fused to an Fc polypeptide to form in amino to carboxy terminal order Azurocidin signal peptide-ENPP1-Fc or Azurocidin signal peptide-ENPP3-Fc, respectively.

17. The viral vector of any one of claims 13-15, wherein said polynucleotide encodes said Azurocidin signal peptide fused to said ENPP1 or said Azurocidin signal peptide fused to said ENPP3, and said ENPP1 or said ENPP3 fused to human serum albumin to form in amino to carboxy terminal order Azurocidin signal peptide-ENPP1-albumin or Azurocidin signal peptide-ENPP3-albumin, respectively.

18. A method of obtaining a recombinant viral vector according to any one of claims 8-17, comprising the steps of:

i. providing a cell comprising a polynucleotide according to any one of claims 1-7,

ii. maintaining the cell under conditions adequate for assembly of the virus, and

iii. purifying the viral vector produced by the cell.

19. A method of providing ENPP1 or ENPP3 protein to a mammal, the method comprising:

administering to said mammal a viral vector according to any one of claims 8-17.

20. A pharmaceutical composition comprising the viral vector of any one of claims 8-17 and a physiologically compatible carrier.

21. A method of preventing or reducing the progression of a disease in a mammal in need thereof, the method comprising administering to said mammal a therapeutically effective amount of the pharmaceutical composition of claim 20, wherein the disease is selected from the group consisting of: X-linked hypophosphatemia (XLH), Chronic kidney disease (CKD), Mineral bone disorders (MBD), vascular calcification, pathological calcification of soft tissue, pathological ossification of soft tissue, Generalized arterial calcification of infants (GACI), and Ossification of posterior longitudinal ligament (OPLL), whereby said disease in said mammal is prevented or its progress reduced.

22. A cell comprising a polynucleotide according to any one of claims 1-7.

23. A method of treating or preventing a disease or disorder of pathological calcification or pathological ossification in a subject in need thereof, comprising administering a therapeutically effective amount of a viral vector which encodes a recombinant ENPP1 or ENPP3 polypeptide to said subject, thereby treating or preventing said disease or disorder.

24. A method of of treating a subject having an ENPP1 protein deficiency, comprising administering a therapeutically effective amount of a viral vector which encodes a recombinant ENPP1 or ENPP3 polypeptide to said subject, thereby treating said subject.

25. The method of claim 23 or 24, wherein said disease or disorder or said ENPP1 protein deficiency is associated with a loss of function mutation in an NPP1 gene or a loss of function mutation in an ABCC6 gene in said subject.

26. The method of claim 23-25, wherein said viral vector encodes recombinant ENPP1 polypeptide.
27. The method of claim 23-25, wherein said viral vector encodes recombinant ENPP3 polypeptide.
28. The method of claim 23-26, wherein said viral vector encodes a recombinant ENPP1-Fc fusion polypeptide or a recombinant ENPP1-albumin fusion polypeptide.
29. The method of claim 27, wherein said viral vector encodes a recombinant ENPP3-Fc fusion polypeptide or a recombinant ENPP3-albumin fusion polypeptide.
30. The method of claim 23-29, wherein said viral vector encodes a recombinant polypeptide comprising a signal peptide fused to ENPP1 or ENPP3.
31. The method of claim 23-30, wherein said vector encodes ENPP1-Fc or ENPP1-albumin.
32. The method of claim 23-30, wherein said signal peptide is an azurocidin signal peptide, an NPP2 signal peptide, or an NPP7 signal peptide.
33. The method of claim 23-30, wherein the viral vector is Adeno-Associated Viral Vector, or Herpes Simplex Vector, or Alphaviral Vector, or Lentiviral Vectors.
34. The method of claim 33, wherein the serotype of Adeno-Associated viral vector (AAV) is AAV1, or AAV2, or AAV3, or AAV4, or AAV5, or AAV6, or AAV7, or AAV8, or AAV9, or AAV-rh74.
35. The method of claim 23-32, wherein the viral vector is an Adeno-Associated viral (AAV) vector encoding a recombinant polypeptide comprising an Azurocidin signal peptide fused to ENPP1-Fc fusion polypeptide.
36. The method of claim 35, wherein said AAV vector encoding said ENPP1-Fc fusion polypeptide is administered to subjects at a dosage of 1×10^{12} to 1×10^{15} vg/kg.
37. The method of claim 35, wherein said dosage is 1×10^{13} to 1×10^{14} vg/kg.
38. The method of claim 35, wherein said AAV vector is administered to a subject at a dosage of 5×10^{11} -$5x10^{15}$ vg/kg.
39. The method of claim 35, wherein said vector is an AAV vector encoding ENPP1-Fc and is administered to a subject at dosage of $1x10^{12}$-$1X10^{15}$ vg/kg.
40. The method of claim 35, wherein administration of said AAV vector encoding ENPP1-Fc polypeptide to a subject produces a dose dependent increase in plasma pyrophosphate (PPi) and a dose dependent increase in plasma ENPP1 concentration in said subject.

41. A viral vector comprising a polynucleotide sequence encoding a polypeptide comprising the catalytic domain of an ENPP1 or an ENPP3 protein.
42. The viral vector of claim 41, wherein polypeptide sequence comprises the extracellular domain of an ENPP1 or ENPP3 protein.
43. The viral vector of claim 41 or 42, wherein the polypeptide comprises the transmembrane domain of an ENPP1 or ENPP3 protein.
44. The viral vector of any one of claims 41-43, wherein the polypeptide comprises the nuclease domain of an ENPP1 or ENPP3 protein.
45. The viral vector of any one of claims 41-44, wherein the polypeptide comprises residues 99-925(Pro Ser Cys to Gln Glu Asp) of SEQ ID NO: 1.
46. The viral vector of any one of claims 41-44, wherein the polypeptide comprises residues 31-875 (Leu Leu Val to Thr Thr Ile) of SEQ ID NO: 7.
47. The viral vector of any one of claims 41-44, wherein the polypeptide comprises residues 191-591 (Val Glu Glu to Gly Ser Leu) of SEQ ID NO: 1.
48. The viral vector of any one of claims 41-44, wherein the polypeptide comprises residues 140-510 (Leu Glu Glu to Glu Val Glu) of SEQ ID NO: 7.
49. The viral vector of any one of claims 41-44, wherein the polypeptide comprises residues 1-827 (Pro Ser Cys to Gln Glu Asp) of SEQ ID NO: 92.
50. The viral vector of any one of claims 41-44, wherein the polypeptide comprises residues 1-833 (Phe Thr Ala to Gln Glu Asp) of SEQ ID NO: 89 or residues 1-830 (Gly Leu Lys to Gln Glu Asp) of SEQ ID NO: 91.
51. The viral vector according to any one of claims 41-50, wherein the viral vector is not an insect viral vector.
52. The viral vector according to any one of claims 41-51, wherein the viral vector infects mammalian cells.
53. The viral vector according to any one of claims 41-52, wherein the polynucleotide sequence encodes a promoter sequence.
54. The viral vector of claim 53, wherein said promoter is a liver specific promoter.
55. The viral vector of claim 54, wherein the liver specific promoter is selected from the group consisting of: albumin promoter, phosphoenol pyruvate carboxykinase (PEPCK) promoter, and alpha-1-antitrypsin promoter.

56. The viral vector of any one of claims 41-55, wherein the polynucleotide sequence comprises a nucleotide sequence encoding a polyadenylation signal.
57. The viral vector of any one of claim 41-55, wherein the polynucleotide encodes a signal peptide amino-terminal to nucleotide sequence encoding the ENPP1 or ENPP3 protein.
58. The viral vector of claim 57, wherein the signal peptide is an Azurocidin signal peptide.
59. The viral vector of any one of claims 41-58, wherein the viral vector is an Adeno-associated viral (AAV) vector.
60. The viral vector of claim 59, said AAV vector having a serotype selected from the group consisting of: AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, and AAV-rh74.
61. The viral vector of any one of claims 41-60, wherein said polynucleotide sequence encodes said Azurocidin signal peptide fused to said ENPP1 or said Azurocidin signal peptide fused to said ENPP3, and said ENPP1 or said ENPP3 fused to an Fc polypeptide to form in amino to carboxy terminal order Azurocidin signal peptide-ENPP1-Fc or Azurocidin signal peptide-ENPP3-Fc, respectively.
62. The viral vector of any one of claims 41-60, wherein said polynucleotide sequence encodes said Azurocidin signal peptide fused to said ENPP1 or said Azurocidin signal peptide fused to said ENPP3, and said ENPP1 or said ENPP3 fused to human serum albumin to form in amino to carboxy terminal order Azurocidin signal peptide-ENPP1-albumin or Azurocidin signal peptide-ENPP3-albumin, respectively.
63. The viral vector of any one of claims 41-62, wherein the polypeptide is a fusion protein comprising: (i) an ENPP1 protein or an ENPP3 protein and (ii) a half-life extending domain.
64. The viral vector of claim 63, wherein the half-life extending domain is an IgG Fc domain or a functional fragment of the IgG Fc domain capable of extending the half-life of the polypeptide in a mammal, relative to the half-life of the polypeptide in the absence of the IgG Fc domain or functional fragment thereof.
65. The viral vector of claim 63, wherein the half-life extending domain is an albumin domain or a functional fragment of the albumin domain capable of extending the half-life of the polypeptide in a mammal, relative to the half-life of the polypeptide in the absence of the albumin domain or functional fragment thereof.

66. The viral vector any one of claims 63-65, wherein the half-life extending domain is carboxyterminal to the ENPP1 or ENPP3 protein in the fusion protein.
67. The viral vector according to claim 64 or 66, wherein the IgG Fc domain comprises the amino acid sequence as shown in SEQ ID NO: 34
68. The viral vector according to claim 65 or 66, wherein the albumin domain comprises the amino acid sequence as shown in SEQ ID NO: 35
69. The viral vector according to any one of claims 41 to 68, wherein the polynucleotide encodes a linker sequence.
70. The viral vector according to claim 69, wherein the linker sequence is selected from the group consisting of SINs: 57 to 88 and 94.
71. The viral vector of any one of claims 63-70, wherein the linker sequence joins the ENPP1 or ENPP3 protein and the half-life extending domain of the fusion protein.
72. The viral vector of any one of claims 41-64, 66, or 67, wherein the polypeptide comprises the amino acid sequence depicted in SEQ ID NO: 89, 91, 92 and 93.
73. A method for producing a recombinant viral vector, the method comprising:

i. providing a cell or population of cells comprising a polynucleotide encoding a polypeptide comprising the catalytic domain of an ENPP1 or an ENPP3 protein, wherein the cell expresses viral proteins essential for packaging and/or assembly of the polynucleotide into a recombinant viral vector; and

ii. maintaining the cell or population of cells under conditions adequate for the assembly of packaging of said recombinant viral vector comprising the polynucleotide.

74. The method of claim 73, wherein the cell is a mammalian cell.
75. The method of claim 74, wherein the mammalian cell is a rodent cell or a human cell.
76. The method of any one of claims 73 to 75, wherein the viral vector is the vector according to any one of claims 41-72.
77. The method of any one of claims 73-76, further comprising purifying the recombinant viral vector from the cell or population of cells, or from the media in which the cell or population of cells were maintained.
78. The recombinant viral vector purified from the method according to claim 77.

79. A pharmaceutical composition comprising the viral vector according to any one of claims 41-72 or the recombinant viral vector of claim 78 and a pharmaceutically acceptable carrier.

80. A method of preventing or reducing the progression of a disease in a mammal in need thereof, the method comprising: administering to said mammal a therapeutically effective amount of the pharmaceutical composition of claim 79 to thereby prevent or reduce the progression of the disease or disorder.

81. The method of claim 80, wherein the mammal is a human.

82. The method of claim 81 or 82, wherein the disease is selected from the group consisting of: X-linked hypophosphatemia (XLH), Chronic kidney disease (CKD), Mineral bone disorders (MBD), vascular calcification, pathological calcification of soft tissue, pathological ossification of soft tissue, PXE, Generalized arterial calcification of infants (GACI), and Ossification of posterior longitudinal ligament (OPLL).

83. A method of treating or preventing a disease or disorder of pathological calcification or pathological ossification in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the viral vector according to any one of claims 41-72 or the pharmaceutical composition of claim 79, thereby treating or preventing said disease or disorder.

84. A method of treating a subject having an ENPP1 protein deficiency, the method comprising administering to the subject a therapeutically effective amount of the viral vector according to any one of claims 41-72 or the pharmaceutical composition of claim 79, thereby treating said subject.

85. The method of claim 84, wherein said disease or disorder or said ENPP1 protein deficiency is associated with a loss of function mutation in an NPP1 gene or a loss of function mutation in an ABCC6 gene in said subject.

86. The method of any one of claims 80-85, wherein the viral vector or pharmaceutical composition is administered at a dosage of 1×10^{12} to 1×10^{15} vg/kg of the subject or mammal.

87. The method of any one of claims 80-85, wherein the viral vector or pharmaceutical composition is administered at a dosage of 1×10^{13} to 1×10^{14} vg/kg of the subject or mammal.

88. The method of any one of claims 80-85, wherein the viral vector or pharmaceutical composition is administered at a dosage of 5×10^{11} -$5x10^{15}$ vg/kg of the subject or mammal.

89. The method of any one of claims 80-85, wherein the viral vector or pharmaceutical composition is administered at a dosage of $1x10^{12}$-$1X10^{15}$ vg/kg of the subject or mammal.

90. The method of any one of claims 80-89, wherein administration of said viral vector or pharmaceutical composition to the subject or mammal increases plasma pyrophosphate (PPi) and/or plasma ENPP1 or ENPP3 concentration in said subject or mammal.

91. The method of any one of claims 80-89, further comprising detecting or measuring in a biological sample obtained from the subject or mammal one or more of the following parameters: (i) the concentration of pyrophosphate, (ii) the expression level of ENPP1 or ENPP3, and (iii) the enzymatic activity of ENPP1 or ENPP3.

92. The method of claim 91, wherein the detecting or measuring occurs before administering the viral vector or pharmaceutical composition.

93. The method of claim 91 or 92, wherein the detecting or measuring occurs at or around the same time as the administering of the viral vector or pharmaceutical composition.

94. The method of any one of claims 91-93, wherein the detecting or measuring occurs following the administration of the viral vector or pharmaceutical composition.

FIG. 1 – SCHEMATIC VIEW OF EXPRESSION VECTORS

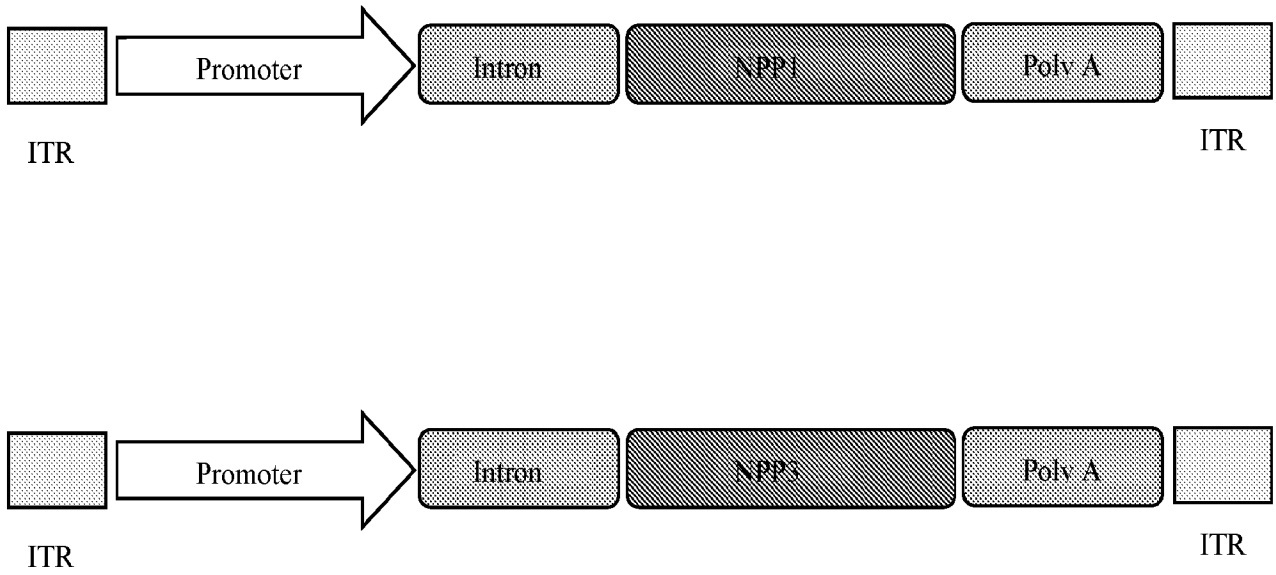
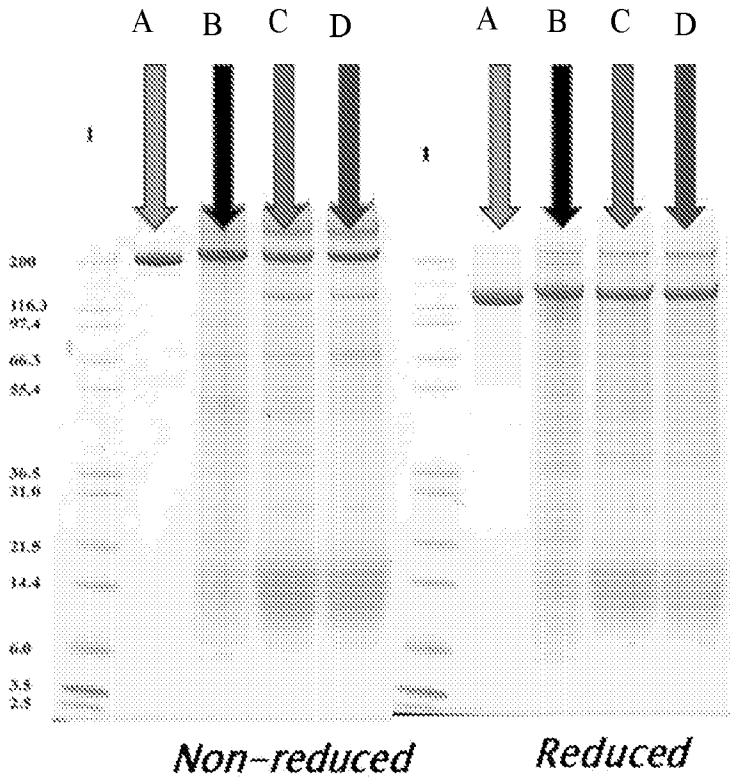


FIG. 2 – COMPARISON OF DIFFERENT SIGNAL SEQUENCES

Signal Sequence	*Titer (mg/L)*
Azurocidin Signal sequence	731
NPP2 Signal Sequence	127
NPP7 Signal Sequence	136



A ENPP1 Reference Standard

B ENPP1 using Azurocidin signal sequence

C ENPP1 using NPP2 signal sequence

D ENPP1 using NPP7 signal sequence

FIG. 3 - PLASMID MAP OF ENPP1-FC

TR141-CMV-ENPP1-FC (4653bp)

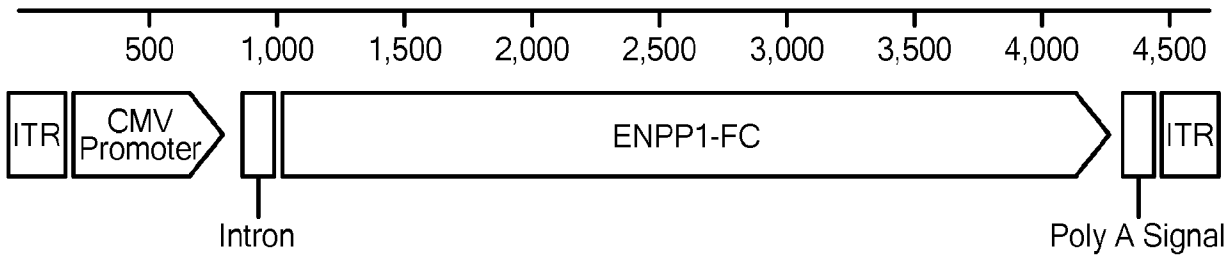


FIG. 4 – SCHEMATIC VIEW OF ADMINSTRATION

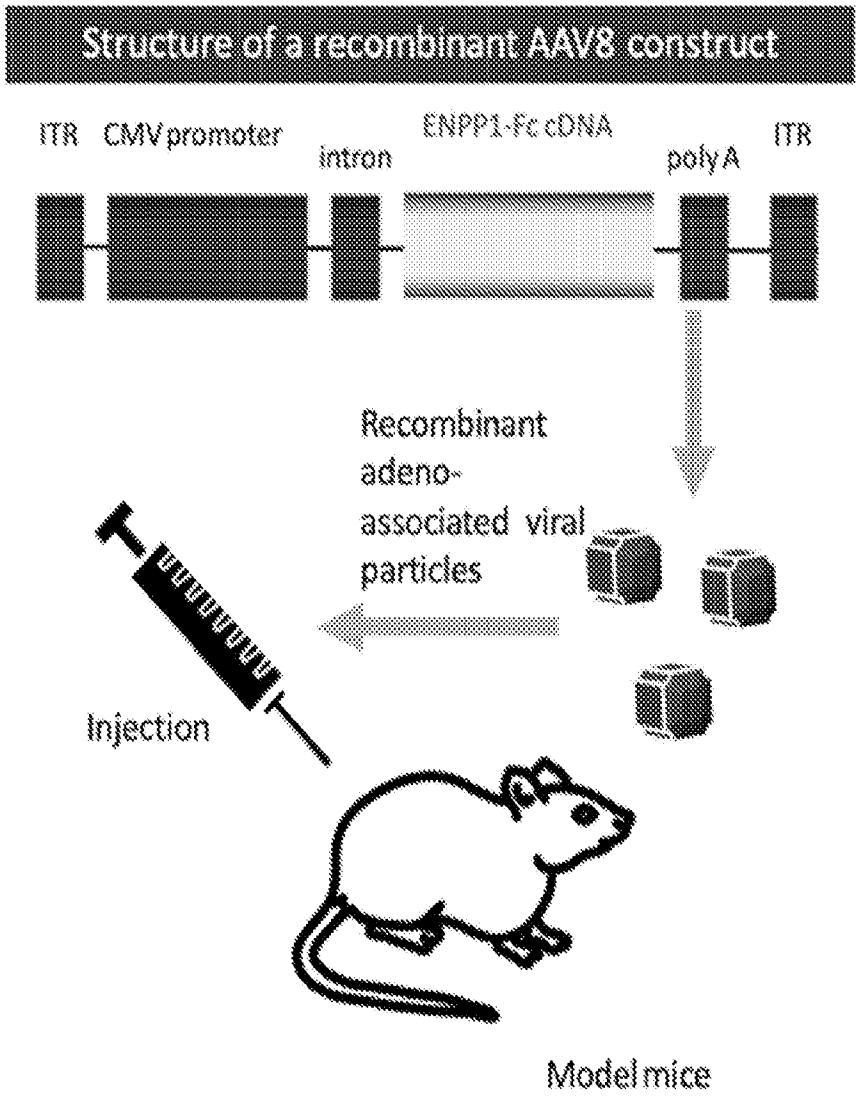


FIG. 5 – DOSE DEPENDENT INCREASE IN ENPP1 ACTIVITY AFTER POST VIRAL VECTOR ADMINISTRATION

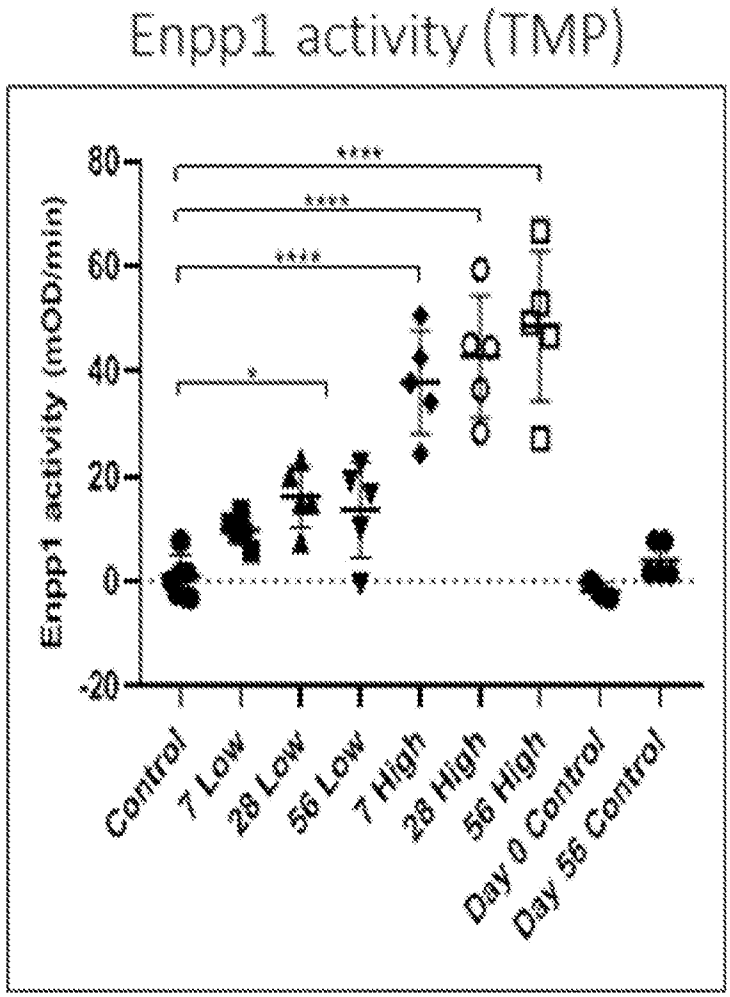


FIG. 6 – DOSE DEPENDENT INCREASE IN ENPP1 CONCENTRATION POST VIRAL VECTOR ADMINISTRATION

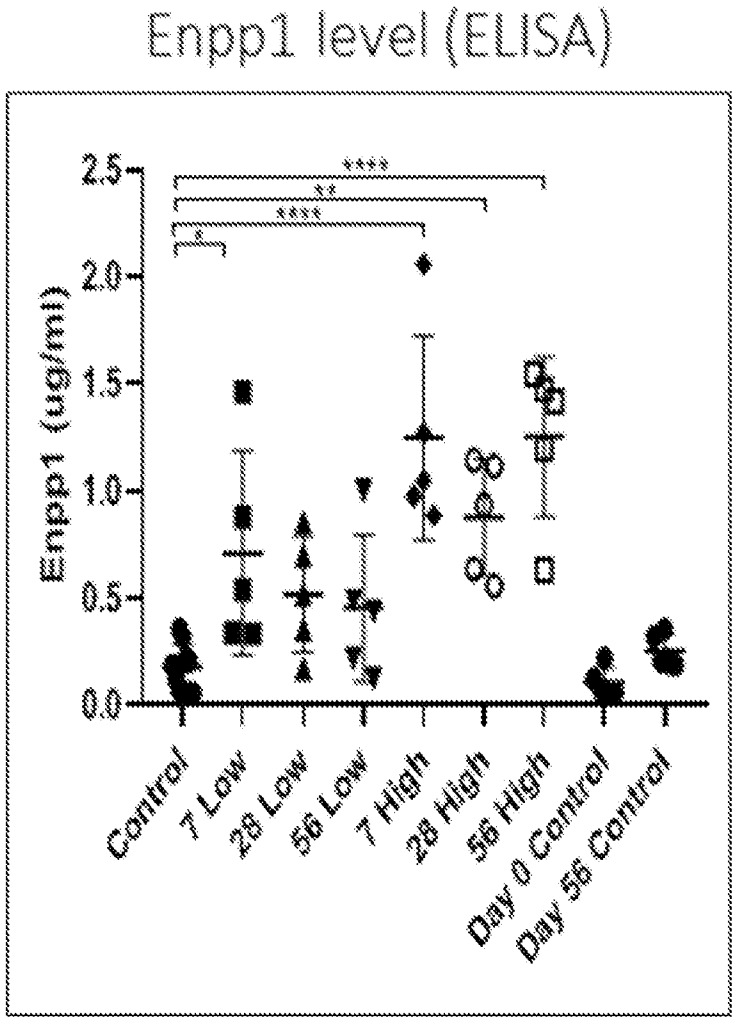


FIG. 7 – DOSE DEPENDENT INCREASE IN PLASMA PYROPHOSPHATE (PPi) LEVELS POST VIRAL VECTOR ADMINISTRATION

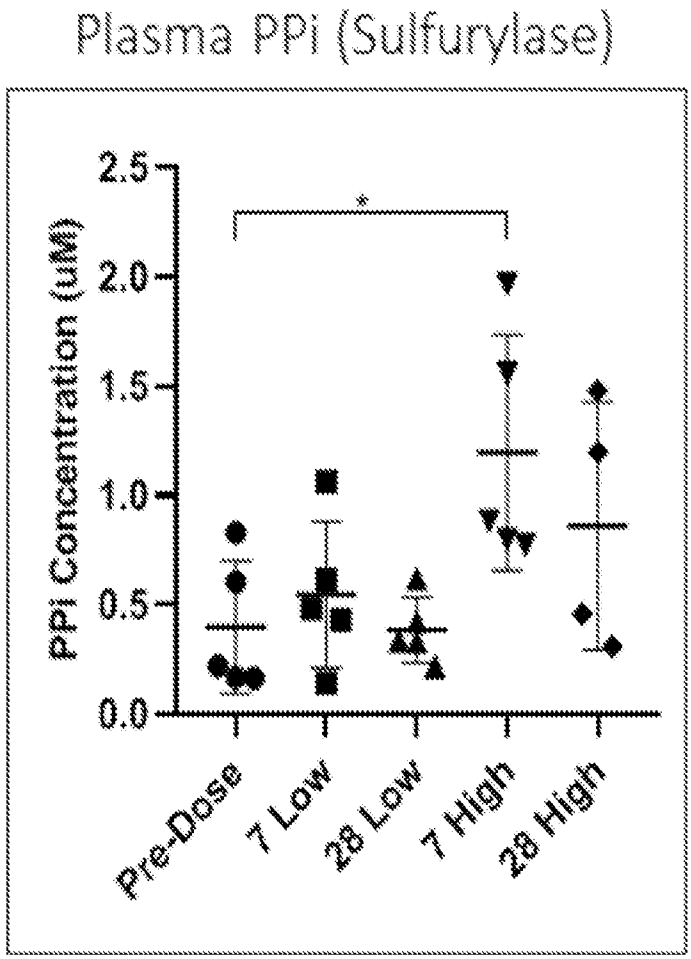


FIG. 8 – PERSISTENT EXPRESSION OF ENPP1 FOR UP TO 112 DAYS POST VIRAL VECTOR ADMINISTRATION

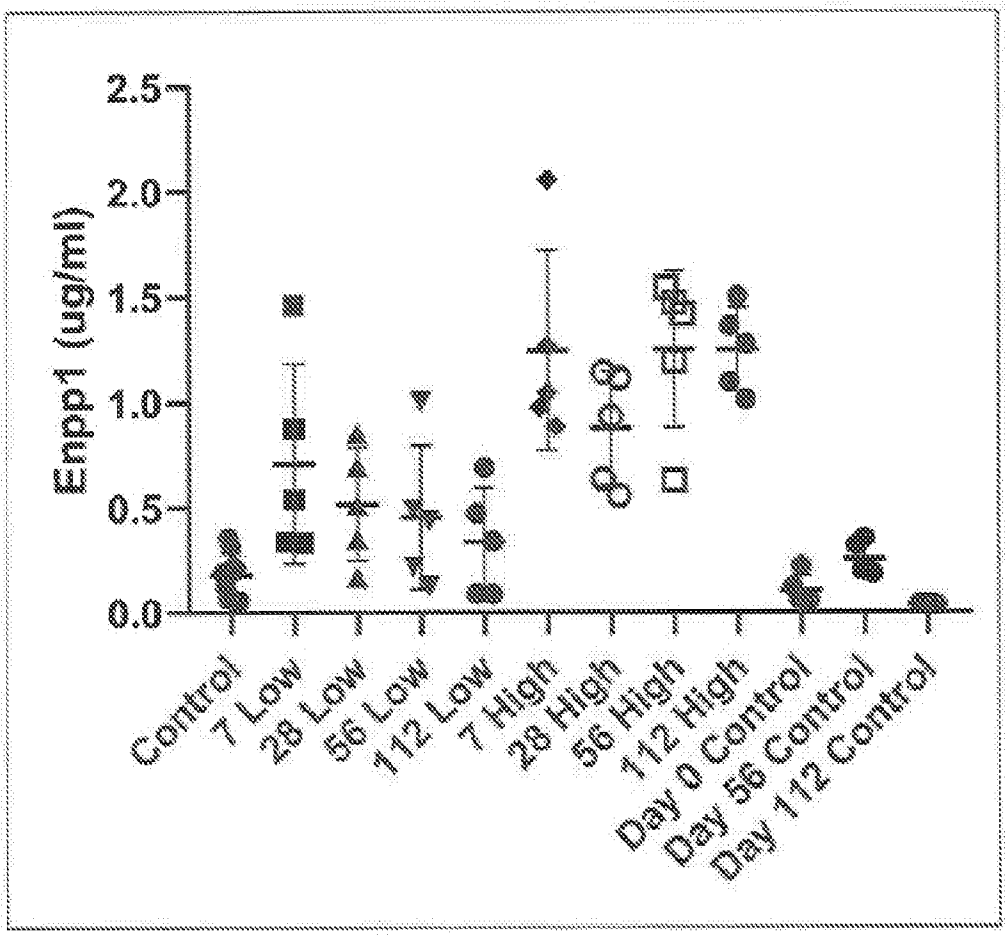
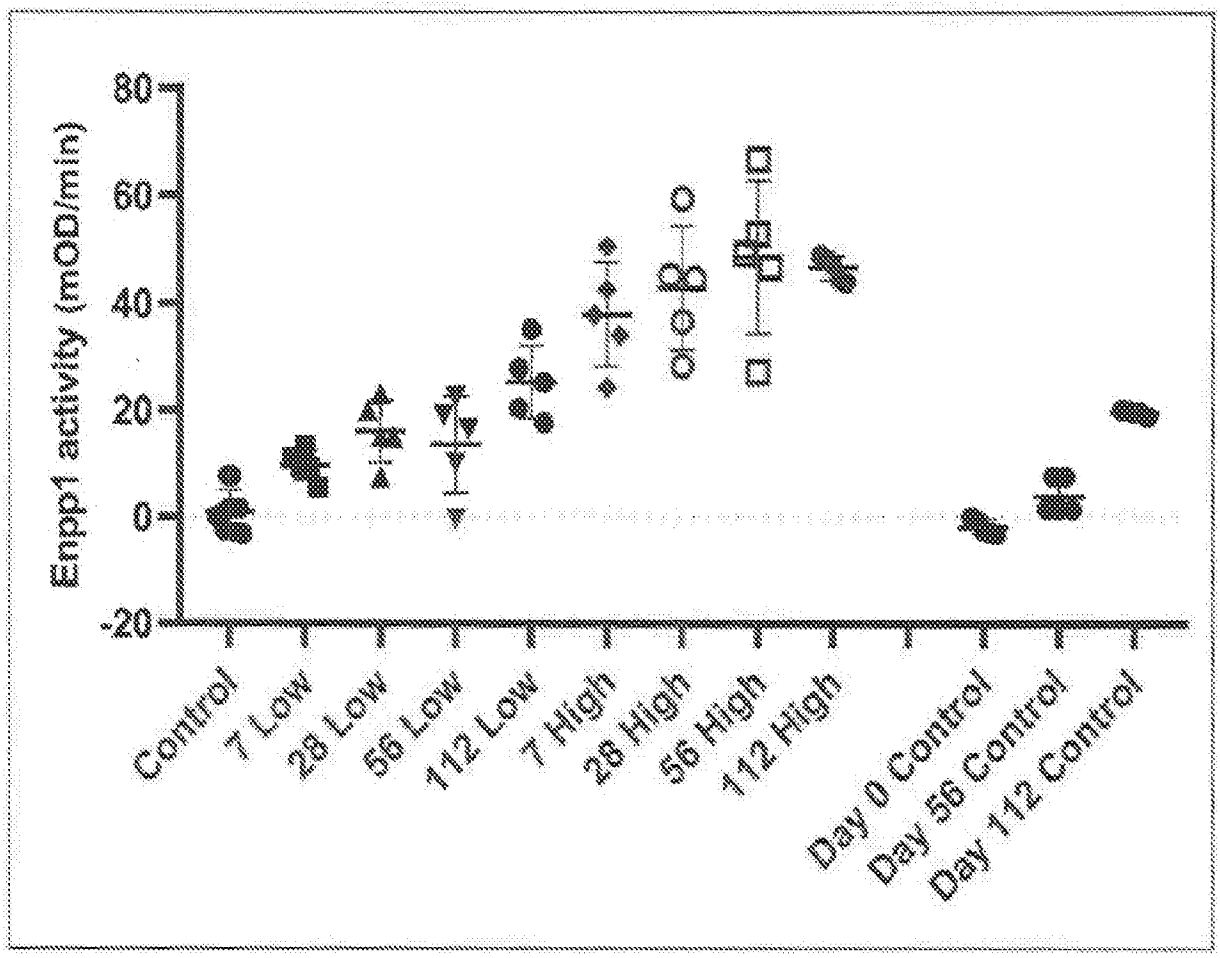


FIG. 9 – DOSE DEPENDENT INCREASE IN ENPP1 ACTIVITY POST VIRAL VECTOR ADMINISTRATION



SEQUENCE LISTING

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Jungles, Steven

<120> TREATMENT OF DISEASES INVOLVING DEFICIENCY OF ENPP1 OR ENPP3.

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<170> PatentIn version 3.5

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20 25 30

Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala Ser
35 40 45

Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala
50 55 60

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

Val Leu Ser Val Cys Val Leu Thr Thr Ile Leu Gly Cys Ile Phe Gly
85 90 95

```
Leu Lys Pro Ser Cys Ala Lys Glu Val Lys Ser Cys Lys Gly Arg Cys
            100                 105                 110

Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala Ala Cys Val Glu
        115                 120                 125

Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys Ile Glu Pro Glu
    130                 135                 140

His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu Lys Arg Leu Thr
145                 150                 155                 160

Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp Lys Gly Asp Cys
                165                 170                 175

Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp Val Glu
            180                 185                 190

Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro Ala Gly Phe Glu
        195                 200                 205

Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe Arg Ala Glu Tyr
    210                 215                 220

Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser Lys Leu Lys Lys
225                 230                 235                 240

Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr Lys Thr
                245                 250                 255

Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu Ser His
            260                 265                 270

Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala Ser Phe
        275                 280                 285

Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys Gly Glu
    290                 295                 300
```

```
Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly Thr Phe
305                 310                 315                 320

Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro Asp Ile
                325                 330                 335

Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Leu Ala
            340                 345                 350

Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His Phe Tyr
        355                 360                 365

Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr Gly Pro
    370                 375                 380

Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly Met Val
385                 390                 395                 400

Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg Cys Leu
                405                 410                 415

Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser Cys Lys
            420                 425                 430

Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn Ile Lys
        435                 440                 445

Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val Pro Asp
    450                 455                 460

Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu Ser Cys
465                 470                 475                 480

Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe Leu Pro
                485                 490                 495

Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu Thr Phe
            500                 505                 510

Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu Arg Lys
        515                 520                 525
```

```
Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser Asn Met
    530                 535                 540

Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys His Gly Ile Glu
545                 550                 555                 560

Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu
                565                 570                 575

Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn
            580                 585                 590

His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His Pro Lys Glu Val
        595                 600                 605

His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp Asn Leu
    610                 615                 620

Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe Gln Thr
625                 630                 635                 640

Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His Glu Thr
                645                 650                 655

Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr Ile Cys
            660                 665                 670

Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp Ile Leu
        675                 680                 685

Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser Phe Ser
    690                 695                 700

Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile Pro Leu
705                 710                 715                 720

Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val Ser
                725                 730                 735
```

```
Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser Gly Ile
            740                 745                 750

Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln Ser
        755                 760                 765

Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys Tyr
    770                 775                 780

Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val Phe Asp
785                 790                 795                 800

Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln Lys
                805                 810                 815

Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe Phe
            820                 825                 830

Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His Cys
        835                 840                 845

Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp Asn
    850                 855                 860

Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu Glu
865                 870                 875                 880

Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile Thr
                885                 890                 895

Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile Leu
            900                 905                 910

Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp
        915                 920                 925
```

<210> 2
<211> 1077
<212> PRT
<213> Artificial Sequence

<220>

<223> Azurocidin-ENPP1-FC

<220>
<221> SIGNAL
<222> (19)..(20)
<223> Cleavage point of the signal sequence

<400> 2

```
Met Thr Arg Leu Thr Val Leu Ala Leu Leu Ala Gly Leu Leu Ala Ser
1               5                  10                  15

Ser Arg Ala Ala Pro Ser Cys Ala Lys Glu Val Lys Ser Cys Lys Gly
            20                  25                  30

Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala Ala Cys
        35                  40                  45

Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys Ile Glu
    50                  55                  60

Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu Lys Arg
65                  70                  75                  80

Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp Lys Gly
                85                  90                  95

Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp
            100                 105                 110

Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro Ala Gly
        115                 120                 125

Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe Arg Ala
    130                 135                 140

Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser Lys Leu
145                 150                 155                 160

Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr
                165                 170                 175
```

```
Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu
            180                 185                 190

Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala
        195                 200                 205

Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys
    210                 215                 220

Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly
225                 230                 235                 240

Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro
                245                 250                 255

Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile
            260                 265                 270

Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His
        275                 280                 285

Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr
    290                 295                 300

Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly
305                 310                 315                 320

Met Val Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg
                325                 330                 335

Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser
            340                 345                 350

Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn
        355                 360                 365

Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val
    370                 375                 380

Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu
385                 390                 395                 400
```

```
Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe
                405                 410                 415

Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu
            420                 425                 430

Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu
        435                 440                 445

Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser
    450                 455                 460

Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys His Gly
465                 470                 475                 480

Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys
                485                 490                 495

Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser
            500                 505                 510

Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His Pro Lys
        515                 520                 525

Glu Val His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp
    530                 535                 540

Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe
545                 550                 555                 560

Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His
                565                 570                 575

Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr
            580                 585                 590

Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp
        595                 600                 605
```

```
Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser
    610                 615                 620

Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile
625                 630                 635                 640

Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys
                645                 650                 655

Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser
            660                 665                 670

Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr
        675                 680                 685

Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg
    690                 695                 700

Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val
705                 710                 715                 720

Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg
                725                 730                 735

Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His
            740                 745                 750

Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu
        755                 760                 765

His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr
    770                 775                 780

Asp Asn Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val
785                 790                 795                 800

Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His
                805                 810                 815

Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp
            820                 825                 830
```

```
Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp Leu
        835                 840                 845

Ile Asn Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
    850                 855                 860

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
865                 870                 875                 880

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
                885                 890                 895

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
            900                 905                 910

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
        915                 920                 925

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
    930                 935                 940

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
945                 950                 955                 960

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
                965                 970                 975

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
            980                 985                 990

Val Ser Leu Thr Cys Leu Val Lys  Gly Phe Tyr Pro Ser  Asp Ile Ala
        995                 1000                1005

Val Glu  Trp Glu Ser Asn Gly  Gln Pro Glu Asn Asn  Tyr Lys Thr
    1010                1015                1020

Thr Pro  Pro Val Leu Asp Ser  Asp Gly Ser Phe Phe  Leu Tyr Ser
    1025                1030                1035
```

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
    1040   1045   1050

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
    1055   1060   1065

Lys Ser Leu Ser Leu Ser Pro Gly Lys
    1070   1075

<210> 3
<211> 1468
<212> PRT
<213> Artificial Sequence

<220>
<223> Azurocidin-ENPP1-Alb

<220>
<221> SIGNAL
<222> (19)..(20)
<223> Cleavage point of the signal sequence

<400> 3

Met Thr Arg Leu Thr Val Leu Ala Leu Leu Ala Gly Leu Leu Ala Ser
1   5   10   15

Ser Arg Ala Ala Pro Ser Cys Ala Lys Glu Val Lys Ser Cys Lys Gly
            20   25   30

Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala Ala Cys
        35   40   45

Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys Ile Glu
    50   55   60

Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu Lys Arg
65   70   75   80

Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp Lys Gly
                85   90   95

Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp
            100   105   110

```
Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro Ala Gly
        115                 120                 125

Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe Arg Ala
    130                 135                 140

Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser Lys Leu
145                 150                 155                 160

Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr
                165                 170                 175

Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu
            180                 185                 190

Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala
        195                 200                 205

Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys
    210                 215                 220

Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly
225                 230                 235                 240

Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro
                245                 250                 255

Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile
            260                 265                 270

Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His
        275                 280                 285

Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr
    290                 295                 300

Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly
305                 310                 315                 320
```

```
Met Val Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg
                325                 330                 335

Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser
            340                 345                 350

Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn
        355                 360                 365

Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val
    370                 375                 380

Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu
385                 390                 395                 400

Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe
                405                 410                 415

Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu
            420                 425                 430

Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu
        435                 440                 445

Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser
    450                 455                 460

Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys His Gly
465                 470                 475                 480

Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys
                485                 490                 495

Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser
            500                 505                 510

Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His Pro Lys
        515                 520                 525

Glu Val His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp
    530                 535                 540
```

```
Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe
545                 550                 555                 560

Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His
                565                 570                 575

Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr
            580                 585                 590

Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp
        595                 600                 605

Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser
    610                 615                 620

Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile
625                 630                 635                 640

Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys
                645                 650                 655

Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser
            660                 665                 670

Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr
        675                 680                 685

Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg
    690                 695                 700

Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val
705                 710                 715                 720

Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg
                725                 730                 735

Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His
            740                 745                 750
```

```
Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu
        755                 760                 765

His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr
    770                 775                 780

Asp Asn Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val
785                 790                 795                 800

Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His
                805                 810                 815

Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp
            820                 825                 830

Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp Leu
        835                 840                 845

Ile Asn Met Lys Trp Val Thr Phe Leu Leu Leu Leu Phe Val Ser Gly
    850                 855                 860

Ser Ala Phe Ser Arg Gly Val Phe Arg Arg Glu Ala His Lys Ser Glu
865                 870                 875                 880

Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu
                885                 890                 895

Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu
            900                 905                 910

His Ala Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val
        915                 920                 925

Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe
    930                 935                 940

Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu
945                 950                 955                 960

Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe
                965                 970                 975
```

```
Leu Gln His Lys Asp Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro
            980                 985                 990

Glu Ala Glu Ala Met Cys Thr Ser  Phe Lys Glu Asn Pro  Thr Thr Phe
        995                 1000                1005

Met Gly  His Tyr Leu His Glu  Val Ala Arg Arg His  Pro Tyr Phe
    1010                1015                1020

Tyr Ala  Pro Glu Leu Leu Tyr  Tyr Ala Glu Gln Tyr  Asn Glu Ile
    1025                1030                1035

Leu Thr  Gln Cys Cys Ala Glu  Ala Asp Lys Glu Ser  Cys Leu Thr
    1040                1045                1050

Pro Lys  Leu Asp Gly Val Lys  Glu Lys Ala Leu Val  Ser Ser Val
    1055                1060                1065

Arg Gln  Arg Met Lys Cys Ser  Ser Met Gln Lys Phe  Gly Glu Arg
    1070                1075                1080

Ala Phe  Lys Ala Trp Ala Val  Ala Arg Leu Ser Gln  Thr Phe Pro
    1085                1090                1095

Asn Ala  Asp Phe Ala Glu Ile  Thr Lys Leu Ala Thr  Asp Leu Thr
    1100                1105                1110

Lys Val  Asn Lys Glu Cys Cys  His Gly Asp Leu Leu  Glu Cys Ala
    1115                1120                1125

Asp Asp  Arg Ala Glu Leu Ala  Lys Tyr Met Cys Glu  Asn Gln Ala
    1130                1135                1140

Thr Ile  Ser Ser Lys Leu Gln  Thr Cys Cys Asp Lys  Pro Leu Leu
    1145                1150                1155

Lys Lys  Ala His Cys Leu Ser  Glu Val Glu His Asp  Thr Met Pro
    1160                1165                1170
```

```
Ala Asp  Leu Pro Ala Ile Ala  Ala Asp Phe Val Glu  Asp Gln Glu
    1175                1180                1185

Val Cys  Lys Asn Tyr Ala Glu  Ala Lys Asp Val Phe  Leu Gly Thr
    1190                1195                1200

Phe Leu  Tyr Glu Tyr Ser Arg  Arg His Pro Asp Tyr  Ser Val Ser
    1205                1210                1215

Leu Leu  Leu Arg Leu Ala Lys  Lys Tyr Glu Ala Thr  Leu Glu Lys
    1220                1225                1230

Cys Cys  Ala Glu Ala Asn Pro  Pro Ala Cys Tyr Gly  Thr Val Leu
    1235                1240                1245

Ala Glu  Phe Gln Pro Leu Val  Glu Glu Pro Lys Asn  Leu Val Lys
    1250                1255                1260

Thr Asn  Cys Asp Leu Tyr Glu  Lys Leu Gly Glu Tyr  Gly Phe Gln
    1265                1270                1275

Asn Ala  Ile Leu Val Arg Tyr  Thr Gln Lys Ala Pro  Gln Val Ser
    1280                1285                1290

Thr Pro  Thr Leu Val Glu Ala  Ala Arg Asn Leu Gly  Arg Val Gly
    1295                1300                1305

Thr Lys  Cys Cys Thr Leu Pro  Glu Asp Gln Arg Leu  Pro Cys Val
    1310                1315                1320

Glu Asp  Tyr Leu Ser Ala Ile  Leu Asn Arg Val Cys  Leu Leu His
    1325                1330                1335

Glu Lys  Thr Pro Val Ser Glu  His Val Thr Lys Cys  Cys Ser Gly
    1340                1345                1350

Ser Leu  Val Glu Arg Arg Pro  Cys Phe Ser Ala Leu  Thr Val Asp
    1355                1360                1365

Glu Thr  Tyr Val Pro Lys Glu  Phe Lys Ala Glu Thr  Phe Thr Phe
    1370                1375                1380
```

```
His Ser  Asp Ile Cys Thr Leu  Pro Glu Lys Glu Lys  Gln Ile Lys
    1385                1390                1395


Lys Gln  Thr Ala Leu Ala Glu  Leu Val Lys His Lys  Pro Lys Ala
    1400                1405                1410


Thr Ala  Glu Gln Leu Lys Thr  Val Met Asp Asp Phe  Ala Gln Phe
    1415                1420                1425


Leu Asp  Thr Cys Cys Lys Ala  Ala Asp Lys Asp Thr  Cys Phe Ser
    1430                1435                1440


Thr Glu  Gly Pro Asn Leu Val  Thr Arg Cys Lys Asp  Ala Leu Ala
    1445                1450                1455


Arg Ser  Trp Ser His Pro Gln  Phe Glu Lys
    1460                1465


<210>  4
<211>  1594
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Azurocidin-ENPP1


<220>
<221>  SIGNAL
<222>  (19)..(20)
<223>  Cleavage point of the signal sequence

<400>  4

Met Thr Arg Leu Thr Val Leu Ala Leu Leu Ala Gly Leu Leu Ala Ser
1               5                  10                  15


Ser Arg Ala Ala Pro Ser Cys Ala Lys Glu Val Lys Ser Cys Lys Gly
            20                  25                  30


Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala Ala Cys
        35                  40                  45
```

```
Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys Ile Glu
    50                  55                  60

Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu Lys Arg
65                  70                  75                  80

Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp Lys Gly
                85                  90                  95

Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp
            100                 105                 110

Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro Ala Gly
        115                 120                 125

Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe Arg Ala
    130                 135                 140

Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser Lys Leu
145                 150                 155                 160

Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr
                165                 170                 175

Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu
            180                 185                 190

Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala
        195                 200                 205

Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys
    210                 215                 220

Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly
225                 230                 235                 240

Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro
                245                 250                 255

Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile
            260                 265                 270
```

```
Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His
        275                 280                 285

Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr
    290                 295                 300

Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly
305                 310                 315                 320

Met Val Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg
                325                 330                 335

Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser
            340                 345                 350

Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn
        355                 360                 365

Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val
    370                 375                 380

Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu
385                 390                 395                 400

Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe
                405                 410                 415

Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu
            420                 425                 430

Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu
        435                 440                 445

Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser
    450                 455                 460

Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys His Gly
465                 470                 475                 480
```

```
Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys
                485                 490                 495

Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser
            500                 505                 510

Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His Pro Lys
        515                 520                 525

Glu Val His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp
    530                 535                 540

Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe
545                 550                 555                 560

Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His
                565                 570                 575

Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr
            580                 585                 590

Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp
        595                 600                 605

Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser
    610                 615                 620

Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile
625                 630                 635                 640

Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys
                645                 650                 655

Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser
            660                 665                 670

Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr
        675                 680                 685

Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg
    690                 695                 700
```

```
Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val
705                 710                 715                 720

Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg
                725                 730                 735

Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His
            740                 745                 750

Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Ala Pro
        755                 760                 765

Ser Cys Ala Lys Glu Val Lys Ser Cys Lys Gly Arg Cys Phe Glu Arg
    770                 775                 780

Thr Phe Gly Asn Cys Arg Cys Asp Ala Ala Cys Val Glu Leu Gly Asn
785                 790                 795                 800

Cys Cys Leu Asp Tyr Gln Glu Thr Cys Ile Glu Pro Glu His Ile Trp
                805                 810                 815

Thr Cys Asn Lys Phe Arg Cys Gly Glu Lys Arg Leu Thr Arg Ser Leu
            820                 825                 830

Cys Ala Cys Ser Asp Asp Cys Lys Asp Lys Gly Asp Cys Cys Ile Asn
        835                 840                 845

Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp Val Glu Glu Pro Cys
    850                 855                 860

Glu Ser Ile Asn Glu Pro Gln Cys Pro Ala Gly Phe Glu Thr Pro Pro
865                 870                 875                 880

Thr Leu Leu Phe Ser Leu Asp Gly Phe Arg Ala Glu Tyr Leu His Thr
                885                 890                 895

Trp Gly Gly Leu Leu Pro Val Ile Ser Lys Leu Lys Lys Cys Gly Thr
            900                 905                 910
```

```
Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr Lys Thr Phe Pro Asn
        915                 920                 925


His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly Ile Ile
    930                 935                 940


Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala Ser Phe Ser Leu Lys
945                 950                 955                 960


Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys Gly Glu Pro Ile Trp
                965                 970                 975


Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly Thr Phe Phe Trp Pro
            980                 985                 990


Gly Ser Asp Val Glu Ile Asn Gly  Ile Phe Pro Asp Ile  Tyr Lys Met
        995                 1000                1005


Tyr Asn  Gly Ser Val Pro Phe  Glu Glu Arg Ile Leu  Ala Val Leu
    1010                1015                1020


Gln Trp  Leu Gln Leu Pro Lys  Asp Glu Arg Pro His  Phe Tyr Thr
    1025                1030                1035


Leu Tyr  Leu Glu Glu Pro Asp  Ser Ser Gly His Ser  Tyr Gly Pro
    1040                1045                1050


Val Ser  Ser Glu Val Ile Lys  Ala Leu Gln Arg Val  Asp Gly Met
    1055                1060                1065


Val Gly  Met Leu Met Asp Gly  Leu Lys Glu Leu Asn  Leu His Arg
    1070                1075                1080


Cys Leu  Asn Leu Ile Leu Ile  Ser Asp His Gly Met  Glu Gln Gly
    1085                1090                1095


Ser Cys  Lys Lys Tyr Ile Tyr  Leu Asn Lys Tyr Leu  Gly Asp Val
    1100                1105                1110


Lys Asn  Ile Lys Val Ile Tyr  Gly Pro Ala Ala Arg  Leu Arg Pro
    1115                1120                1125
```

```
Ser Asp  Val Pro Asp Lys Tyr  Tyr Ser Phe Asn Tyr  Glu Gly Ile
    1130                1135                1140

Ala Arg  Asn Leu Ser Cys Arg  Glu Pro Asn Gln His  Phe Lys Pro
    1145                1150                1155

Tyr Leu  Lys His Phe Leu Pro  Lys Arg Leu His Phe  Ala Lys Ser
    1160                1165                1170

Asp Arg  Ile Glu Pro Leu Thr  Phe Tyr Leu Asp Pro  Gln Trp Gln
    1175                1180                1185

Leu Ala  Leu Asn Pro Ser Glu  Arg Lys Tyr Cys Gly  Ser Gly Phe
    1190                1195                1200

His Gly  Ser Asp Asn Val Phe  Ser Asn Met Gln Ala  Leu Phe Val
    1205                1210                1215

Gly Tyr  Gly Pro Gly Phe Lys  His Gly Ile Glu Ala  Asp Thr Phe
    1220                1225                1230

Glu Asn  Ile Glu Val Tyr Asn  Leu Met Cys Asp Leu  Leu Asn Leu
    1235                1240                1245

Thr Pro  Ala Pro Asn Asn Gly  Thr His Gly Ser Leu  Asn His Leu
    1250                1255                1260

Leu Lys  Asn Pro Val Tyr Thr  Pro Lys His Pro Lys  Glu Val His
    1265                1270                1275

Pro Leu  Val Gln Cys Pro Phe  Thr Arg Asn Pro Arg  Asp Asn Leu
    1280                1285                1290

Gly Cys  Ser Cys Asn Pro Ser  Ile Leu Pro Ile Glu  Asp Phe Gln
    1295                1300                1305

Thr Gln  Phe Asn Leu Thr Val  Ala Glu Glu Lys Ile  Ile Lys His
    1310                1315                1320
```

```
Glu Thr  Leu Pro Tyr Gly Arg  Pro Arg Val Leu Gln  Lys Glu Asn
    1325                1330                1335

Thr Ile  Cys Leu Leu Ser Gln  His Gln Phe Met Ser  Gly Tyr Ser
    1340                1345                1350

Gln Asp  Ile Leu Met Pro Leu  Trp Thr Ser Tyr Thr  Val Asp Arg
    1355                1360                1365

Asn Asp  Ser Phe Ser Thr Glu  Asp Phe Ser Asn Cys  Leu Tyr Gln
    1370                1375                1380

Asp Phe  Arg Ile Pro Leu Ser  Pro Val His Lys Cys  Ser Phe Tyr
    1385                1390                1395

Lys Asn  Asn Thr Lys Val Ser  Tyr Gly Phe Leu Ser  Pro Pro Gln
    1400                1405                1410

Leu Asn  Lys Asn Ser Ser Gly  Ile Tyr Ser Glu Ala  Leu Leu Thr
    1415                1420                1425

Thr Asn  Ile Val Pro Met Tyr  Gln Ser Phe Gln Val  Ile Trp Arg
    1430                1435                1440

Tyr Phe  His Asp Thr Leu Leu  Arg Lys Tyr Ala Glu  Glu Arg Asn
    1445                1450                1455

Gly Val  Asn Val Val Ser Gly  Pro Val Phe Asp Phe  Asp Tyr Asp
    1460                1465                1470

Gly Arg  Cys Asp Ser Leu Glu  Asn Leu Arg Gln Lys  Arg Arg Val
    1475                1480                1485

Ile Arg  Asn Gln Glu Ile Leu  Ile Pro Thr His Phe  Phe Ile Val
    1490                1495                1500

Leu Thr  Ser Cys Lys Asp Thr  Ser Gln Thr Pro Leu  His Cys Glu
    1505                1510                1515

Asn Leu  Asp Thr Leu Ala Phe  Ile Leu Pro His Arg  Thr Asp Asn
    1520                1525                1530
```

Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu
    1535   1540   1545

Glu Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His
    1550   1555   1560

Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser
    1565   1570   1575

Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu
    1580   1585   1590

Asp

<210> 5
<211> 888
<212> PRT
<213> Artificial Sequence

<220>
<223> ENPP2 Amino Acid Sequence - Wild Type

<400> 5

Met Ala Arg Arg Ser Ser Phe Gln Ser Cys Gln Ile Ile Ser Leu Phe
1   5   10   15

Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly Phe Thr Ala His Arg
            20   25   30

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

Asp Ser Pro Trp Thr Asn Ile Ser Gly Ser Cys Lys Gly Arg Cys Phe
    50   55   60

Glu Leu Gln Glu Ala Gly Pro Pro Asp Cys Arg Cys Asp Asn Leu Cys
65   70   75   80

Lys Ser Tyr Thr Ser Cys Cys His Asp Phe Asp Glu Leu Cys Leu Lys
                85   90   95

```
Thr Ala Arg Gly Trp Glu Cys Thr Lys Asp Arg Cys Gly Glu Val Arg
            100                 105                 110

Asn Glu Glu Asn Ala Cys His Cys Ser Glu Asp Cys Leu Ala Arg Gly
        115                 120                 125

Asp Cys Cys Thr Asn Tyr Gln Val Val Cys Lys Gly Glu Ser His Trp
    130                 135                 140

Val Asp Asp Asp Cys Glu Glu Ile Lys Ala Ala Glu Cys Pro Ala Gly
145                 150                 155                 160

Phe Val Arg Pro Pro Leu Ile Ile Phe Ser Val Asp Gly Phe Arg Ala
                165                 170                 175

Ser Tyr Met Lys Lys Gly Ser Lys Val Met Pro Asn Ile Glu Lys Leu
            180                 185                 190

Arg Ser Cys Gly Thr His Ser Pro Tyr Met Arg Pro Val Tyr Pro Thr
        195                 200                 205

Lys Thr Phe Pro Asn Leu Tyr Thr Leu Ala Thr Gly Leu Tyr Pro Glu
    210                 215                 220

Ser His Gly Ile Val Gly Asn Ser Met Tyr Asp Pro Val Phe Asp Ala
225                 230                 235                 240

Thr Phe His Leu Arg Gly Arg Glu Lys Phe Asn His Arg Trp Trp Gly
                245                 250                 255

Gly Gln Pro Leu Trp Ile Thr Ala Thr Lys Gln Gly Val Lys Ala Gly
            260                 265                 270

Thr Phe Phe Trp Ser Val Val Ile Pro His Glu Arg Arg Ile Leu Thr
        275                 280                 285

Ile Leu Gln Trp Leu Thr Leu Pro Asp His Glu Arg Pro Ser Val Tyr
    290                 295                 300
```

```
Ala Phe Tyr Ser Glu Gln Pro Asp Phe Ser Gly His Lys Tyr Gly Pro
305                 310                 315                 320

Phe Gly Pro Glu Met Thr Asn Pro Leu Arg Glu Ile Asp Lys Ile Val
                325                 330                 335

Gly Gln Leu Met Asp Gly Leu Lys Gln Leu Lys Leu His Arg Cys Val
            340                 345                 350

Asn Val Ile Phe Val Gly Asp His Gly Met Glu Asp Val Thr Cys Asp
        355                 360                 365

Arg Thr Glu Phe Leu Ser Asn Tyr Leu Thr Asn Val Asp Asp Ile Thr
    370                 375                 380

Leu Val Pro Gly Thr Leu Gly Arg Ile Arg Ser Lys Phe Ser Asn Asn
385                 390                 395                 400

Ala Lys Tyr Asp Pro Lys Ala Ile Ile Ala Asn Leu Thr Cys Lys Lys
                405                 410                 415

Pro Asp Gln His Phe Lys Pro Tyr Leu Lys Gln His Leu Pro Lys Arg
            420                 425                 430

Leu His Tyr Ala Asn Asn Arg Arg Ile Glu Asp Ile His Leu Leu Val
        435                 440                 445

Glu Arg Arg Trp His Val Ala Arg Lys Pro Leu Asp Val Tyr Lys Lys
    450                 455                 460

Pro Ser Gly Lys Cys Phe Phe Gln Gly Asp His Gly Phe Asp Asn Lys
465                 470                 475                 480

Val Asn Ser Met Gln Thr Val Phe Val Gly Tyr Gly Ser Thr Phe Lys
                485                 490                 495

Tyr Lys Thr Lys Val Pro Pro Phe Glu Asn Ile Glu Leu Tyr Asn Val
            500                 505                 510

Met Cys Asp Leu Leu Gly Leu Lys Pro Ala Pro Asn Asn Gly Thr His
        515                 520                 525
```

```
Gly Ser Leu Asn His Leu Leu Arg Thr Asn Thr Phe Arg Pro Thr Met
    530                 535                 540

Pro Glu Glu Val Thr Arg Pro Asn Tyr Pro Gly Ile Met Tyr Leu Gln
545                 550                 555                 560

Ser Asp Phe Asp Leu Gly Cys Thr Cys Asp Asp Lys Val Glu Pro Lys
                565                 570                 575

Asn Lys Leu Asp Glu Leu Asn Lys Arg Leu His Thr Lys Gly Ser Thr
            580                 585                 590

Glu Ala Glu Thr Arg Lys Phe Arg Gly Ser Arg Asn Glu Asn Lys Glu
        595                 600                 605

Asn Ile Asn Gly Asn Phe Glu Pro Arg Lys Glu Arg His Leu Leu Tyr
    610                 615                 620

Gly Arg Pro Ala Val Leu Tyr Arg Thr Arg Tyr Asp Ile Leu Tyr His
625                 630                 635                 640

Thr Asp Phe Glu Ser Gly Tyr Ser Glu Ile Phe Leu Met Pro Leu Trp
                645                 650                 655

Thr Ser Tyr Thr Val Ser Lys Gln Ala Glu Val Ser Ser Val Pro Asp
            660                 665                 670

His Leu Thr Ser Cys Val Arg Pro Asp Val Arg Val Ser Pro Ser Phe
        675                 680                 685

Ser Gln Asn Cys Leu Ala Tyr Lys Asn Asp Lys Gln Met Ser Tyr Gly
    690                 695                 700

Phe Leu Phe Pro Pro Tyr Leu Ser Ser Ser Pro Glu Ala Lys Tyr Asp
705                 710                 715                 720

Ala Phe Leu Val Thr Asn Met Val Pro Met Tyr Pro Ala Phe Lys Arg
                725                 730                 735
```

```
Val Trp Asn Tyr Phe Gln Arg Val Leu Val Lys Lys Tyr Ala Ser Glu
            740                 745                 750

Arg Asn Gly Val Asn Val Ile Ser Gly Pro Ile Phe Asp Tyr Asp Tyr
        755                 760                 765

Asp Gly Leu His Asp Thr Glu Asp Lys Ile Lys Gln Tyr Val Glu Gly
    770                 775                 780

Ser Ser Ile Pro Val Pro Thr His Tyr Tyr Ser Ile Ile Thr Ser Cys
785                 790                 795                 800

Leu Asp Phe Thr Gln Pro Ala Asp Lys Cys Asp Gly Pro Leu Ser Val
                805                 810                 815

Ser Ser Phe Ile Leu Pro His Arg Pro Asp Asn Glu Glu Ser Cys Asn
            820                 825                 830

Ser Ser Glu Asp Glu Ser Lys Trp Val Glu Glu Leu Met Lys Met His
        835                 840                 845

Thr Ala Arg Val Arg Asp Ile Glu His Leu Thr Ser Leu Asp Phe Phe
    850                 855                 860

Arg Lys Thr Ser Arg Ser Tyr Pro Glu Ile Leu Thr Leu Lys Thr Tyr
865                 870                 875                 880

Leu His Thr Tyr Glu Ser Glu Ile
                885


<210>  6
<211>  827
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Extracellular Domain of ENPP3

<400>  6

Glu Lys Gln Gly Ser Cys Arg Lys Lys Cys Phe Asp Ala Ser Phe Arg
1               5                   10                  15
```

```
Gly Leu Glu Asn Cys Arg Cys Asp Val Ala Cys Lys Asp Arg Gly Asp
            20                  25                  30

Cys Cys Trp Asp Phe Glu Asp Thr Cys Val Glu Ser Thr Arg Ile Trp
        35                  40                  45

Met Cys Asn Lys Phe Arg Cys Gly Glu Thr Arg Leu Glu Ala Ser Leu
    50                  55                  60

Cys Ser Cys Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys Cys Ala Asp
65                  70                  75                  80

Tyr Lys Ser Val Cys Gln Gly Glu Thr Ser Trp Leu Glu Glu Asn Cys
                85                  90                  95

Asp Thr Ala Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp Leu Pro Pro
            100                 105                 110

Val Ile Leu Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr Leu Tyr Thr
        115                 120                 125

Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys Thr Cys Gly Ile
    130                 135                 140

His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr Phe Pro Asn
145                 150                 155                 160

His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly Ile Ile
                165                 170                 175

Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser Leu Ser
            180                 185                 190

Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro Met Trp
        195                 200                 205

Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe Trp Pro
    210                 215                 220

Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr Met Pro
225                 230                 235                 240
```

```
Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu Leu Lys
                245                 250                 255

Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr Met Tyr
            260                 265                 270

Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val Ser Ala
        275                 280                 285

Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala Phe Gly Met Leu
    290                 295                 300

Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn Ile Ile
305                 310                 315                 320

Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys Met Glu
                325                 330                 335

Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr Met Tyr Glu
            340                 345                 350

Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro His Asp Phe Phe
        355                 360                 365

Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg Lys Pro
    370                 375                 380

Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys Arg Leu
385                 390                 395                 400

His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His Leu Phe Val Asp
                405                 410                 415

Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys Gly Gly
            420                 425                 430

Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala Ile Phe
        435                 440                 445
```

```
Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu Pro Phe
    450                 455                 460

Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg Ile Gln
465                 470                 475                 480

Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His Leu Leu Lys
                485                 490                 495

Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys Phe Ser
            500                 505                 510

Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu Asp Cys Phe
        515                 520                 525

Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn Gln Met
    530                 535                 540

Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val Asn Leu
545                 550                 555                 560

Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val Asp His Cys Leu
                565                 570                 575

Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala Met Arg Met
            580                 585                 590

Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp Thr Ser Pro
        595                 600                 605

Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp Val Arg Val Pro
    610                 615                 620

Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys Asn Ile
625                 630                 635                 640

Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser Asp Ser
                645                 650                 655

Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro Met Tyr Glu Glu
            660                 665                 670
```

```
Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu Leu Ile Lys His
        675                 680                 685

Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile Phe Asp
    690                 695                 700

Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr Lys His
705                 710                 715                 720

Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val Val Leu
                725                 730                 735

Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro Gly Trp
            740                 745                 750

Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn Val Glu
        755                 760                 765

Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu Arg Phe
    770                 775                 780

Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr Gly Leu
785                 790                 795                 800

Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu Gln Leu
                805                 810                 815

Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile
            820                 825
```

<210> 7
<211> 875
<212> PRT
<213> Artificial Sequence

<220>
<223> NPP3 Amino Acid Sequence

<400> 7

```
Met Glu Ser Thr Leu Thr Leu Ala Thr Glu Gln Pro Val Lys Lys Asn
1               5                   10                  15
```

```
Thr Leu Lys Lys Tyr Lys Ile Ala Cys Ile Val Leu Leu Ala Leu Leu
            20                  25                  30

Val Ile Met Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys Leu
        35                  40                  45

Glu Lys Gln Gly Ser Cys Arg Lys Lys Cys Phe Asp Ala Ser Phe Arg
    50                  55                  60

Gly Leu Glu Asn Cys Arg Cys Asp Val Ala Cys Lys Asp Arg Gly Asp
65                  70                  75                  80

Cys Cys Trp Asp Phe Glu Asp Thr Cys Val Glu Ser Thr Arg Ile Trp
                85                  90                  95

Met Cys Asn Lys Phe Arg Cys Gly Glu Thr Arg Leu Glu Ala Ser Leu
            100                 105                 110

Cys Ser Cys Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys Cys Ala Asp
        115                 120                 125

Tyr Lys Ser Val Cys Gln Gly Glu Thr Ser Trp Leu Glu Glu Asn Cys
    130                 135                 140

Asp Thr Ala Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp Leu Pro Pro
145                 150                 155                 160

Val Ile Leu Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr Leu Tyr Thr
                165                 170                 175

Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys Thr Cys Gly Ile
            180                 185                 190

His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr Phe Pro Asn
        195                 200                 205

His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly Ile Ile
    210                 215                 220
```

```
Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser Leu Ser
225                 230                 235                 240

Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro Met Trp
                245                 250                 255

Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe Trp Pro
            260                 265                 270

Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr Met Pro
        275                 280                 285

Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu Leu Lys
    290                 295                 300

Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr Met Tyr
305                 310                 315                 320

Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val Ser Ala
                325                 330                 335

Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala Phe Gly Met Leu
            340                 345                 350

Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn Ile Ile
        355                 360                 365

Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys Met Glu
    370                 375                 380

Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr Met Tyr Glu
385                 390                 395                 400

Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro His Asp Phe Phe
                405                 410                 415

Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg Lys Pro
            420                 425                 430

Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys Arg Leu
        435                 440                 445
```

```
His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His Leu Phe Val Asp
    450                 455                 460

Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys Gly Gly
465                 470                 475                 480

Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala Ile Phe
                485                 490                 495

Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu Pro Phe
            500                 505                 510

Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg Ile Gln
        515                 520                 525

Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His Leu Leu Lys
    530                 535                 540

Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys Phe Ser
545                 550                 555                 560

Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu Asp Cys Phe
                565                 570                 575

Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn Gln Met
            580                 585                 590

Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val Asn Leu
        595                 600                 605

Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val Asp His Cys Leu
    610                 615                 620

Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala Met Arg Met
625                 630                 635                 640

Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp Thr Ser Pro
                645                 650                 655
```

```
Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp Val Arg Val Pro
            660                 665                 670

Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys Asn Ile
        675                 680                 685

Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser Asp Ser
    690                 695                 700

Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro Met Tyr Glu Glu
705                 710                 715                 720

Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu Leu Ile Lys His
                725                 730                 735

Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile Phe Asp
            740                 745                 750

Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr Lys His
        755                 760                 765

Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val Val Leu
    770                 775                 780

Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro Gly Trp
785                 790                 795                 800

Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn Val Glu
                805                 810                 815

Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu Arg Phe
            820                 825                 830

Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr Gly Leu
        835                 840                 845

Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu Gln Leu
    850                 855                 860

Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile
865                 870                 875
```

<210> 8
<211> 1073
<212> PRT
<213> Artificial Sequence

<220>
<223> Azurocidin-ENPP3-FC

<220>
<221> SIGNAL
<222> (19)..(20)
<223> Cleavage point of the signal sequence

<220>
<221> MISC_FEATURE
<222> (847)..(1074)
<223> Indicate Fc sequence

<400> 8

```
Met Thr Arg Leu Thr Val Leu Ala Leu Leu Ala Gly Leu Leu Ala Ser
1               5                  10                  15


Ser Arg Ala Ala Lys Gln Gly Ser Cys Arg Lys Lys Cys Phe Asp Ala
            20                  25                  30


Ser Phe Arg Gly Leu Glu Asn Cys Arg Cys Asp Val Ala Cys Lys Asp
        35                  40                  45


Arg Gly Asp Cys Cys Trp Asp Phe Glu Asp Thr Cys Val Glu Ser Thr
    50                  55                  60


Arg Ile Trp Met Cys Asn Lys Phe Arg Cys Gly Glu Thr Arg Leu Glu
65                  70                  75                  80


Ala Ser Leu Cys Ser Cys Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys
                85                  90                  95


Cys Ala Asp Tyr Lys Ser Val Cys Gln Gly Glu Thr Ser Trp Leu Glu
            100                 105                 110


Glu Asn Cys Asp Thr Ala Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp
        115                 120                 125
```

```
Leu Pro Pro Val Ile Leu Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr
    130                 135                 140

Leu Tyr Thr Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys Thr
145                 150                 155                 160

Cys Gly Ile His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr
                165                 170                 175

Phe Pro Asn His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser His
            180                 185                 190

Gly Ile Ile Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn Phe
        195                 200                 205

Ser Leu Ser Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly Gln
    210                 215                 220

Pro Met Asn Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr
225                 230                 235                 240

Phe Trp Pro Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser Ile
                245                 250                 255

Tyr Met Pro Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser Thr
            260                 265                 270

Leu Leu Lys Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr
        275                 280                 285

Thr Met Tyr Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly Pro
    290                 295                 300

Val Ser Ala Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala Phe
305                 310                 315                 320

Gly Met Leu Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys Val
                325                 330                 335

Asn Ile Ile Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys Asn
```

```
            340                 345                 350

Lys Met Glu Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr
        355                 360                 365

Met Tyr Glu Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro His
    370                 375                 380

Asp Phe Phe Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser Cys
385                 390                 395                 400

Arg Lys Pro Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro
                405                 410                 415

Lys Arg Leu His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His Leu
            420                 425                 430

Phe Val Asp Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr Asn
        435                 440                 445

Cys Gly Gly Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu
    450                 455                 460

Ala Ile Phe Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu Val
465                 470                 475                 480

Glu Pro Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu
                485                 490                 495

Arg Ile Gln Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His
            500                 505                 510

Leu Leu Lys Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val Ser
        515                 520                 525

Lys Phe Ser Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu
    530                 535                 540

Asp Cys Phe Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln Val
545                 550                 555                 560
```

```
Asn Gln Met Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val Lys
                565                 570                 575

Val Asn Leu Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val Asp
            580                 585                 590

His Cys Leu Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala
        595                 600                 605

Met Arg Met Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp
    610                 615                 620

Thr Ser Pro Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp Val
625                 630                 635                 640

Arg Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp
                645                 650                 655

Lys Asn Ile Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr
            660                 665                 670

Ser Asp Ser Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro Met
        675                 680                 685

Tyr Glu Glu Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu Leu
    690                 695                 700

Ile Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro
705                 710                 715                 720

Ile Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu Ile
                725                 730                 735

Thr Lys His Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr Phe
            740                 745                 750

Val Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys
        755                 760                 765

Pro Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro Thr
```

```
    770                 775                 780

Asn Val Glu Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val Glu
785                 790                 795                 800

Glu Arg Phe Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu
                805                 810                 815

Thr Gly Leu Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile
            820                 825                 830

Leu Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile Asp Lys
        835                 840                 845

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
    850                 855                 860

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
865                 870                 875                 880

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
                885                 890                 895

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
            900                 905                 910

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
        915                 920                 925

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
    930                 935                 940

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
945                 950                 955                 960

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
                965                 970                 975

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
            980                 985                 990
```

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
        995   1000   1005

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
    1010   1015   1020

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
    1025   1030   1035

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
    1040   1045   1050

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    1055   1060   1065

Leu Ser Pro Gly Lys
    1070

<210> 9
<211> 1464
<212> PRT
<213> Artificial Sequence

<220>
<223> Azurocidin-ENPP3-Albumin

<220>
<221> SIGNAL
<222> (19)..(20)
<223> Cleavage point of the signal sequence

<220>
<221> MISC_FEATURE
<222> (847)..(1465)
<223> Indicate albumin sequence

<400> 9

Met Thr Arg Leu Thr Val Leu Ala Leu Leu Ala Gly Leu Leu Ala Ser
1   5   10   15

Ser Arg Ala Ala Lys Gln Gly Ser Cys Arg Lys Lys Cys Phe Asp Ala
            20   25   30

```
Ser Phe Arg Gly Leu Glu Asn Cys Arg Cys Asp Val Ala Cys Lys Asp
        35                  40                  45

Arg Gly Asp Cys Cys Trp Asp Phe Glu Asp Thr Cys Val Glu Ser Thr
    50                  55                  60

Arg Ile Trp Met Cys Asn Lys Phe Arg Cys Gly Glu Thr Arg Leu Glu
65                  70                  75                  80

Ala Ser Leu Cys Ser Cys Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys
                85                  90                  95

Cys Ala Asp Tyr Lys Ser Val Cys Gln Gly Glu Thr Ser Trp Leu Glu
            100                 105                 110

Glu Asn Cys Asp Thr Ala Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp
        115                 120                 125

Leu Pro Pro Val Ile Leu Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr
    130                 135                 140

Leu Tyr Thr Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys Thr
145                 150                 155                 160

Cys Gly Ile His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr
                165                 170                 175

Phe Pro Asn His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser His
            180                 185                 190

Gly Ile Ile Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn Phe
        195                 200                 205

Ser Leu Ser Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly Gln
    210                 215                 220

Pro Met Asn Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr
225                 230                 235                 240

Phe Trp Pro Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser Ile
                245                 250                 255
```

```
Tyr Met Pro Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser Thr
            260                 265                 270

Leu Leu Lys Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr
        275                 280                 285

Thr Met Tyr Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly Pro
    290                 295                 300

Val Ser Ala Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala Phe
305                 310                 315                 320

Gly Met Leu Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys Val
                325                 330                 335

Asn Ile Ile Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys Asn
            340                 345                 350

Lys Met Glu Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr
        355                 360                 365

Met Tyr Glu Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro His
    370                 375                 380

Asp Phe Phe Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser Cys
385                 390                 395                 400

Arg Lys Pro Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro
                405                 410                 415

Lys Arg Leu His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His Leu
            420                 425                 430

Phe Val Asp Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr Asn
        435                 440                 445

Cys Gly Gly Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu
    450                 455                 460
```

```
Ala Ile Phe Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu Val
465                 470                 475                 480

Glu Pro Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu
                485                 490                 495

Arg Ile Gln Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His
            500                 505                 510

Leu Leu Lys Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val Ser
        515                 520                 525

Lys Phe Ser Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu
    530                 535                 540

Asp Cys Phe Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln Val
545                 550                 555                 560

Asn Gln Met Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val Lys
                565                 570                 575

Val Asn Leu Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val Asp
            580                 585                 590

His Cys Leu Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala
        595                 600                 605

Met Arg Met Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp
    610                 615                 620

Thr Ser Pro Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp Val
625                 630                 635                 640

Arg Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp
                645                 650                 655

Lys Asn Ile Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr
            660                 665                 670

Ser Asp Ser Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro Met
        675                 680                 685
```

```
Tyr Glu Glu Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu Leu
    690                 695                 700

Ile Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro
705                 710                 715                 720

Ile Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu Ile
                725                 730                 735

Thr Lys His Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr Phe
            740                 745                 750

Val Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys
        755                 760                 765

Pro Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro Thr
    770                 775                 780

Asn Val Glu Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val Glu
785                 790                 795                 800

Glu Arg Phe Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu
                805                 810                 815

Thr Gly Leu Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile
            820                 825                 830

Leu Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile Met Lys
        835                 840                 845

Trp Val Thr Phe Leu Leu Leu Leu Phe Val Ser Gly Ser Ala Phe Ser
    850                 855                 860

Arg Gly Val Phe Arg Arg Glu Ala His Lys Ser Glu Ile Ala His Arg
865                 870                 875                 880

Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala
                885                 890                 895
```

```
Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys Leu
            900                 905                 910

Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Ser
        915                 920                 925

Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu
    930                 935                 940

Cys Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys
945                 950                 955                 960

Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys
                965                 970                 975

Asp Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala
            980                 985                 990

Met Cys Thr Ser Phe Lys Glu Asn  Pro Thr Thr Phe Met  Gly His Tyr
        995                 1000                1005

Leu His  Glu Val Ala Arg Arg  His Pro Tyr Phe Tyr  Ala Pro Glu
    1010                1015                1020

Leu Leu  Tyr Tyr Ala Glu Gln  Tyr Asn Glu Ile Leu  Thr Gln Cys
    1025                1030                1035

Cys Ala  Glu Ala Asp Lys Glu  Ser Cys Leu Thr Pro  Lys Leu Asp
    1040                1045                1050

Gly Val  Lys Glu Lys Ala Leu  Val Ser Ser Val Arg  Gln Arg Met
    1055                1060                1065

Lys Cys  Ser Ser Met Gln Lys  Phe Gly Glu Arg Ala  Phe Lys Ala
    1070                1075                1080

Trp Ala  Val Ala Arg Leu Ser  Gln Thr Phe Pro Asn  Ala Asp Phe
    1085                1090                1095

Ala Glu  Ile Thr Lys Leu Ala  Thr Asp Leu Thr Lys  Val Asn Lys
    1100                1105                1110
```

```
Glu Cys  Cys His Gly Asp Leu  Leu Glu Cys Ala Asp  Asp Arg Ala
    1115                1120                1125

Glu Leu  Ala Lys Tyr Met Cys  Glu Asn Gln Ala Thr  Ile Ser Ser
    1130                1135                1140

Lys Leu  Gln Thr Cys Cys Asp  Lys Pro Leu Leu Lys  Lys Ala His
    1145                1150                1155

Cys Leu  Ser Glu Val Glu His  Asp Thr Met Pro Ala  Asp Leu Pro
    1160                1165                1170

Ala Ile  Ala Ala Asp Phe Val  Glu Asp Gln Glu Val  Cys Lys Asn
    1175                1180                1185

Tyr Ala  Glu Ala Lys Asp Val  Phe Leu Gly Thr Phe  Leu Tyr Glu
    1190                1195                1200

Tyr Ser  Arg Arg His Pro Asp  Tyr Ser Val Ser Leu  Leu Leu Arg
    1205                1210                1215

Leu Ala  Lys Lys Tyr Glu Ala  Thr Leu Glu Lys Cys  Cys Ala Glu
    1220                1225                1230

Ala Asn  Pro Pro Ala Cys Tyr  Gly Thr Val Leu Ala  Glu Phe Gln
    1235                1240                1245

Pro Leu  Val Glu Glu Pro Lys  Asn Leu Val Lys Thr  Asn Cys Asp
    1250                1255                1260

Leu Tyr  Glu Lys Leu Gly Glu  Tyr Gly Phe Gln Asn  Ala Ile Leu
    1265                1270                1275

Val Arg  Tyr Thr Gln Lys Ala  Pro Gln Val Ser Thr  Pro Thr Leu
    1280                1285                1290

Val Glu  Ala Ala Arg Asn Leu  Gly Arg Val Gly Thr  Lys Cys Cys
    1295                1300                1305
```

```
Thr Leu  Pro Glu Asp Gln Arg  Leu Pro Cys Val Glu  Asp Tyr Leu
    1310                1315                1320

Ser Ala  Ile Leu Asn Arg Val  Cys Leu Leu His Glu  Lys Thr Pro
    1325                1330                1335

Val Ser  Glu His Val Thr Lys  Cys Cys Ser Gly Ser  Leu Val Glu
    1340                1345                1350

Arg Arg  Pro Cys Phe Ser Ala  Leu Thr Val Asp Glu  Thr Tyr Val
    1355                1360                1365

Pro Lys  Glu Phe Lys Ala Glu  Thr Phe Thr Phe His  Ser Asp Ile
    1370                1375                1380

Cys Thr  Leu Pro Glu Lys Glu  Lys Gln Ile Lys Lys  Gln Thr Ala
    1385                1390                1395

Leu Ala  Glu Leu Val Lys His  Lys Pro Lys Ala Thr  Ala Glu Gln
    1400                1405                1410

Leu Lys  Thr Val Met Asp Asp  Phe Ala Gln Phe Leu  Asp Thr Cys
    1415                1420                1425

Cys Lys  Ala Ala Asp Lys Asp  Thr Cys Phe Ser Thr  Glu Gly Pro
    1430                1435                1440

Asn Leu  Val Thr Arg Cys Lys  Asp Ala Leu Ala Arg  Ser Trp Ser
    1445                1450                1455

His Pro  Gln Phe Glu Lys
    1460
```

<210> 10
<211> 846
<212> PRT
<213> Artificial Sequence

<220>
<223> Azurocidin-ENPP3

<220>

<221> SIGNAL
<222> (19)..(20)
<223> Cleavage point of the signal sequence

<400> 10

```
Met Thr Arg Leu Thr Val Leu Ala Leu Leu Ala Gly Leu Leu Ala Ser
1               5                  10                  15


Ser Arg Ala Ala Lys Gln Gly Ser Cys Arg Lys Lys Cys Phe Asp Ala
            20                  25                  30


Ser Phe Arg Gly Leu Glu Asn Cys Arg Cys Asp Val Ala Cys Lys Asp
        35                  40                  45


Arg Gly Asp Cys Cys Trp Asp Phe Glu Asp Thr Cys Val Glu Ser Thr
    50                  55                  60


Arg Ile Trp Met Cys Asn Lys Phe Arg Cys Gly Glu Thr Arg Leu Glu
65                  70                  75                  80


Ala Ser Leu Cys Ser Cys Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys
                85                  90                  95


Cys Ala Asp Tyr Lys Ser Val Cys Gln Gly Glu Thr Ser Trp Leu Glu
            100                 105                 110


Glu Asn Cys Asp Thr Ala Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp
        115                 120                 125


Leu Pro Pro Val Ile Leu Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr
    130                 135                 140


Leu Tyr Thr Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys Thr
145                 150                 155                 160


Cys Gly Ile His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr
                165                 170                 175


Phe Pro Asn His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser His
            180                 185                 190
```

```
Gly Ile Ile Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn Phe
        195                 200                 205

Ser Leu Ser Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly Gln
    210                 215                 220

Pro Met Asn Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr
225                 230                 235                 240

Phe Trp Pro Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser Ile
                245                 250                 255

Tyr Met Pro Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser Thr
            260                 265                 270

Leu Leu Lys Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr
        275                 280                 285

Thr Met Tyr Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly Pro
    290                 295                 300

Val Ser Ala Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala Phe
305                 310                 315                 320

Gly Met Leu Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys Val
                325                 330                 335

Asn Ile Ile Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys Asn
            340                 345                 350

Lys Met Glu Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr
        355                 360                 365

Met Tyr Glu Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro His
    370                 375                 380

Asp Phe Phe Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser Cys
385                 390                 395                 400

Arg Lys Pro Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro
                405                 410                 415
```

```
Lys Arg Leu His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His Leu
            420                 425                 430

Phe Val Asp Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr Asn
        435                 440                 445

Cys Gly Gly Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu
    450                 455                 460

Ala Ile Phe Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu Val
465                 470                 475                 480

Glu Pro Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu
                485                 490                 495

Arg Ile Gln Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His
            500                 505                 510

Leu Leu Lys Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val Ser
        515                 520                 525

Lys Phe Ser Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu
    530                 535                 540

Asp Cys Phe Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln Val
545                 550                 555                 560

Asn Gln Met Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val Lys
                565                 570                 575

Val Asn Leu Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val Asp
            580                 585                 590

His Cys Leu Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala
        595                 600                 605

Met Arg Met Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp
    610                 615                 620
```

```
Thr Ser Pro Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp Val
625                 630                 635                 640

Arg Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp
                645                 650                 655

Lys Asn Ile Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr
            660                 665                 670

Ser Asp Ser Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro Met
        675                 680                 685

Tyr Glu Glu Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu Leu
    690                 695                 700

Ile Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro
705                 710                 715                 720

Ile Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu Ile
                725                 730                 735

Thr Lys His Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr Phe
            740                 745                 750

Val Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys
        755                 760                 765

Pro Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro Thr
    770                 775                 780

Asn Val Glu Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val Glu
785                 790                 795                 800

Glu Arg Phe Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu
                805                 810                 815

Thr Gly Leu Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile
            820                 825                 830

Leu Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile
        835                 840                 845
```

<210> 11
<211> 453
<212> PRT
<213> Artificial Sequence

<220>
<223> ENPP4 Amino Acid Sequence - Wild Type

<400> 11

```
Met Lys Leu Leu Val Ile Leu Leu Phe Ser Gly Leu Ile Thr Gly Phe
1               5                  10                  15


Arg Ser Asp Ser Ser Ser Ser Leu Pro Pro Lys Leu Leu Leu Val Ser
            20                  25                  30


Phe Asp Gly Phe Arg Ala Asp Tyr Leu Lys Asn Tyr Glu Phe Pro His
        35                  40                  45


Leu Gln Asn Phe Ile Lys Glu Gly Val Leu Val Glu His Val Lys Asn
    50                  55                  60


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


Leu Tyr Glu Glu Ser His Gly Ile Val Ala Asn Ser Met Tyr Asp Ala
                85                  90                  95


Val Thr Lys Lys His Phe Ser Asp Ser Asn Asp Lys Asp Pro Phe Trp
            100                 105                 110


Trp Asn Glu Ala Val Pro Ile Trp Val Thr Asn Gln Leu Gln Glu Asn
        115                 120                 125


Arg Ser Ser Ala Ala Ala Met Trp Pro Gly Thr Asp Val Pro Ile His
    130                 135                 140


Asp Thr Ile Ser Ser Tyr Phe Met Asn Tyr Asn Ser Ser Val Ser Phe
145                 150                 155                 160


Glu Glu Arg Leu Asn Asn Ile Thr Met Trp Leu Asn Asn Ser Asn Pro
                165                 170                 175
```

```
Pro Val Thr Phe Ala Thr Leu Tyr Trp Glu Glu Pro Asp Ala Ser Gly
            180                 185                 190

His Lys Tyr Gly Pro Glu Asp Lys Glu Asn Met Ser Arg Val Leu Lys
        195                 200                 205

Lys Ile Asp Asp Leu Ile Gly Asp Leu Val Gln Arg Leu Lys Met Leu
    210                 215                 220

Gly Leu Trp Glu Asn Leu Asn Val Ile Ile Thr Ser Asp His Gly Met
225                 230                 235                 240

Thr Gln Cys Ser Gln Asp Arg Leu Ile Asn Leu Asp Ser Cys Ile Asp
                245                 250                 255

His Ser Tyr Tyr Thr Leu Ile Asp Leu Ser Pro Val Ala Ala Ile Leu
            260                 265                 270

Pro Lys Ile Asn Arg Thr Glu Val Tyr Asn Lys Leu Lys Asn Cys Ser
        275                 280                 285

Pro His Met Asn Val Tyr Leu Lys Glu Asp Ile Pro Asn Arg Phe Tyr
    290                 295                 300

Tyr Gln His Asn Asp Arg Ile Gln Pro Ile Ile Leu Val Ala Asp Glu
305                 310                 315                 320

Gly Trp Thr Ile Val Leu Asn Glu Ser Ser Gln Lys Leu Gly Asp His
                325                 330                 335

Gly Tyr Asp Asn Ser Leu Pro Ser Met His Pro Phe Leu Ala Ala His
            340                 345                 350

Gly Pro Ala Phe His Lys Gly Tyr Lys His Ser Thr Ile Asn Ile Val
        355                 360                 365

Asp Ile Tyr Pro Met Met Cys His Ile Leu Gly Leu Lys Pro His Pro
    370                 375                 380
```

```
Asn Asn Gly Thr Phe Gly His Thr Lys Cys Leu Leu Val Asp Gln Trp
385                 390                 395                 400


Cys Ile Asn Leu Pro Glu Ala Ile Ala Ile Val Ile Gly Ser Leu Leu
                405                 410                 415


Val Leu Thr Met Leu Thr Cys Leu Ile Ile Ile Met Gln Asn Arg Leu
            420                 425                 430


Ser Val Pro Arg Pro Phe Ser Arg Leu Gln Leu Gln Glu Asp Asp Asp
        435                 440                 445


Asp Pro Leu Ile Gly
    450


<210>  12
<211>  850
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  ENPP51 Amino Acid Sequence


<220>
<221>  SIGNAL
<222>  (24)..(25)
<223>  Cleavage position at the signal peptide sequence

<400>  12

Met Thr Ser Lys Phe Leu Leu Val Ser Phe Ile Leu Ala Ala Leu Ser
1               5                   10                  15


Leu Ser Thr Thr Phe Ser Leu Gln Pro Ser Cys Ala Lys Glu Val Lys
            20                  25                  30


Ser Cys Lys Gly Arg Cys Phe Glu Arg Thr Phe Ser Asn Cys Arg Cys
        35                  40                  45


Asp Ala Ala Cys Val Ser Leu Gly Asn Cys Cys Leu Asp Phe Gln Glu
    50                  55                  60


Thr Cys Val Glu Pro Thr His Ile Trp Thr Cys Asn Lys Phe Arg Cys
65                  70                  75                  80
```

```
Gly Glu Lys Arg Leu Ser Arg Phe Val Cys Ser Cys Ala Asp Asp Cys
                85                  90                  95

Lys Thr His Asn Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln Asp
            100                 105                 110

Lys Lys Ser Trp Val Glu Glu Thr Cys Glu Ser Ile Asp Thr Pro Glu
        115                 120                 125

Cys Pro Ala Glu Phe Glu Ser Pro Pro Thr Leu Leu Phe Ser Leu Asp
    130                 135                 140

Gly Phe Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro Val
145                 150                 155                 160

Ile Ser Lys Leu Lys Asn Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro
                165                 170                 175

Met Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly
            180                 185                 190

Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro
        195                 200                 205

Lys Met Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro
    210                 215                 220

Leu Trp Tyr Lys Gly Gln Pro Ile Trp Val Thr Ala Asn His Gln Glu
225                 230                 235                 240

Val Lys Ser Gly Thr Tyr Phe Trp Pro Gly Ser Asp Val Glu Ile Asp
                245                 250                 255

Gly Ile Leu Pro Asp Ile Tyr Lys Val Tyr Asn Gly Ser Val Pro Phe
            260                 265                 270

Glu Glu Arg Ile Leu Ala Val Leu Glu Trp Leu Gln Leu Pro Ser His
        275                 280                 285
```

```
Glu Arg Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser
    290                 295                 300

Gly His Ser His Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln
305                 310                 315                 320

Lys Val Asp Arg Leu Val Gly Met Leu Met Asp Gly Leu Lys Asp Leu
                325                 330                 335

Gly Leu Asp Lys Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met
            340                 345                 350

Glu Gln Gly Ser Cys Lys Lys Tyr Val Tyr Leu Asn Lys Tyr Leu Gly
        355                 360                 365

Asp Val Asn Asn Val Lys Val Val Tyr Gly Pro Ala Ala Arg Leu Arg
    370                 375                 380

Pro Thr Asp Val Pro Glu Thr Tyr Tyr Ser Phe Asn Tyr Glu Ala Leu
385                 390                 395                 400

Ala Lys Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Arg Pro Tyr
                405                 410                 415

Leu Lys Pro Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg
            420                 425                 430

Ile Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu
        435                 440                 445

Asn Pro Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp
    450                 455                 460

Asn Leu Phe Ser Asn Met Gln Ala Leu Phe Ile Gly Tyr Gly Pro Ala
465                 470                 475                 480

Phe Lys His Gly Ala Glu Val Asp Ser Phe Glu Asn Ile Glu Val Tyr
                485                 490                 495

Asn Leu Met Cys Asp Leu Leu Gly Leu Ile Pro Ala Pro Asn Asn Gly
            500                 505                 510
```

```
Ser His Gly Ser Leu Asn His Leu Leu Lys Lys Pro Ile Tyr Asn Pro
        515                 520                 525

Ser His Pro Lys Glu Glu Gly Phe Leu Ser Gln Cys Pro Ile Lys Ser
    530                 535                 540

Thr Ser Asn Asp Leu Gly Cys Thr Cys Asp Pro Trp Ile Val Pro Ile
545                 550                 555                 560

Lys Asp Phe Glu Lys Gln Leu Asn Leu Thr Thr Glu Asp Val Asp Asp
                565                 570                 575

Ile Tyr His Met Thr Val Pro Tyr Gly Arg Pro Arg Ile Leu Leu Lys
            580                 585                 590

Gln His Arg Val Cys Leu Leu Gln Gln Gln Gln Phe Leu Thr Gly Tyr
        595                 600                 605

Ser Leu Asp Leu Leu Met Pro Leu Trp Ala Ser Tyr Thr Phe Leu Ser
    610                 615                 620

Asn Asp Gln Phe Ser Arg Asp Asp Phe Ser Asn Cys Leu Tyr Gln Asp
625                 630                 635                 640

Leu Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Tyr Tyr Lys Ser
                645                 650                 655

Asn Ser Lys Leu Ser Tyr Gly Phe Leu Thr Pro Pro Arg Leu Asn Arg
            660                 665                 670

Val Ser Asn His Ile Tyr Ser Glu Ala Leu Leu Thr Ser Asn Ile Val
        675                 680                 685

Pro Met Tyr Gln Ser Phe Gln Val Ile Trp His Tyr Leu His Asp Thr
    690                 695                 700

Leu Leu Gln Arg Tyr Ala His Glu Arg Asn Gly Ile Asn Val Val Ser
705                 710                 715                 720
```

```
Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Tyr Asp Ser Leu Glu
                725                 730                 735

Ile Leu Lys Gln Asn Ser Arg Val Ile Arg Ser Gln Glu Ile Leu Ile
            740                 745                 750

Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Gln Leu Ser Glu
        755                 760                 765

Thr Pro Leu Glu Cys Ser Ala Leu Glu Ser Ser Ala Tyr Ile Leu Pro
    770                 775                 780

His Arg Pro Asp Asn Ile Glu Ser Cys Thr His Gly Lys Arg Glu Ser
785                 790                 795                 800

Ser Trp Val Glu Glu Leu Leu Thr Leu His Arg Ala Arg Val Thr Asp
                805                 810                 815

Val Glu Leu Ile Thr Gly Leu Ser Phe Tyr Gln Asp Arg Gln Glu Ser
            820                 825                 830

Val Ser Glu Leu Leu Arg Leu Lys Thr His Leu Pro Ile Phe Ser Gln
        835                 840                 845

Glu Asp
    850
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<210> 13
<211> 1474
<212> PRT
<213> Artificial Sequence

<220>
<223> ENPP51 - ALB Amino Acid Sequence

<220>
<221> SIGNAL
<222> (24)..(25)
<223> Cleavage position at the signal peptide sequence

<220>
<221> MISC_FEATURE
<222> (857)..(1474)
<223> Indicate albumin sequence

<400> 13

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Met Thr Ser Lys Phe Leu Leu Val Ser Phe Ile Leu Ala Ala Leu Ser
1               5                  10                  15

Leu Ser Thr Thr Phe Ser Leu Gln Pro Ser Cys Ala Lys Glu Val Lys
            20                  25                  30

Ser Cys Lys Gly Arg Cys Phe Glu Arg Thr Phe Ser Asn Cys Arg Cys
        35                  40                  45

Asp Ala Ala Cys Val Ser Leu Gly Asn Cys Cys Leu Asp Phe Gln Glu
    50                  55                  60

Thr Cys Val Glu Pro Thr His Ile Trp Thr Cys Asn Lys Phe Arg Cys
65                  70                  75                  80

Gly Glu Lys Arg Leu Ser Arg Phe Val Cys Ser Cys Ala Asp Asp Cys
                85                  90                  95

Lys Thr His Asn Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln Asp
            100                 105                 110

Lys Lys Ser Trp Val Glu Glu Thr Cys Glu Ser Ile Asp Thr Pro Glu
        115                 120                 125

Cys Pro Ala Glu Phe Glu Ser Pro Pro Thr Leu Leu Phe Ser Leu Asp
    130                 135                 140

Gly Phe Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro Val
145                 150                 155                 160

Ile Ser Lys Leu Lys Asn Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro
                165                 170                 175

Met Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly
            180                 185                 190

Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro
        195                 200                 205
```

```
Lys Met Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro
    210                 215                 220

Leu Trp Tyr Lys Gly Gln Pro Ile Trp Val Thr Ala Asn His Gln Glu
225                 230                 235                 240

Val Lys Ser Gly Thr Tyr Phe Trp Pro Gly Ser Asp Val Glu Ile Asp
                245                 250                 255

Gly Ile Leu Pro Asp Ile Tyr Lys Val Tyr Asn Gly Ser Val Pro Phe
            260                 265                 270

Glu Glu Arg Ile Leu Ala Val Leu Glu Trp Leu Gln Leu Pro Ser His
        275                 280                 285

Glu Arg Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser
    290                 295                 300

Gly His Ser His Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln
305                 310                 315                 320

Lys Val Asp Arg Leu Val Gly Met Leu Met Asp Gly Leu Lys Asp Leu
                325                 330                 335

Gly Leu Asp Lys Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met
            340                 345                 350

Glu Gln Gly Ser Cys Lys Lys Tyr Val Tyr Leu Asn Lys Tyr Leu Gly
        355                 360                 365

Asp Val Asn Asn Val Lys Val Val Tyr Gly Pro Ala Ala Arg Leu Arg
    370                 375                 380

Pro Thr Asp Val Pro Glu Thr Tyr Tyr Ser Phe Asn Tyr Glu Ala Leu
385                 390                 395                 400

Ala Lys Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Arg Pro Tyr
                405                 410                 415

Leu Lys Pro Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg
```

```
            420                 425                 430

Ile Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu
        435                 440                 445

Asn Pro Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp
    450                 455                 460

Asn Leu Phe Ser Asn Met Gln Ala Leu Phe Ile Gly Tyr Gly Pro Ala
465                 470                 475                 480

Phe Lys His Gly Ala Glu Val Asp Ser Phe Glu Asn Ile Glu Val Tyr
                485                 490                 495

Asn Leu Met Cys Asp Leu Leu Gly Leu Ile Pro Ala Pro Asn Asn Gly
            500                 505                 510

Ser His Gly Ser Leu Asn His Leu Leu Lys Lys Pro Ile Tyr Asn Pro
        515                 520                 525

Ser His Pro Lys Glu Glu Gly Phe Leu Ser Gln Cys Pro Ile Lys Ser
    530                 535                 540

Thr Ser Asn Asp Leu Gly Cys Thr Cys Asp Pro Trp Ile Val Pro Ile
545                 550                 555                 560

Lys Asp Phe Glu Lys Gln Leu Asn Leu Thr Thr Glu Asp Val Asp Asp
                565                 570                 575

Ile Tyr His Met Thr Val Pro Tyr Gly Arg Pro Arg Ile Leu Leu Lys
            580                 585                 590

Gln His Arg Val Cys Leu Leu Gln Gln Gln Gln Phe Leu Thr Gly Tyr
        595                 600                 605

Ser Leu Asp Leu Leu Met Pro Leu Trp Ala Ser Tyr Thr Phe Leu Ser
    610                 615                 620

Asn Asp Gln Phe Ser Arg Asp Asp Phe Ser Asn Cys Leu Tyr Gln Asp
625                 630                 635                 640
```

```
Leu Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Tyr Tyr Lys Ser
                645                 650                 655

Asn Ser Lys Leu Ser Tyr Gly Phe Leu Thr Pro Pro Arg Leu Asn Arg
            660                 665                 670

Val Ser Asn His Ile Tyr Ser Glu Ala Leu Leu Thr Ser Asn Ile Val
        675                 680                 685

Pro Met Tyr Gln Ser Phe Gln Val Ile Trp His Tyr Leu His Asp Thr
    690                 695                 700

Leu Leu Gln Arg Tyr Ala His Glu Arg Asn Gly Ile Asn Val Val Ser
705                 710                 715                 720

Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Tyr Asp Ser Leu Glu
                725                 730                 735

Ile Leu Lys Gln Asn Ser Arg Val Ile Arg Ser Gln Glu Ile Leu Ile
            740                 745                 750

Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Gln Leu Ser Glu
        755                 760                 765

Thr Pro Leu Glu Cys Ser Ala Leu Glu Ser Ser Ala Tyr Ile Leu Pro
    770                 775                 780

His Arg Pro Asp Asn Ile Glu Ser Cys Thr His Gly Lys Arg Glu Ser
785                 790                 795                 800

Ser Trp Val Glu Glu Leu Leu Thr Leu His Arg Ala Arg Val Thr Asp
                805                 810                 815

Val Glu Leu Ile Thr Gly Leu Ser Phe Tyr Gln Asp Arg Gln Glu Ser
            820                 825                 830

Val Ser Glu Leu Leu Arg Leu Lys Thr His Leu Pro Ile Phe Ser Gln
        835                 840                 845

Glu Asp Gly Gly Ser Gly Gly Ser Met Lys Trp Val Thr Phe Leu Leu
```

```
    850                 855                 860

Leu Leu Phe Val Ser Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg
865                 870                 875                 880

Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu
                885                 890                 895

Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln
            900                 905                 910

Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu Val Thr Asp
        915                 920                 925

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys
    930                 935                 940

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu
945                 950                 955                 960

Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro
                965                 970                 975

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Ser Leu
            980                 985                 990

Pro Pro Phe Glu Arg Pro Glu Ala  Glu Ala Met Cys Thr  Ser Phe Lys
        995                 1000                1005

Glu Asn  Pro Thr Thr Phe Met  Gly His Tyr Leu His  Glu Val Ala
    1010                1015                1020

Arg Arg  His Pro Tyr Phe Tyr  Ala Pro Glu Leu Leu  Tyr Tyr Ala
    1025                1030                1035

Glu Gln  Tyr Asn Glu Ile Leu  Thr Gln Cys Cys Ala  Glu Ala Asp
    1040                1045                1050

Lys Glu  Ser Cys Leu Thr Pro  Lys Leu Asp Gly Val  Lys Glu Lys
    1055                1060                1065
```

```
Ala Leu  Val Ser Ser Val Arg  Gln Arg Met Lys Cys  Ser Ser Met
    1070                1075                1080

Gln Lys  Phe Gly Glu Arg Ala  Phe Lys Ala Trp Ala  Val Ala Arg
    1085                1090                1095

Leu Ser  Gln Thr Phe Pro Asn  Ala Asp Phe Ala Glu  Ile Thr Lys
    1100                1105                1110

Leu Ala  Thr Asp Leu Thr Lys  Val Asn Lys Glu Cys  Cys His Gly
    1115                1120                1125

Asp Leu  Leu Glu Cys Ala Asp  Asp Arg Ala Glu Leu  Ala Lys Tyr
    1130                1135                1140

Met Cys  Glu Asn Gln Ala Thr  Ile Ser Ser Lys Leu  Gln Thr Cys
    1145                1150                1155

Cys Asp  Lys Pro Leu Leu Lys  Lys Ala His Cys Leu  Ser Glu Val
    1160                1165                1170

Glu His  Asp Thr Met Pro Ala  Asp Leu Pro Ala Ile  Ala Ala Asp
    1175                1180                1185

Phe Val  Glu Asp Gln Glu Val  Cys Lys Asn Tyr Ala  Glu Ala Lys
    1190                1195                1200

Asp Val  Phe Leu Gly Thr Phe  Leu Tyr Glu Tyr Ser  Arg Arg His
    1205                1210                1215

Pro Asp  Tyr Ser Val Ser Leu  Leu Leu Arg Leu Ala  Lys Lys Tyr
    1220                1225                1230

Glu Ala  Thr Leu Glu Lys Cys  Cys Ala Glu Ala Asn  Pro Pro Ala
    1235                1240                1245

Cys Tyr  Gly Thr Val Leu Ala  Glu Phe Gln Pro Leu  Val Glu Glu
    1250                1255                1260

Pro Lys  Asn Leu Val Lys Thr  Asn Cys Asp Leu Tyr  Glu Lys Leu
```

```
    1265                1270                1275

Gly Glu  Tyr Gly Phe Gln Asn  Ala Ile Leu Val Arg  Tyr Thr Gln
    1280                1285                1290

Lys Ala  Pro Gln Val Ser Thr  Pro Thr Leu Val Glu  Ala Ala Arg
    1295                1300                1305

Asn Leu  Gly Arg Val Gly Thr  Lys Cys Cys Thr Leu  Pro Glu Asp
    1310                1315                1320

Gln Arg  Leu Pro Cys Val Glu  Asp Tyr Leu Ser Ala  Ile Leu Asn
    1325                1330                1335

Arg Val  Cys Leu Leu His Glu  Lys Thr Pro Val Ser  Glu His Val
    1340                1345                1350

Thr Lys  Cys Cys Ser Gly Ser  Leu Val Glu Arg Arg  Pro Cys Phe
    1355                1360                1365

Ser Ala  Leu Thr Val Asp Glu  Thr Tyr Val Pro Lys  Glu Phe Lys
    1370                1375                1380

Ala Glu  Thr Phe Thr Phe His  Ser Asp Ile Cys Thr  Leu Pro Glu
    1385                1390                1395

Lys Glu  Lys Gln Ile Lys Lys  Gln Thr Ala Leu Ala  Glu Leu Val
    1400                1405                1410

Lys His  Lys Pro Lys Ala Thr  Ala Glu Gln Leu Lys  Thr Val Met
    1415                1420                1425

Asp Asp  Phe Ala Gln Phe Leu  Asp Thr Cys Cys Lys  Ala Ala Asp
    1430                1435                1440

Lys Asp  Thr Cys Phe Ser Thr  Glu Gly Pro Asn Leu  Val Thr Arg
    1445                1450                1455

Cys Lys  Asp Ala Leu Ala Arg  Ser Trp Ser His Pro  Gln Phe Glu
    1460                1465                1470
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Lys

<210> 14
<211> 1074
<212> PRT
<213> Artificial Sequence

<220>
<223> ENPP5-NPP3-Fc sequence

<220>
<221> SIGNAL
<222> (22)..(23)
<223> Cleavage position at the signal peptide sequence

<220>
<221> MISC_FEATURE
<222> (848)..(1074)
<223> Indicate albumin sequence

<400> 14

Met Thr Ser Lys Phe Leu Leu Val Ser Phe Ile Leu Ala Ala Leu Ser
1   5   10   15

Leu Ser Thr Thr Phe Ser Lys Gln Gly Ser Cys Arg Lys Lys Cys Phe
            20   25   30

Asp Ala Ser Phe Arg Gly Leu Glu Asn Cys Arg Cys Asp Val Ala Cys
        35   40   45

Lys Asp Arg Gly Asp Cys Cys Trp Asp Phe Glu Asp Thr Cys Val Glu
    50   55   60

Ser Thr Arg Ile Trp Met Cys Asn Lys Phe Arg Cys Gly Glu Arg Leu
65   70   75   80

Glu Ala Ser Leu Cys Ser Cys Ser Asp Asp Cys Leu Gln Arg Lys Asp
                85   90   95

Cys Cys Ala Asp Tyr Lys Ser Val Cys Gln Gly Glu Thr Ser Trp Leu
            100   105   110

```
Glu Glu Asn Cys Asp Thr Ala Gln Gln Ser Gln Cys Pro Glu Gly Phe
        115                 120                 125

Asp Leu Pro Pro Val Ile Leu Phe Ser Met Asp Gly Phe Arg Ala Glu
    130                 135                 140

Tyr Leu Tyr Thr Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys
145                 150                 155                 160

Thr Cys Gly Ile His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys
                165                 170                 175

Thr Phe Pro Asn His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser
            180                 185                 190

His Gly Ile Ile Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn
        195                 200                 205

Phe Ser Leu Ser Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly
    210                 215                 220

Gln Pro Met Trp Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr
225                 230                 235                 240

Tyr Phe Trp Pro Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser
                245                 250                 255

Ile Tyr Met Pro Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser
            260                 265                 270

Thr Leu Leu Lys Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe
        275                 280                 285

Tyr Thr Met Tyr Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly
    290                 295                 300

Pro Val Ser Ala Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala
305                 310                 315                 320

Phe Gly Met Leu Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys
                325                 330                 335
```

```
Val Asn Ile Ile Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys
            340                 345                 350

Asn Lys Met Glu Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe
        355                 360                 365

Tyr Met Tyr Glu Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro
    370                 375                 380

His Asp Phe Phe Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser
385                 390                 395                 400

Cys Arg Lys Pro Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu
                405                 410                 415

Pro Lys Arg Leu His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His
            420                 425                 430

Leu Phe Val Asp Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr
        435                 440                 445

Asn Cys Gly Gly Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met
    450                 455                 460

Glu Ala Ile Phe Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu
465                 470                 475                 480

Val Glu Pro Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu
                485                 490                 495

Leu Arg Ile Gln Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn
            500                 505                 510

His Leu Leu Lys Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val
        515                 520                 525

Ser Lys Phe Ser Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser
    530                 535                 540
```

```
Leu Asp Cys Phe Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln
545                 550                 555                 560

Val Asn Gln Met Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val
                565                 570                 575

Lys Val Asn Leu Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val
            580                 585                 590

Asp His Cys Leu Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys
        595                 600                 605

Ala Met Arg Met Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly
    610                 615                 620

Asp Thr Ser Pro Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp
625                 630                 635                 640

Val Arg Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala
                645                 650                 655

Asp Lys Asn Ile Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg
            660                 665                 670

Thr Ser Asp Ser Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro
        675                 680                 685

Met Tyr Glu Glu Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu
    690                 695                 700

Leu Ile Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly
705                 710                 715                 720

Pro Ile Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu
                725                 730                 735

Ile Thr Lys His Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr
            740                 745                 750

Phe Val Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn
        755                 760                 765
```

```
Cys Pro Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro
    770                 775                 780

Thr Asn Val Glu Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val
785                 790                 795                 800

Glu Glu Arg Phe Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu
                805                 810                 815

Leu Thr Gly Leu Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu
            820                 825                 830

Ile Leu Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile Asp
        835                 840                 845

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
    850                 855                 860

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
865                 870                 875                 880

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
                885                 890                 895

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
            900                 905                 910

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
        915                 920                 925

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
    930                 935                 940

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
945                 950                 955                 960

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
                965                 970                 975
```

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
980 985 990

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
995 1000 1005

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
1010 1015 1020

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
1025 1030 1035

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
1040 1045 1050

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
1055 1060 1065

Ser Leu Ser Pro Gly Lys
1070

<210> 15
<211> 1469
<212> PRT
<213> Artificial Sequence

<220>
<223> ENPP5-NPP3-Albumin sequence

<220>
<221> SIGNAL
<222> (22)..(23)
<223> Cleavage position at the signal peptide sequence

<220>
<221> MISC_FEATURE
<222> (848)..(1469)
<223> Indicate albumin sequence

<400> 15

Met Thr Ser Lys Phe Leu Leu Val Ser Phe Ile Leu Ala Ala Leu Ser
1 5 10 15

Leu Ser Thr Thr Phe Ser Lys Gln Gly Ser Cys Arg Lys Lys Cys Phe

```
            20                  25                  30

Asp Ala Ser Phe Arg Gly Leu Glu Asn Cys Arg Cys Asp Val Ala Cys
        35                  40                  45

Lys Asp Arg Gly Asp Cys Cys Trp Asp Phe Glu Asp Thr Cys Val Glu
    50                  55                  60

Ser Thr Arg Ile Trp Met Cys Asn Lys Phe Arg Cys Gly Glu Arg Leu
65                  70                  75                  80

Glu Ala Ser Leu Cys Ser Cys Ser Asp Asp Cys Leu Gln Arg Lys Asp
                85                  90                  95

Cys Cys Ala Asp Tyr Lys Ser Val Cys Gln Gly Glu Thr Ser Trp Leu
            100                 105                 110

Glu Glu Asn Cys Asp Thr Ala Gln Gln Ser Gln Cys Pro Glu Gly Phe
        115                 120                 125

Asp Leu Pro Pro Val Ile Leu Phe Ser Met Asp Gly Phe Arg Ala Glu
    130                 135                 140

Tyr Leu Tyr Thr Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys
145                 150                 155                 160

Thr Cys Gly Ile His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys
                165                 170                 175

Thr Phe Pro Asn His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser
            180                 185                 190

His Gly Ile Ile Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn
        195                 200                 205

Phe Ser Leu Ser Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly
    210                 215                 220

Gln Pro Met Trp Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr
225                 230                 235                 240
```

```
Tyr Phe Trp Pro Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser
                245                 250                 255

Ile Tyr Met Pro Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser
            260                 265                 270

Thr Leu Leu Lys Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe
        275                 280                 285

Tyr Thr Met Tyr Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly
    290                 295                 300

Pro Val Ser Ala Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala
305                 310                 315                 320

Phe Gly Met Leu Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys
                325                 330                 335

Val Asn Ile Ile Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys
            340                 345                 350

Asn Lys Met Glu Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe
        355                 360                 365

Tyr Met Tyr Glu Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro
    370                 375                 380

His Asp Phe Phe Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser
385                 390                 395                 400

Cys Arg Lys Pro Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu
                405                 410                 415

Pro Lys Arg Leu His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His
            420                 425                 430

Leu Phe Val Asp Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr
        435                 440                 445

Asn Cys Gly Gly Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met
```

```
    450                 455                 460

Glu Ala Ile Phe Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu
465                 470                 475                 480

Val Glu Pro Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu
                485                 490                 495

Leu Arg Ile Gln Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn
            500                 505                 510

His Leu Leu Lys Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val
        515                 520                 525

Ser Lys Phe Ser Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser
    530                 535                 540

Leu Asp Cys Phe Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln
545                 550                 555                 560

Val Asn Gln Met Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val
                565                 570                 575

Lys Val Asn Leu Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val
            580                 585                 590

Asp His Cys Leu Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys
        595                 600                 605

Ala Met Arg Met Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly
    610                 615                 620

Asp Thr Ser Pro Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp
625                 630                 635                 640

Val Arg Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala
                645                 650                 655

Asp Lys Asn Ile Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg
            660                 665                 670
```

```
Thr Ser Asp Ser Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro
        675                 680                 685

Met Tyr Glu Glu Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu
    690                 695                 700

Leu Ile Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly
705                 710                 715                 720

Pro Ile Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu
                725                 730                 735

Ile Thr Lys His Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr
            740                 745                 750

Phe Val Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn
        755                 760                 765

Cys Pro Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro
    770                 775                 780

Thr Asn Val Glu Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val
785                 790                 795                 800

Glu Glu Arg Phe Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu
                805                 810                 815

Leu Thr Gly Leu Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu
            820                 825                 830

Ile Leu Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile Gly
        835                 840                 845

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Met Lys Trp
    850                 855                 860

Val Thr Phe Leu Leu Leu Leu Phe Val Ser Gly Ser Ala Phe Ser Arg
865                 870                 875                 880

Gly Val Phe Arg Arg Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr
```

```
               885                 890                 895

Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe
            900                 905                 910

Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val
        915                 920                 925

Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
    930                 935                 940

Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
945                 950                 955                 960

Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys
               965                 970                 975

Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
            980                 985                 990

Asp Asn Pro Ser Leu Pro Pro Phe  Glu Arg Pro Glu Ala  Glu Ala Met
        995                 1000                1005

Cys Thr  Ser Phe Lys Glu Asn  Pro Thr Thr Phe Met  Gly His Tyr
    1010                1015                1020

Leu His  Glu Val Ala Arg Arg  His Pro Tyr Phe Tyr  Ala Pro Glu
    1025                1030                1035

Leu Leu  Tyr Tyr Ala Glu Gln  Tyr Asn Glu Ile Leu  Thr Gln Cys
    1040                1045                1050

Cys Ala  Glu Ala Asp Lys Glu  Ser Cys Leu Thr Pro  Lys Leu Asp
    1055                1060                1065

Gly Val  Lys Glu Lys Ala Leu  Val Ser Ser Val Arg  Gln Arg Met
    1070                1075                1080

Lys Cys  Ser Ser Met Gln Lys  Phe Gly Glu Arg Ala  Phe Lys Ala
    1085                1090                1095
```

```
Trp Ala  Val Ala Arg Leu Ser  Gln Thr Phe Pro Asn  Ala Asp Phe
    1100                1105                1110

Ala Glu  Ile Thr Lys Leu Ala  Thr Asp Leu Thr Lys  Val Asn Lys
    1115                1120                1125

Glu Cys  Cys His Gly Asp Leu  Leu Glu Cys Ala Asp  Asp Arg Ala
    1130                1135                1140

Glu Leu  Ala Lys Tyr Met Cys  Glu Asn Gln Ala Thr  Ile Ser Ser
    1145                1150                1155

Lys Leu  Gln Thr Cys Cys Asp  Lys Pro Leu Leu Lys  Lys Ala His
    1160                1165                1170

Cys Leu  Ser Glu Val Glu His  Asp Thr Met Pro Ala  Asp Leu Pro
    1175                1180                1185

Ala Ile  Ala Ala Asp Phe Val  Glu Asp Gln Glu Val  Cys Lys Asn
    1190                1195                1200

Tyr Ala  Glu Ala Lys Asp Val  Phe Leu Gly Thr Phe  Leu Tyr Glu
    1205                1210                1215

Tyr Ser  Arg Arg His Pro Asp  Tyr Ser Val Ser Leu  Leu Leu Arg
    1220                1225                1230

Leu Ala  Lys Lys Tyr Glu Ala  Thr Leu Glu Lys Cys  Cys Ala Glu
    1235                1240                1245

Ala Asn  Pro Pro Ala Cys Tyr  Gly Thr Val Leu Ala  Glu Phe Gln
    1250                1255                1260

Pro Leu  Val Glu Glu Pro Lys  Asn Leu Val Lys Thr  Asn Cys Asp
    1265                1270                1275

Leu Tyr  Glu Lys Leu Gly Glu  Tyr Gly Phe Gln Asn  Ala Ile Leu
    1280                1285                1290

Val Arg  Tyr Thr Gln Lys Ala  Pro Gln Val Ser Thr  Pro Thr Leu
```

1295 1300 1305

Val Glu Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys
1310 1315 1320

Thr Leu Pro Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu
1325 1330 1335

Ser Ala Ile Leu Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro
1340 1345 1350

Val Ser Glu His Val Thr Lys Cys Cys Ser Gly Ser Leu Val Glu
1355 1360 1365

Arg Arg Pro Cys Phe Ser Ala Leu Thr Val Asp Glu Thr Tyr Val
1370 1375 1380

Pro Lys Glu Phe Lys Ala Glu Thr Phe Thr Phe His Ser Asp Ile
1385 1390 1395

Cys Thr Leu Pro Glu Lys Glu Lys Gln Ile Lys Lys Gln Thr Ala
1400 1405 1410

Leu Ala Glu Leu Val Lys His Lys Pro Lys Ala Thr Ala Glu Gln
1415 1420 1425

Leu Lys Thr Val Met Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys
1430 1435 1440

Cys Lys Ala Ala Asp Lys Asp Thr Cys Phe Ser Thr Glu Gly Pro
1445 1450 1455

Asn Leu Val Thr Arg Cys Lys Asp Ala Leu Ala
1460 1465

<210> 16
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> ENPP5 Protein Export Signal Sequence

<220>
<221> MISC_FEATURE
<222> (23)..(23)
<223> X can be any amino acid

<400> 16

Met Thr Ser Lys Phe Leu Leu Val Ser Phe Ile Leu Ala Ala Leu Ser
1   5   10   15

Leu Ser Thr Thr Phe Ser Xaa
            20

<210> 17
<211> 1079
<212> PRT
<213> Artificial Sequence

<220>
<223> ENPP51-Fc

<220>
<221> SIGNAL
<222> (22)..(23)
<223> Cleavage position at the signal peptide sequence

<220>
<221> MISC_FEATURE
<222> (853)..(1079)
<223> Indicate Fc sequence

<400> 17

Met Thr Ser Lys Phe Leu Leu Val Ser Phe Ile Leu Ala Ala Leu Ser
1   5   10   15

Leu Ser Thr Thr Phe Ser Gly Leu Lys Pro Ser Cys Ala Lys Glu Val
            20   25   30

Lys Ser Cys Lys Gly Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg
        35   40   45

Cys Asp Ala Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln
    50   55   60

```
Glu Thr Cys Ile Glu Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg
65                  70                  75                  80

Cys Gly Glu Lys Arg Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp
                85                  90                  95

Cys Lys Asp Lys Gly Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln
            100                 105                 110

Gly Glu Lys Ser Trp Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro
        115                 120                 125

Gln Cys Pro Ala Gly Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu
    130                 135                 140

Asp Gly Phe Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro
145                 150                 155                 160

Val Ile Ser Lys Leu Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg
                165                 170                 175

Pro Val Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr
            180                 185                 190

Gly Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp
        195                 200                 205

Pro Lys Met Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn
    210                 215                 220

Pro Glu Trp Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln
225                 230                 235                 240

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

Asn Gly Ile Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro
            260                 265                 270

Phe Glu Glu Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys
        275                 280                 285
```

```
Asp Glu Arg Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser
    290                 295                 300

Ser Gly His Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu
305                 310                 315                 320

Gln Arg Val Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu
                325                 330                 335

Leu Asn Leu His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly
            340                 345                 350

Met Glu Gln Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu
        355                 360                 365

Gly Asp Val Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu
    370                 375                 380

Arg Pro Ser Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly
385                 390                 395                 400

Ile Ala Arg Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro
                405                 410                 415

Tyr Leu Lys His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp
            420                 425                 430

Arg Ile Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala
        435                 440                 445

Leu Asn Pro Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser
    450                 455                 460

Asp Asn Val Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro
465                 470                 475                 480

Gly Phe Lys His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val
                485                 490                 495
```

```
Tyr Asn Leu Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn
            500                 505                 510

Gly Thr His Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr
        515                 520                 525

Pro Lys His Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr
    530                 535                 540

Arg Asn Pro Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu
545                 550                 555                 560

Pro Ile Glu Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu
                565                 570                 575

Lys Ile Ile Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu
            580                 585                 590

Gln Lys Glu Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser
        595                 600                 605

Gly Tyr Ser Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val
    610                 615                 620

Asp Arg Asn Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr
625                 630                 635                 640

Gln Asp Phe Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr
                645                 650                 655

Lys Asn Asn Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu
            660                 665                 670

Asn Lys Asn Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn
        675                 680                 685

Ile Val Pro Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His
    690                 695                 700

Asp Thr Leu Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val
705                 710                 715                 720
```

```
Val Ser Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser
                725                 730                 735

Leu Glu Asn Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile
            740                 745                 750

Leu Ile Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr
        755                 760                 765

Ser Gln Thr Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile
    770                 775                 780

Leu Pro His Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His
785                 790                 795                 800

Asp Ser Ser Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile
                805                 810                 815

Thr Asp Val Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys
            820                 825                 830

Glu Pro Val Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe
        835                 840                 845

Ser Gln Glu Asp Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
    850                 855                 860

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
865                 870                 875                 880

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
                885                 890                 895

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
            900                 905                 910

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
        915                 920                 925
```

```
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
    930                 935                 940

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
945                 950                 955                 960

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
                965                 970                 975

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
            980                 985                 990

Asn Gln Val Ser Leu Thr Cys Leu  Val Lys Gly Phe Tyr  Pro Ser Asp
        995                 1000                1005

Ile Ala  Val Glu Trp Glu Ser  Asn Gly Gln Pro Glu  Asn Asn Tyr
    1010                1015                1020

Lys Thr  Thr Pro Pro Val Leu  Asp Ser Asp Gly Ser  Phe Phe Leu
    1025                1030                1035

Tyr Ser  Lys Leu Thr Val Asp  Lys Ser Arg Trp Gln  Gln Gly Asn
    1040                1045                1050

Val Phe  Ser Cys Ser Val Met  His Glu Ala Leu His  Asn His Tyr
    1055                1060                1065

Thr Gln  Lys Ser Leu Ser Leu  Ser Pro Gly Lys
    1070                1075
```

<210> 18
<211> 1082
<212> PRT
<213> Artificial Sequence

<220>
<223> ENPP71-Fc Amino Acid Sequence

<220>
<221> SIGNAL
<222> (22)..(23)
<223> Cleavage position at the signal peptide sequence

<220>
<221> MISC_FEATURE
<222> (856)..(1082)
<223> Indicate Fc sequence

<400> 18

```
Met Arg Gly Pro Ala Val Leu Leu Thr Val Ala Leu Ala Thr Leu Leu
1               5                  10                  15


Ala Pro Gly Ala Gly Ala Gly Leu Lys Pro Ser Cys Ala Lys Glu Val
            20                  25                  30


Lys Ser Cys Lys Gly Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg
        35                  40                  45


Cys Asp Ala Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln
    50                  55                  60


Glu Thr Cys Ile Glu Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg
65                  70                  75                  80


Cys Gly Glu Lys Arg Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp
                85                  90                  95


Cys Lys Asp Lys Gly Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln
            100                 105                 110


Gly Glu Lys Ser Trp Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro
        115                 120                 125


Gln Cys Pro Ala Gly Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu
    130                 135                 140


Asp Gly Phe Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro
145                 150                 155                 160


Val Ile Ser Lys Leu Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg
                165                 170                 175


Pro Val Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr
            180                 185                 190
```

```
Gly Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp
        195                 200                 205

Pro Lys Met Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn
    210                 215                 220

Pro Glu Trp Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln
225                 230                 235                 240

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

Asn Gly Ile Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro
            260                 265                 270

Phe Glu Glu Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys
        275                 280                 285

Asp Glu Arg Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser
    290                 295                 300

Ser Gly His Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu
305                 310                 315                 320

Gln Arg Val Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu
                325                 330                 335

Leu Asn Leu His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly
            340                 345                 350

Met Glu Gln Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu
        355                 360                 365

Gly Asp Val Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu
    370                 375                 380

Arg Pro Ser Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly
385                 390                 395                 400

Ile Ala Arg Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro
```

```
                405                 410                 415

Tyr Leu Lys His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp
            420                 425                 430

Arg Ile Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala
        435                 440                 445

Leu Asn Pro Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser
    450                 455                 460

Asp Asn Val Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro
465                 470                 475                 480

Gly Phe Lys His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val
                485                 490                 495

Tyr Asn Leu Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn
            500                 505                 510

Gly Thr His Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr
        515                 520                 525

Pro Lys His Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr
    530                 535                 540

Arg Asn Pro Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu
545                 550                 555                 560

Pro Ile Glu Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu
                565                 570                 575

Lys Ile Ile Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu
            580                 585                 590

Gln Lys Glu Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser
        595                 600                 605

Gly Tyr Ser Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val
    610                 615                 620
```

```
Asp Arg Asn Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr
625                 630                 635                 640

Gln Asp Phe Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr
                645                 650                 655

Lys Asn Asn Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu
            660                 665                 670

Asn Lys Asn Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn
        675                 680                 685

Ile Val Pro Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His
    690                 695                 700

Asp Thr Leu Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val
705                 710                 715                 720

Val Ser Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser
                725                 730                 735

Leu Glu Asn Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile
            740                 745                 750

Leu Ile Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr
        755                 760                 765

Ser Gln Thr Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile
    770                 775                 780

Leu Pro His Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His
785                 790                 795                 800

Asp Ser Ser Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile
                805                 810                 815

Thr Asp Val Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys
            820                 825                 830

Glu Pro Val Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe
```

```
        835                 840                 845

Ser Gln Glu Asp Leu Ile Asn Asp Lys Thr His Thr Cys Pro Pro Cys
    850                 855                 860

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
865                 870                 875                 880

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
                885                 890                 895

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
            900                 905                 910

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
        915                 920                 925

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
    930                 935                 940

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
945                 950                 955                 960

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
                965                 970                 975

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
            980                 985                 990

Met Thr Lys Asn Gln Val Ser Leu  Thr Cys Leu Val Lys  Gly Phe Tyr
        995                 1000                1005

Pro Ser  Asp Ile Ala Val Glu  Trp Glu Ser Asn Gly  Gln Pro Glu
    1010                1015                1020

Asn Asn  Tyr Lys Thr Thr Pro  Pro Val Leu Asp Ser  Asp Gly Ser
    1025                1030                1035

Phe Phe  Leu Tyr Ser Lys Leu  Thr Val Asp Lys Ser  Arg Trp Gln
    1040                1045                1050
```

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
    1055   1060   1065

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    1070   1075   1080

<210> 19
<211> 849
<212> PRT
<213> Artificial Sequence

<220>
<223> ENPP71 (lacking NPP1 N-Terminus GLK) Amino Acid Sequence

<220>
<221> SIGNAL
<222> (22)..(23)
<223> Cleavage position at the signal peptide sequence

<400> 19

Met Arg Gly Pro Ala Val Leu Leu Thr Val Ala Leu Ala Thr Leu Leu
1   5   10   15

Ala Pro Gly Ala Gly Ala Pro Ser Cys Ala Lys Glu Val Lys Ser Cys
            20   25   30

Lys Gly Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala
        35   40   45

Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys
    50   55   60

Ile Glu Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu
65   70   75   80

Lys Arg Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp
                85   90   95

Lys Gly Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys
            100   105   110

Ser Trp Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro

```
        115                 120                 125

Ala Gly Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe
    130                 135                 140

Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser
145                 150                 155                 160

Lys Leu Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr
                165                 170                 175

Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr
            180                 185                 190

Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met
        195                 200                 205

Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp
    210                 215                 220

Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys
225                 230                 235                 240

Ser Gly Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile
                245                 250                 255

Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu
            260                 265                 270

Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg
        275                 280                 285

Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His
    290                 295                 300

Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val
305                 310                 315                 320

Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu
                325                 330                 335
```

```
His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln
            340                 345                 350

Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val
        355                 360                 365

Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser
    370                 375                 380

Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg
385                 390                 395                 400

Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys
                405                 410                 415

His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu
            420                 425                 430

Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro
        435                 440                 445

Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val
    450                 455                 460

Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys
465                 470                 475                 480

His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu
                485                 490                 495

Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His
            500                 505                 510

Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His
        515                 520                 525

Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro
    530                 535                 540

Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu
```

```
545                 550                 555                 560

Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile
                565                 570                 575

Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu
            580                 585                 590

Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser
        595                 600                 605

Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn
    610                 615                 620

Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe
625                 630                 635                 640

Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn
                645                 650                 655

Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn
            660                 665                 670

Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro
        675                 680                 685

Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu
    690                 695                 700

Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly
705                 710                 715                 720

Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn
                725                 730                 735

Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro
            740                 745                 750

Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr
        755                 760                 765
```

```
Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His
    770                 775                 780

Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser
785                 790                 795                 800

Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val
                805                 810                 815

Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val
            820                 825                 830

Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu
        835                 840                 845

Asp
```

<210> 20
<211> 1079
<212> PRT
<213> Artificial Sequence

<220>
<223> ENPP71 (lacking NPP1 N-Terminus GLK) - Fc Amino Acid Sequence

<220>
<221> SIGNAL
<222> (22)..(23)
<223> Cleavage position at the signal peptide sequence

<220>
<221> MISC_FEATURE
<222> (854)..(1079)
<223> Indicate Fc sequence

<400> 20

```
Met Arg Gly Pro Ala Val Leu Leu Thr Val Ala Leu Ala Thr Leu Leu
1               5                   10                  15

Ala Pro Gly Ala Gly Ala Pro Ser Cys Ala Lys Glu Val Lys Ser Cys
            20                  25                  30
```

```
Lys Gly Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala
        35                  40                  45

Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys
    50                  55                  60

Ile Glu Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu
65                  70                  75                  80

Lys Arg Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp
                85                  90                  95

Lys Gly Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys
            100                 105                 110

Ser Trp Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro
        115                 120                 125

Ala Gly Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe
    130                 135                 140

Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser
145                 150                 155                 160

Lys Leu Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr
                165                 170                 175

Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr
            180                 185                 190

Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met
        195                 200                 205

Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp
    210                 215                 220

Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys
225                 230                 235                 240

Ser Gly Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile
                245                 250                 255
```

```
Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu
            260                 265                 270

Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg
        275                 280                 285

Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His
    290                 295                 300

Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val
305                 310                 315                 320

Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu
                325                 330                 335

His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln
            340                 345                 350

Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val
        355                 360                 365

Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser
    370                 375                 380

Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg
385                 390                 395                 400

Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys
                405                 410                 415

His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu
            420                 425                 430

Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro
        435                 440                 445

Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val
    450                 455                 460
```

```
Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys
465                 470                 475                 480

His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu
                485                 490                 495

Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His
            500                 505                 510

Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His
        515                 520                 525

Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro
    530                 535                 540

Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu
545                 550                 555                 560

Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile
                565                 570                 575

Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu
            580                 585                 590

Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser
        595                 600                 605

Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn
    610                 615                 620

Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe
625                 630                 635                 640

Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn
                645                 650                 655

Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn
            660                 665                 670

Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro
        675                 680                 685
```

```
Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu
    690                 695                 700

Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly
705                 710                 715                 720

Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn
                725                 730                 735

Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro
            740                 745                 750

Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr
        755                 760                 765

Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His
    770                 775                 780

Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser
785                 790                 795                 800

Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val
                805                 810                 815

Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val
            820                 825                 830

Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu
        835                 840                 845

Asp Leu Ile Asn Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
    850                 855                 860

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
865                 870                 875                 880

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
                885                 890                 895
```

```
Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
            900                 905                 910

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
        915                 920                 925

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
    930                 935                 940

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
945                 950                 955                 960

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
                965                 970                 975

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
            980                 985                 990

Asn Gln Val Ser Leu Thr Cys Leu  Val Lys Gly Phe Tyr  Pro Ser Asp
        995                 1000                1005

Ile Ala  Val Glu Trp Glu Ser  Asn Gly Gln Pro Glu  Asn Asn Tyr
    1010                1015                1020

Lys Thr  Thr Pro Pro Val Leu  Asp Ser Asp Gly Ser  Phe Phe Leu
    1025                1030                1035

Tyr Ser  Lys Leu Thr Val Asp  Lys Ser Arg Trp Gln  Gln Gly Asn
    1040                1045                1050

Val Phe  Ser Cys Ser Val Met  His Glu Ala Leu His  Asn His Tyr
    1055                1060                1065

Thr Gln  Lys Ser Leu Ser Leu  Ser Pro Gly Lys
    1070                1075
```

<210> 21
<211> 1474
<212> PRT
<213> Artificial Sequence

<220>

<223> ENPP71 (lacking NPP1 N-Terminus GLK) - ALB Amino Acid Sequence

<220>
<221> SIGNAL
<222> (22)..(23)
<223> Cleavage position at the signal peptide sequence

<220>
<221> MISC_FEATURE
<222> (857)..(1474)
<223> Indicate albumin sequence

<400> 21

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Met Arg Gly Pro Ala Val Leu Leu Thr Val Ala Leu Ala Thr Leu Leu
1               5                  10                  15


Ala Pro Gly Ala Gly Ala Pro Ser Cys Ala Lys Glu Val Lys Ser Cys
            20                  25                  30


Lys Gly Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala
        35                  40                  45


Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys
    50                  55                  60


Ile Glu Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu
65                  70                  75                  80


Lys Arg Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp
                85                  90                  95


Lys Gly Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys
            100                 105                 110


Ser Trp Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro
        115                 120                 125


Ala Gly Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe
    130                 135                 140


Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser
145                 150                 155                 160
```

```
Lys Leu Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr
               165                 170                 175

Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr
            180                 185                 190

Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met
        195                 200                 205

Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp
    210                 215                 220

Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys
225                 230                 235                 240

Ser Gly Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile
               245                 250                 255

Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu
            260                 265                 270

Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg
        275                 280                 285

Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His
    290                 295                 300

Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val
305                 310                 315                 320

Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu
               325                 330                 335

His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln
            340                 345                 350

Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val
        355                 360                 365

Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser
```

```
    370                 375                 380

Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg
385                 390                 395                 400

Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys
                405                 410                 415

His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu
            420                 425                 430

Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro
        435                 440                 445

Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val
    450                 455                 460

Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys
465                 470                 475                 480

His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu
                485                 490                 495

Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His
            500                 505                 510

Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His
        515                 520                 525

Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro
    530                 535                 540

Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu
545                 550                 555                 560

Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile
                565                 570                 575

Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu
            580                 585                 590
```

```
Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser
        595                 600                 605

Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn
    610                 615                 620

Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe
625                 630                 635                 640

Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn
                645                 650                 655

Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn
            660                 665                 670

Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro
        675                 680                 685

Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu
    690                 695                 700

Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly
705                 710                 715                 720

Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn
                725                 730                 735

Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro
            740                 745                 750

Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr
        755                 760                 765

Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His
    770                 775                 780

Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser
785                 790                 795                 800

Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val
```

```
               805                 810                 815

Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val
            820                 825                 830

Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu
        835                 840                 845

Asp Arg Ser Gly Ser Gly Gly Ser Met Lys Trp Val Thr Phe Leu Leu
    850                 855                 860

Leu Leu Phe Val Ser Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg
865                 870                 875                 880

Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu
               885                 890                 895

Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln
            900                 905                 910

Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu Val Thr Asp
        915                 920                 925

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys
    930                 935                 940

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu
945                 950                 955                 960

Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro
               965                 970                 975

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Ser Leu
            980                 985                 990

Pro Pro Phe Glu Arg Pro Glu Ala  Glu Ala Met Cys Thr  Ser Phe Lys
        995                 1000                1005

Glu Asn  Pro Thr Thr Phe Met  Gly His Tyr Leu His  Glu Val Ala
    1010                1015                1020
```

```
Arg Arg  His Pro Tyr Phe Tyr  Ala Pro Glu Leu Leu  Tyr Tyr Ala
    1025                1030                1035

Glu Gln  Tyr Asn Glu Ile Leu  Thr Gln Cys Cys Ala  Glu Ala Asp
    1040                1045                1050

Lys Glu  Ser Cys Leu Thr Pro  Lys Leu Asp Gly Val  Lys Glu Lys
    1055                1060                1065

Ala Leu  Val Ser Ser Val Arg  Gln Arg Met Lys Cys  Ser Ser Met
    1070                1075                1080

Gln Lys  Phe Gly Glu Arg Ala  Phe Lys Ala Trp Ala  Val Ala Arg
    1085                1090                1095

Leu Ser  Gln Thr Phe Pro Asn  Ala Asp Phe Ala Glu  Ile Thr Lys
    1100                1105                1110

Leu Ala  Thr Asp Leu Thr Lys  Val Asn Lys Glu Cys  Cys His Gly
    1115                1120                1125

Asp Leu  Leu Glu Cys Ala Asp  Asp Arg Ala Glu Leu  Ala Lys Tyr
    1130                1135                1140

Met Cys  Glu Asn Gln Ala Thr  Ile Ser Ser Lys Leu  Gln Thr Cys
    1145                1150                1155

Cys Asp  Lys Pro Leu Leu Lys  Lys Ala His Cys Leu  Ser Glu Val
    1160                1165                1170

Glu His  Asp Thr Met Pro Ala  Asp Leu Pro Ala Ile  Ala Ala Asp
    1175                1180                1185

Phe Val  Glu Asp Gln Glu Val  Cys Lys Asn Tyr Ala  Glu Ala Lys
    1190                1195                1200

Asp Val  Phe Leu Gly Thr Phe  Leu Tyr Glu Tyr Ser  Arg Arg His
    1205                1210                1215

Pro Asp  Tyr Ser Val Ser Leu  Leu Leu Arg Leu Ala  Lys Lys Tyr
```

```
    1220                1225                1230

Glu Ala  Thr Leu Glu Lys Cys  Cys Ala Glu Ala Asn  Pro Pro Ala
    1235                1240                1245

Cys Tyr  Gly Thr Val Leu Ala  Glu Phe Gln Pro Leu  Val Glu Glu
    1250                1255                1260

Pro Lys  Asn Leu Val Lys Thr  Asn Cys Asp Leu Tyr  Glu Lys Leu
    1265                1270                1275

Gly Glu  Tyr Gly Phe Gln Asn  Ala Ile Leu Val Arg  Tyr Thr Gln
    1280                1285                1290

Lys Ala  Pro Gln Val Ser Thr  Pro Thr Leu Val Glu  Ala Ala Arg
    1295                1300                1305

Asn Leu  Gly Arg Val Gly Thr  Lys Cys Cys Thr Leu  Pro Glu Asp
    1310                1315                1320

Gln Arg  Leu Pro Cys Val Glu  Asp Tyr Leu Ser Ala  Ile Leu Asn
    1325                1330                1335

Arg Val  Cys Leu Leu His Glu  Lys Thr Pro Val Ser  Glu His Val
    1340                1345                1350

Thr Lys  Cys Cys Ser Gly Ser  Leu Val Glu Arg Arg  Pro Cys Phe
    1355                1360                1365

Ser Ala  Leu Thr Val Asp Glu  Thr Tyr Val Pro Lys  Glu Phe Lys
    1370                1375                1380

Ala Glu  Thr Phe Thr Phe His  Ser Asp Ile Cys Thr  Leu Pro Glu
    1385                1390                1395

Lys Glu  Lys Gln Ile Lys Lys  Gln Thr Ala Leu Ala  Glu Leu Val
    1400                1405                1410

Lys His  Lys Pro Lys Ala Thr  Ala Glu Gln Leu Lys  Thr Val Met
    1415                1420                1425
```

Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp
    1430   1435   1440

Lys Asp Thr Cys Phe Ser Thr Glu Gly Pro Asn Leu Val Thr Arg
    1445   1450   1455

Cys Lys Asp Ala Leu Ala Arg Ser Trp Ser His Pro Gln Phe Glu
    1460   1465   1470

Lys

<210> 22
<211> 1072
<212> PRT
<213> Artificial Sequence

<220>
<223> ENPP7-NPP3-Fc sequence

<220>
<221> SIGNAL
<222> (20)..(21)
<223> Cleavage position at the signal peptide sequence

<220>
<221> MISC_FEATURE
<222> (846)..(1072)
<223> Indicate Fc sequence

<400> 22

Met Arg Gly Pro Ala Val Leu Leu Thr Val Ala Leu Ala Thr Leu Leu
1   5   10   15

Ala Pro Gly Ala Lys Gln Gly Ser Cys Arg Lys Lys Cys Phe Asp Ala
            20   25   30

Ser Phe Arg Gly Leu Glu Asn Cys Arg Cys Asp Val Ala Cys Lys Asp
        35   40   45

Arg Gly Asp Cys Cys Trp Asp Phe Glu Asp Thr Cys Val Glu Ser Thr
    50   55   60

```
Arg Ile Trp Met Cys Asn Lys Phe Arg Cys Gly Glu Arg Leu Glu Ala
65                  70                  75                  80

Ser Leu Cys Ser Cys Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys Cys
                85                  90                  95

Ala Asp Tyr Lys Ser Val Cys Gln Gly Glu Thr Ser Trp Leu Glu Glu
            100                 105                 110

Asn Cys Asp Thr Ala Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp Leu
        115                 120                 125

Pro Pro Val Ile Leu Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr Leu
    130                 135                 140

Tyr Thr Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys Thr Cys
145                 150                 155                 160

Gly Ile His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr Phe
                165                 170                 175

Pro Asn His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly
            180                 185                 190

Ile Ile Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser
        195                 200                 205

Leu Ser Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro
    210                 215                 220

Met Trp Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe
225                 230                 235                 240

Trp Pro Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr
                245                 250                 255

Met Pro Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu
            260                 265                 270

Leu Lys Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr
        275                 280                 285
```

```
Met Tyr Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val
    290                 295                 300

Ser Ala Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala Phe Gly
305                 310                 315                 320

Met Leu Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn
                325                 330                 335

Ile Ile Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys
            340                 345                 350

Met Glu Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr Met
        355                 360                 365

Tyr Glu Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro His Asp
    370                 375                 380

Phe Phe Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg
385                 390                 395                 400

Lys Pro Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys
                405                 410                 415

Arg Leu His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His Leu Phe
            420                 425                 430

Val Asp Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys
        435                 440                 445

Gly Gly Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala
    450                 455                 460

Ile Phe Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu
465                 470                 475                 480

Pro Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg
                485                 490                 495
```

```
Ile Gln Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His Leu
            500                 505                 510

Leu Lys Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys
        515                 520                 525

Phe Ser Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu Asp
    530                 535                 540

Cys Phe Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn
545                 550                 555                 560

Gln Met Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val
                565                 570                 575

Asn Leu Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val Asp His
            580                 585                 590

Cys Leu Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala Met
        595                 600                 605

Arg Met Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp Thr
    610                 615                 620

Ser Pro Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp Val Arg
625                 630                 635                 640

Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys
                645                 650                 655

Asn Ile Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser
            660                 665                 670

Asp Ser Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro Met Tyr
        675                 680                 685

Glu Glu Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu Leu Ile
    690                 695                 700

Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile
705                 710                 715                 720
```

```
Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr
                725                 730                 735

Lys His Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val
            740                 745                 750

Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro
        755                 760                 765

Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn
    770                 775                 780

Val Glu Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu
785                 790                 795                 800

Arg Phe Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr
                805                 810                 815

Gly Leu Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu
            820                 825                 830

Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile Asp Lys Thr
        835                 840                 845

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
    850                 855                 860

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
865                 870                 875                 880

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
                885                 890                 895

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
            900                 905                 910

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
        915                 920                 925
```

```
Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
    930                 935                 940

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
945                 950                 955                 960

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
                965                 970                 975

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
            980                 985                 990

Leu Val Lys Gly Phe Tyr Pro Ser  Asp Ile Ala Val Glu  Trp Glu Ser
        995                 1000                1005

Asn Gly  Gln Pro Glu Asn Asn  Tyr Lys Thr Thr Pro  Pro Val Leu
    1010                1015                1020

Asp Ser  Asp Gly Ser Phe Phe  Leu Tyr Ser Lys Leu  Thr Val Asp
    1025                1030                1035

Lys Ser  Arg Trp Gln Gln Gly  Asn Val Phe Ser Cys  Ser Val Met
    1040                1045                1050

His Glu  Ala Leu His Asn His  Tyr Thr Gln Lys Ser  Leu Ser Leu
    1055                1060                1065

Ser Pro  Gly Lys
    1070
```

<210> 23
<211> 1396
<212> PRT
<213> Artificial Sequence

<220>
<223> ENPP71-Albumin

<220>
<221> SIGNAL
<222> (23)..(24)
<223> Cleavage position at the signal peptide sequence

<220>
<221> MISC_FEATURE
<222> (857)..(1396)
<223> Indicate Fc sequence

<400> 23

Met Arg Gly Pro Ala Val Leu Leu Thr Val Ala Leu Ala Thr Leu Leu
1 5 10 15

Ala Pro Gly Ala Gly Leu Lys Pro Ser Cys Ala Lys Glu Val Lys Ser
20 25 30

Cys Lys Gly Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp
35 40 45

Ala Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr
50 55 60

Cys Ile Glu Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly
65 70 75 80

Glu Lys Arg Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys
85 90 95

Asp Lys Gly Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu
100 105 110

Lys Ser Trp Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys
115 120 125

Pro Ala Gly Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly
130 135 140

Phe Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile
145 150 155 160

Ser Lys Leu Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val
165 170 175

Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu
180 185 190

```
Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys
        195                 200                 205

Met Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu
    210                 215                 220

Trp Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu
225                 230                 235                 240

Lys Ser Gly Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly
                245                 250                 255

Ile Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu
            260                 265                 270

Glu Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu
        275                 280                 285

Arg Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly
    290                 295                 300

His Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg
305                 310                 315                 320

Val Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn
                325                 330                 335

Leu His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu
            340                 345                 350

Gln Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp
        355                 360                 365

Val Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro
    370                 375                 380

Ser Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala
385                 390                 395                 400

Arg Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu
```

```
                405                 410                 415

Lys His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile
            420                 425                 430

Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn
        435                 440                 445

Pro Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn
    450                 455                 460

Val Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe
465                 470                 475                 480

Lys His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn
                485                 490                 495

Leu Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr
            500                 505                 510

His Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys
        515                 520                 525

His Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn
    530                 535                 540

Pro Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile
545                 550                 555                 560

Glu Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile
                565                 570                 575

Ile Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys
            580                 585                 590

Glu Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr
        595                 600                 605

Ser Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg
    610                 615                 620
```

```
Asn Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp
625                 630                 635                 640

Phe Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn
                645                 650                 655

Asn Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys
            660                 665                 670

Asn Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val
        675                 680                 685

Pro Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr
    690                 695                 700

Leu Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser
705                 710                 715                 720

Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu
                725                 730                 735

Asn Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile
            740                 745                 750

Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln
        755                 760                 765

Thr Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro
    770                 775                 780

His Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His Asp Ser
785                 790                 795                 800

Ser Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp
                805                 810                 815

Val Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro
            820                 825                 830

Val Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln
```

```
        835                 840                 845

Glu Asp Gly Gly Ser Gly Gly Ser Met Lys Trp Val Thr Phe Leu Leu
    850                 855                 860

Leu Leu Phe Val Ser Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg
865                 870                 875                 880

Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu
                885                 890                 895

Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln
            900                 905                 910

Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu Val Thr Asp
        915                 920                 925

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys
    930                 935                 940

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu
945                 950                 955                 960

Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro
                965                 970                 975

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Ser Leu
            980                 985                 990

Pro Pro Phe Glu Arg Pro Glu Ala  Glu Ala Met Cys Thr  Ser Phe Lys
        995                 1000                1005

Glu Asn  Pro Thr Thr Phe Met  Gly His Tyr Leu His  Glu Val Ala
    1010                1015                1020

Arg Arg  His Pro Tyr Phe Tyr  Ala Pro Glu Leu Leu  Tyr Tyr Ala
    1025                1030                1035

Glu Gln  Tyr Asn Glu Ile Leu  Thr Gln Cys Cys Ala  Glu Ala Asp
    1040                1045                1050
```

```
Lys Glu  Ser Cys Leu Thr Pro  Lys Leu Asp Gly Val  Lys Glu Lys
    1055                1060                1065

Ala Leu  Val Ser Ser Val Arg  Gln Arg Met Lys Cys  Ser Ser Met
    1070                1075                1080

Gln Lys  Phe Gly Glu Arg Ala  Phe Lys Ala Trp Ala  Val Ala Arg
    1085                1090                1095

Leu Ser  Gln Thr Phe Pro Asn  Ala Asp Phe Ala Glu  Ile Thr Lys
    1100                1105                1110

Leu Ala  Thr Asp Leu Thr Lys  Val Asn Lys Glu Cys  Cys His Gly
    1115                1120                1125

Asp Leu  Leu Glu Cys Ala Asp  Asp Arg Ala Glu Leu  Ala Lys Tyr
    1130                1135                1140

Met Cys  Glu Asn Gln Ala Thr  Ile Ser Ser Lys Leu  Gln Thr Cys
    1145                1150                1155

Cys Asp  Lys Pro Leu Leu Lys  Lys Ala His Cys Leu  Ser Glu Val
    1160                1165                1170

Glu His  Asp Thr Met Pro Ala  Asp Leu Pro Ala Ile  Ala Ala Asp
    1175                1180                1185

Phe Val  Glu Asp Gln Glu Val  Cys Lys Asn Tyr Ala  Glu Ala Lys
    1190                1195                1200

Asp Val  Phe Leu Gly Thr Phe  Leu Tyr Glu Tyr Ser  Arg Arg His
    1205                1210                1215

Pro Asp  Tyr Ser Val Ser Leu  Leu Leu Arg Leu Ala  Lys Lys Tyr
    1220                1225                1230

Glu Ala  Thr Leu Glu Lys Cys  Cys Ala Glu Ala Asn  Pro Pro Ala
    1235                1240                1245

Cys Tyr  Gly Thr Val Leu Ala  Glu Phe Gln Pro Leu  Val Glu Glu
```

```
    1250                1255                1260

Pro Lys  Asn Leu Val Lys Thr  Asn Cys Asp Leu Tyr  Glu Lys Leu
    1265                1270                1275

Gly Glu  Tyr Gly Phe Gln Asn  Ala Ile Leu Val Arg  Tyr Thr Gln
    1280                1285                1290

Lys Ala  Pro Gln Val Ser Thr  Pro Thr Leu Val Glu  Ala Ala Arg
    1295                1300                1305

Asn Leu  Gly Arg Val Gly Thr  Lys Cys Cys Thr Leu  Pro Glu Asp
    1310                1315                1320

Gln Arg  Leu Pro Cys Val Glu  Asp Tyr Leu Ser Ala  Ile Leu Asn
    1325                1330                1335

Arg Val  Cys Leu Leu His Glu  Lys Thr Pro Val Ser  Glu His Val
    1340                1345                1350

Thr Lys  Cys Cys Ser Gly Ser  Leu Val Glu Arg Arg  Pro Cys Phe
    1355                1360                1365

Ser Ala  Leu Thr Val Asp Glu  Thr Tyr Val Pro Lys  Glu Phe Lys
    1370                1375                1380

Ala Glu  Thr Phe Thr Phe His  Ser Asp Ile Cys Thr  Leu
    1385                1390                1395


<210>  24
<211>  1467
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  ENPP7-NPP3-Albumin


<220>
<221>  SIGNAL
<222>  (20)..(21)
<223>  Cleavage position at the signal peptide sequence

<220>
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<221> MISC_FEATURE
<222> (860)..(1467)
<223> Indicate albumin sequence

<400> 24

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Met Arg Gly Pro Ala Val Leu Leu Thr Val Ala Leu Ala Thr Leu Leu
1               5                  10                  15


Ala Pro Gly Ala Lys Gln Gly Ser Cys Arg Lys Lys Cys Phe Asp Ala
            20                  25                  30


Ser Phe Arg Gly Leu Glu Asn Cys Arg Cys Asp Val Ala Cys Lys Asp
        35                  40                  45


Arg Gly Asp Cys Cys Trp Asp Phe Glu Asp Thr Cys Val Glu Ser Thr
    50                  55                  60


Arg Ile Trp Met Cys Asn Lys Phe Arg Cys Gly Glu Arg Leu Glu Ala
65                  70                  75                  80


Ser Leu Cys Ser Cys Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys Cys
                85                  90                  95


Ala Asp Tyr Lys Ser Val Cys Gln Gly Glu Thr Ser Trp Leu Glu Glu
            100                 105                 110


Asn Cys Asp Thr Ala Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp Leu
        115                 120                 125


Pro Pro Val Ile Leu Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr Leu
    130                 135                 140


Tyr Thr Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys Thr Cys
145                 150                 155                 160


Gly Ile His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr Phe
                165                 170                 175


Pro Asn His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly
            180                 185                 190
```

```
Ile Ile Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser
        195                 200                 205

Leu Ser Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro
    210                 215                 220

Met Trp Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe
225                 230                 235                 240

Trp Pro Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr
                245                 250                 255

Met Pro Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu
            260                 265                 270

Leu Lys Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr
        275                 280                 285

Met Tyr Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val
    290                 295                 300

Ser Ala Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala Phe Gly
305                 310                 315                 320

Met Leu Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn
                325                 330                 335

Ile Ile Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys
            340                 345                 350

Met Glu Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr Met
        355                 360                 365

Tyr Glu Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro His Asp
    370                 375                 380

Phe Phe Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg
385                 390                 395                 400

Lys Pro Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys
                405                 410                 415
```

```
Arg Leu His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His Leu Phe
            420                 425                 430

Val Asp Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys
        435                 440                 445

Gly Gly Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala
    450                 455                 460

Ile Phe Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu
465                 470                 475                 480

Pro Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg
                485                 490                 495

Ile Gln Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His Leu
            500                 505                 510

Leu Lys Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys
        515                 520                 525

Phe Ser Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu Asp
    530                 535                 540

Cys Phe Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn
545                 550                 555                 560

Gln Met Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val
                565                 570                 575

Asn Leu Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val Asp His
            580                 585                 590

Cys Leu Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala Met
        595                 600                 605

Arg Met Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp Thr
    610                 615                 620
```

```
Ser Pro Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp Val Arg
625                 630                 635                 640

Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys
                645                 650                 655

Asn Ile Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser
            660                 665                 670

Asp Ser Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro Met Tyr
        675                 680                 685

Glu Glu Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu Leu Ile
    690                 695                 700

Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile
705                 710                 715                 720

Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr
                725                 730                 735

Lys His Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val
            740                 745                 750

Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro
        755                 760                 765

Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn
    770                 775                 780

Val Glu Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu
785                 790                 795                 800

Arg Phe Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr
                805                 810                 815

Gly Leu Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu
            820                 825                 830

Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile Gly Gly Gly
        835                 840                 845
```

```
Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Met Lys Trp Val Thr
    850                 855                 860

Phe Leu Leu Leu Leu Phe Val Ser Gly Ser Ala Phe Ser Arg Gly Val
865                 870                 875                 880

Phe Arg Arg Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp
                885                 890                 895

Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln
            900                 905                 910

Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu
        915                 920                 925

Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn
    930                 935                 940

Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile
945                 950                 955                 960

Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys
                965                 970                 975

Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn
            980                 985                 990

Pro Ser Leu Pro Pro Phe Glu Arg  Pro Glu Ala Glu Ala  Met Cys Thr
        995                 1000                1005

Ser Phe  Lys Glu Asn Pro Thr  Thr Phe Met Gly His  Tyr Leu His
    1010                1015                1020

Glu Val  Ala Arg Arg His Pro  Tyr Phe Tyr Ala Pro  Glu Leu Leu
    1025                1030                1035

Tyr Tyr  Ala Glu Gln Tyr Asn  Glu Ile Leu Thr Gln  Cys Cys Ala
    1040                1045                1050
```

```
Glu Ala  Asp Lys Glu Ser Cys  Leu Thr Pro Lys Leu  Asp Gly Val
    1055                 1060                 1065

Lys Glu  Lys Ala Leu Val Ser  Ser Val Arg Gln Arg  Met Lys Cys
    1070                 1075                 1080

Ser Ser  Met Gln Lys Phe Gly  Glu Arg Ala Phe Lys  Ala Trp Ala
    1085                 1090                 1095

Val Ala  Arg Leu Ser Gln Thr  Phe Pro Asn Ala Asp  Phe Ala Glu
    1100                 1105                 1110

Ile Thr  Lys Leu Ala Thr Asp  Leu Thr Lys Val Asn  Lys Glu Cys
    1115                 1120                 1125

Cys His  Gly Asp Leu Leu Glu  Cys Ala Asp Asp Arg  Ala Glu Leu
    1130                 1135                 1140

Ala Lys  Tyr Met Cys Glu Asn  Gln Ala Thr Ile Ser  Ser Lys Leu
    1145                 1150                 1155

Gln Thr  Cys Cys Asp Lys Pro  Leu Leu Lys Lys Ala  His Cys Leu
    1160                 1165                 1170

Ser Glu  Val Glu His Asp Thr  Met Pro Ala Asp Leu  Pro Ala Ile
    1175                 1180                 1185

Ala Ala  Asp Phe Val Glu Asp  Gln Glu Val Cys Lys  Asn Tyr Ala
    1190                 1195                 1200

Glu Ala  Lys Asp Val Phe Leu  Gly Thr Phe Leu Tyr  Glu Tyr Ser
    1205                 1210                 1215

Arg Arg  His Pro Asp Tyr Ser  Val Ser Leu Leu Leu  Arg Leu Ala
    1220                 1225                 1230

Lys Lys  Tyr Glu Ala Thr Leu  Glu Lys Cys Cys Ala  Glu Ala Asn
    1235                 1240                 1245

Pro Pro  Ala Cys Tyr Gly Thr  Val Leu Ala Glu Phe  Gln Pro Leu
    1250                 1255                 1260
```

```
Val Glu  Glu Pro Lys Asn Leu  Val Lys Thr Asn Cys  Asp Leu Tyr
    1265                1270                1275

Glu Lys  Leu Gly Glu Tyr Gly  Phe Gln Asn Ala Ile  Leu Val Arg
    1280                1285                1290

Tyr Thr  Gln Lys Ala Pro Gln  Val Ser Thr Pro Thr  Leu Val Glu
    1295                1300                1305

Ala Ala  Arg Asn Leu Gly Arg  Val Gly Thr Lys Cys  Cys Thr Leu
    1310                1315                1320

Pro Glu  Asp Gln Arg Leu Pro  Cys Val Glu Asp Tyr  Leu Ser Ala
    1325                1330                1335

Ile Leu  Asn Arg Val Cys Leu  Leu His Glu Lys Thr  Pro Val Ser
    1340                1345                1350

Glu His  Val Thr Lys Cys Cys  Ser Gly Ser Leu Val  Glu Arg Arg
    1355                1360                1365

Pro Cys  Phe Ser Ala Leu Thr  Val Asp Glu Thr Tyr  Val Pro Lys
    1370                1375                1380

Glu Phe  Lys Ala Glu Thr Phe  Thr Phe His Ser Asp  Ile Cys Thr
    1385                1390                1395

Leu Pro  Glu Lys Glu Lys Gln  Ile Lys Lys Gln Thr  Ala Leu Ala
    1400                1405                1410

Glu Leu  Val Lys His Lys Pro  Lys Ala Thr Ala Glu  Gln Leu Lys
    1415                1420                1425

Thr Val  Met Asp Asp Phe Ala  Gln Phe Leu Asp Thr  Cys Cys Lys
    1430                1435                1440

Ala Ala  Asp Lys Asp Thr Cys  Phe Ser Thr Glu Gly  Pro Asn Leu
    1445                1450                1455
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Val Thr Arg Cys Lys Asp Ala Leu Ala
    1460   1465

<210> 25
<211> 1507
<212> PRT
<213> Artificial Sequence

<220>
<223> ENPP7-ENPP3-Albumin

<220>
<221> SIGNAL
<222> (20)..(21)
<223> Cleavage position at the signal peptide sequence

<220>
<221> MISC_FEATURE
<222> (900)..(1506)
<223> Indicate albumin sequence

<400> 25

Met Arg Gly Pro Ala Val Leu Leu Thr Val Ala Leu Ala Thr Leu Leu
1   5   10   15

Ala Pro Gly Ala Lys Gln Gly Ser Cys Arg Lys Lys Cys Phe Asp Ala
            20   25   30

Ser Phe Arg Gly Leu Glu Asn Cys Arg Cys Asp Val Ala Cys Lys Asp
        35   40   45

Arg Gly Asp Cys Cys Trp Asp Phe Glu Asp Thr Cys Val Glu Ser Thr
    50   55   60

Arg Ile Trp Met Cys Asn Lys Phe Arg Cys Gly Glu Arg Leu Glu Ala
65   70   75   80

Ser Leu Cys Ser Cys Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys Cys
                85   90   95

Ala Asp Tyr Lys Ser Val Cys Gln Gly Glu Thr Ser Trp Leu Glu Glu
            100   105   110

Asn Cys Asp Thr Ala Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp Leu

```
        115                 120                 125

Pro Pro Val Ile Leu Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr Leu
    130                 135                 140

Tyr Thr Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys Thr Cys
145                 150                 155                 160

Gly Ile His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr Phe
                165                 170                 175

Pro Asn His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly
            180                 185                 190

Ile Ile Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser
        195                 200                 205

Leu Ser Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro
    210                 215                 220

Met Trp Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe
225                 230                 235                 240

Trp Pro Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr
                245                 250                 255

Met Pro Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu
            260                 265                 270

Leu Lys Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr
        275                 280                 285

Met Tyr Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val
    290                 295                 300

Ser Ala Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala Phe Gly
305                 310                 315                 320

Met Leu Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn
                325                 330                 335
```

```
Ile Ile Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys
            340                 345                 350

Met Glu Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr Met
        355                 360                 365

Tyr Glu Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro His Asp
    370                 375                 380

Phe Phe Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg
385                 390                 395                 400

Lys Pro Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys
                405                 410                 415

Arg Leu His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His Leu Phe
            420                 425                 430

Val Asp Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys
        435                 440                 445

Gly Gly Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala
    450                 455                 460

Ile Phe Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu
465                 470                 475                 480

Pro Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg
                485                 490                 495

Ile Gln Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His Leu
            500                 505                 510

Leu Lys Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys
        515                 520                 525

Phe Ser Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu Asp
    530                 535                 540

Cys Phe Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn
```

```
545                 550                 555                 560

Gln Met Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val
                565                 570                 575

Asn Leu Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val Asp His
            580                 585                 590

Cys Leu Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala Met
        595                 600                 605

Arg Met Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp Thr
    610                 615                 620

Ser Pro Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp Val Arg
625                 630                 635                 640

Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys
                645                 650                 655

Asn Ile Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser
            660                 665                 670

Asp Ser Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro Met Tyr
        675                 680                 685

Glu Glu Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu Leu Ile
    690                 695                 700

Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile
705                 710                 715                 720

Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr
                725                 730                 735

Lys His Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val
            740                 745                 750

Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro
        755                 760                 765
```

```
Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn
    770                 775                 780

Val Glu Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu
785                 790                 795                 800

Arg Phe Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr
                805                 810                 815

Gly Leu Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu
            820                 825                 830

Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile Asp Lys Thr
        835                 840                 845

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
    850                 855                 860

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
865                 870                 875                 880

Thr Pro Glu Val Thr Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
                885                 890                 895

Gly Gly Ser Met Lys Trp Val Thr Phe Leu Leu Leu Leu Phe Val Ser
            900                 905                 910

Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg Glu Ala His Lys Ser
        915                 920                 925

Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly
    930                 935                 940

Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp
945                 950                 955                 960

Glu His Ala Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys
                965                 970                 975

Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu
```

```
           980                 985                 990

Phe Gly Asp Lys Leu Cys Ala Ile  Pro Asn Leu Arg Glu  Asn Tyr Gly
        995                1000                1005

Glu Leu  Ala Asp Cys Cys Thr  Lys Gln Glu Pro Glu  Arg Asn Glu
    1010                1015                1020

Cys Phe  Leu Gln His Lys Asp  Asp Asn Pro Ser Leu  Pro Pro Phe
    1025                1030                1035

Glu Arg  Pro Glu Ala Glu Ala  Met Cys Thr Ser Phe  Lys Glu Asn
    1040                1045                1050

Pro Thr  Thr Phe Met Gly His  Tyr Leu His Glu Val  Ala Arg Arg
    1055                1060                1065

His Pro  Tyr Phe Tyr Ala Pro  Glu Leu Leu Tyr Tyr  Ala Glu Gln
    1070                1075                1080

Tyr Asn  Glu Ile Leu Thr Gln  Cys Cys Ala Glu Ala  Asp Lys Glu
    1085                1090                1095

Ser Cys  Leu Thr Pro Lys Leu  Asp Gly Val Lys Glu  Lys Ala Leu
    1100                1105                1110

Val Ser  Ser Val Arg Gln Arg  Met Lys Cys Ser Ser  Met Gln Lys
    1115                1120                1125

Phe Gly  Glu Arg Ala Phe Lys  Ala Trp Ala Val Ala  Arg Leu Ser
    1130                1135                1140

Gln Thr  Phe Pro Asn Ala Asp  Phe Ala Glu Ile Thr  Lys Leu Ala
    1145                1150                1155

Thr Asp  Leu Thr Lys Val Asn  Lys Glu Cys Cys His  Gly Asp Leu
    1160                1165                1170

Leu Glu  Cys Ala Asp Asp Arg  Ala Glu Leu Ala Lys  Tyr Met Cys
    1175                1180                1185
```

```
Glu Asn  Gln Ala Thr Ile Ser  Ser Lys Leu Gln Thr  Cys Cys Asp
    1190                 1195                 1200

Lys Pro  Leu Leu Lys Lys Ala  His Cys Leu Ser Glu  Val Glu His
    1205                 1210                 1215

Asp Thr  Met Pro Ala Asp Leu  Pro Ala Ile Ala Ala  Asp Phe Val
    1220                 1225                 1230

Glu Asp  Gln Glu Val Cys Lys  Asn Tyr Ala Glu Ala  Lys Asp Val
    1235                 1240                 1245

Phe Leu  Gly Thr Phe Leu Tyr  Glu Tyr Ser Arg Arg  His Pro Asp
    1250                 1255                 1260

Tyr Ser  Val Ser Leu Leu Leu  Arg Leu Ala Lys Lys  Tyr Glu Ala
    1265                 1270                 1275

Thr Leu  Glu Lys Cys Cys Ala  Glu Ala Asn Pro Pro  Ala Cys Tyr
    1280                 1285                 1290

Gly Thr  Val Leu Ala Glu Phe  Gln Pro Leu Val Glu  Glu Pro Lys
    1295                 1300                 1305

Asn Leu  Val Lys Thr Asn Cys  Asp Leu Tyr Glu Lys  Leu Gly Glu
    1310                 1315                 1320

Tyr Gly  Phe Gln Asn Ala Ile  Leu Val Arg Tyr Thr  Gln Lys Ala
    1325                 1330                 1335

Pro Gln  Val Ser Thr Pro Thr  Leu Val Glu Ala Ala  Arg Asn Leu
    1340                 1345                 1350

Gly Arg  Val Gly Thr Lys Cys  Cys Thr Leu Pro Glu  Asp Gln Arg
    1355                 1360                 1365

Leu Pro  Cys Val Glu Asp Tyr  Leu Ser Ala Ile Leu  Asn Arg Val
    1370                 1375                 1380

Cys Leu  Leu His Glu Lys Thr  Pro Val Ser Glu His  Val Thr Lys
```

1385 1390 1395

Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe Ser Ala
1400 1405 1410

Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys Ala Glu
1415 1420 1425

Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu Lys Glu
1430 1435 1440

Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val Lys His
1445 1450 1455

Lys Pro Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met Asp Asp
1460 1465 1470

Phe Ala Gln Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp Lys Asp
1475 1480 1485

Thr Cys Phe Ser Thr Glu Gly Pro Asn Leu Val Thr Arg Cys Lys
1490 1495 1500

Asp Ala Leu Ala
1505

<210> 26
<211> 852
<212> PRT
<213> Artificial Sequence

<220>
<223> ENPP71 Amino Acid Sequence

<220>
<221> SIGNAL
<222> (22)..(23)
<223> Cleavage position at the signal peptide sequence

<400> 26

Met Arg Gly Pro Ala Val Leu Leu Thr Val Ala Leu Ala Thr Leu Leu
1 5 10 15

```
Ala Pro Gly Ala Gly Ala Gly Leu Lys Pro Ser Cys Ala Lys Glu Val
            20                  25                  30

Lys Ser Cys Lys Gly Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg
        35                  40                  45

Cys Asp Ala Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln
    50                  55                  60

Glu Thr Cys Ile Glu Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg
65                  70                  75                  80

Cys Gly Glu Lys Arg Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp
                85                  90                  95

Cys Lys Asp Lys Gly Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln
            100                 105                 110

Gly Glu Lys Ser Trp Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro
        115                 120                 125

Gln Cys Pro Ala Gly Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu
    130                 135                 140

Asp Gly Phe Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro
145                 150                 155                 160

Val Ile Ser Lys Leu Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg
                165                 170                 175

Pro Val Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr
            180                 185                 190

Gly Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp
        195                 200                 205

Pro Lys Met Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn
    210                 215                 220

Pro Glu Trp Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln
```

```
225                 230                 235                 240

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

Asn Gly Ile Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro
            260                 265                 270

Phe Glu Glu Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys
        275                 280                 285

Asp Glu Arg Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser
    290                 295                 300

Ser Gly His Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu
305                 310                 315                 320

Gln Arg Val Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu
                325                 330                 335

Leu Asn Leu His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly
            340                 345                 350

Met Glu Gln Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu
        355                 360                 365

Gly Asp Val Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu
    370                 375                 380

Arg Pro Ser Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly
385                 390                 395                 400

Ile Ala Arg Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro
                405                 410                 415

Tyr Leu Lys His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp
            420                 425                 430

Arg Ile Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala
        435                 440                 445
```

```
Leu Asn Pro Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser
    450                 455                 460

Asp Asn Val Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro
465                 470                 475                 480

Gly Phe Lys His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val
                485                 490                 495

Tyr Asn Leu Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn
            500                 505                 510

Gly Thr His Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr
        515                 520                 525

Pro Lys His Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr
    530                 535                 540

Arg Asn Pro Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu
545                 550                 555                 560

Pro Ile Glu Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu
                565                 570                 575

Lys Ile Ile Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu
            580                 585                 590

Gln Lys Glu Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser
        595                 600                 605

Gly Tyr Ser Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val
    610                 615                 620

Asp Arg Asn Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr
625                 630                 635                 640

Gln Asp Phe Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr
                645                 650                 655

Lys Asn Asn Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu
```

```
            660                 665                 670

Asn Lys Asn Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn
        675                 680                 685

Ile Val Pro Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His
    690                 695                 700

Asp Thr Leu Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val
705                 710                 715                 720

Val Ser Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser
                725                 730                 735

Leu Glu Asn Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile
            740                 745                 750

Leu Ile Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr
        755                 760                 765

Ser Gln Thr Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile
    770                 775                 780

Leu Pro His Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His
785                 790                 795                 800

Asp Ser Ser Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile
                805                 810                 815

Thr Asp Val Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys
            820                 825                 830

Glu Pro Val Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe
        835                 840                 845

Ser Gln Glu Asp
    850


<210>  27
<211>  925
<212>  PRT
```

<213> Artificial Sequence

<220>
<223> ENPP121 Amino Acid Sequence

<220>
<221> SIGNAL
<222> (92)..(93)
<223> Cleavage position at the signal peptide sequence

<400> 27

```
Met Glu Arg Asp Gly Cys Ala Gly Gly Gly Ser Arg Gly Gly Glu Gly
1               5                   10                  15


Gly Arg Ala Pro Arg Glu Gly Pro Ala Gly Asn Gly Arg Asp Arg Gly
            20                  25                  30


Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala Ser
        35                  40                  45


Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala
    50                  55                  60


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


Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly Phe Thr Ala Gly
                85                  90                  95


Leu Lys Pro Ser Cys Ala Lys Glu Val Lys Ser Cys Lys Gly Arg Cys
            100                 105                 110


Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala Ala Cys Val Glu
        115                 120                 125


Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys Ile Glu Pro Glu
    130                 135                 140


His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu Lys Arg Leu Thr
145                 150                 155                 160


Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp Lys Gly Asp Cys
```

```
                165                 170                 175

Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp Val Glu
            180                 185                 190

Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro Ala Gly Phe Glu
        195                 200                 205

Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe Arg Ala Glu Tyr
    210                 215                 220

Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser Lys Leu Lys Lys
225                 230                 235                 240

Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr Lys Thr
                245                 250                 255

Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu Ser His
            260                 265                 270

Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala Ser Phe
        275                 280                 285

Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys Gly Glu
    290                 295                 300

Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly Thr Phe
305                 310                 315                 320

Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro Asp Ile
                325                 330                 335

Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Leu Ala
            340                 345                 350

Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His Phe Tyr
        355                 360                 365

Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr Gly Pro
    370                 375                 380
```

```
Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly Met Val
385                 390                 395                 400


Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg Cys Leu
                405                 410                 415


Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser Cys Lys
            420                 425                 430


Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn Ile Lys
        435                 440                 445


Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val Pro Asp
    450                 455                 460


Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu Ser Cys
465                 470                 475                 480


Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe Leu Pro
                485                 490                 495


Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu Thr Phe
            500                 505                 510


Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu Arg Lys
        515                 520                 525


Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser Asn Met
    530                 535                 540


Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys His Gly Ile Glu
545                 550                 555                 560


Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu
                565                 570                 575


Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn
            580                 585                 590


His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His Pro Lys Glu Val
```

```
        595                 600                 605

His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp Asn Leu
    610                 615                 620

Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe Gln Thr
625                 630                 635                 640

Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His Glu Thr
                645                 650                 655

Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr Ile Cys
            660                 665                 670

Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp Ile Leu
        675                 680                 685

Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser Phe Ser
    690                 695                 700

Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile Pro Leu
705                 710                 715                 720

Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val Ser
                725                 730                 735

Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser Gly Ile
            740                 745                 750

Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln Ser
        755                 760                 765

Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys Tyr
    770                 775                 780

Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val Phe Asp
785                 790                 795                 800

Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln Lys
                805                 810                 815
```

Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe Phe
820 825 830

Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His Cys
835 840 845

Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp Asn
850 855 860

Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu Glu
865 870 875 880

Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile Thr
885 890 895

Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile Leu
900 905 910

Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp
915 920 925

<210> 28
<211> 1155
<212> PRT
<213> Artificial Sequence

<220>
<223> ENPP121-Fc Amino Acid Sequence

<220>
<221> SIGNAL
<222> (92)..(93)
<223> Cleavage position at the signal peptide sequence

<220>
<221> MISC_FEATURE
<222> (929)..(1155)
<223> Indicate Fc sequence

<400> 28

Met Glu Arg Asp Gly Cys Ala Gly Gly Gly Ser Arg Gly Gly Glu Gly
1 5 10 15

```
Gly Arg Ala Pro Arg Glu Gly Pro Ala Gly Asn Gly Arg Asp Arg Gly
            20                  25                  30

Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala Ser
        35                  40                  45

Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala
    50                  55                  60

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

Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly Phe Thr Ala Gly
                85                  90                  95

Leu Lys Pro Ser Cys Ala Lys Glu Val Lys Ser Cys Lys Gly Arg Cys
            100                 105                 110

Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala Ala Cys Val Glu
        115                 120                 125

Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys Ile Glu Pro Glu
    130                 135                 140

His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu Lys Arg Leu Thr
145                 150                 155                 160

Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp Lys Gly Asp Cys
                165                 170                 175

Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp Val Glu
            180                 185                 190

Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro Ala Gly Phe Glu
        195                 200                 205

Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe Arg Ala Glu Tyr
    210                 215                 220

Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser Lys Leu Lys Lys
225                 230                 235                 240
```

```
Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr Lys Thr
                245                 250                 255

Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu Ser His
            260                 265                 270

Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala Ser Phe
        275                 280                 285

Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys Gly Glu
    290                 295                 300

Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly Thr Phe
305                 310                 315                 320

Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro Asp Ile
                325                 330                 335

Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Leu Ala
            340                 345                 350

Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His Phe Tyr
        355                 360                 365

Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr Gly Pro
    370                 375                 380

Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly Met Val
385                 390                 395                 400

Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg Cys Leu
                405                 410                 415

Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser Cys Lys
            420                 425                 430

Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn Ile Lys
        435                 440                 445
```

```
Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val Pro Asp
    450                 455                 460

Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu Ser Cys
465                 470                 475                 480

Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe Leu Pro
                485                 490                 495

Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu Thr Phe
            500                 505                 510

Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu Arg Lys
        515                 520                 525

Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser Asn Met
    530                 535                 540

Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys His Gly Ile Glu
545                 550                 555                 560

Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu
                565                 570                 575

Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn
            580                 585                 590

His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His Pro Lys Glu Val
        595                 600                 605

His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp Asn Leu
    610                 615                 620

Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe Gln Thr
625                 630                 635                 640

Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His Glu Thr
                645                 650                 655

Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr Ile Cys
            660                 665                 670
```

```
Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp Ile Leu
        675                 680                 685

Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser Phe Ser
    690                 695                 700

Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile Pro Leu
705                 710                 715                 720

Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val Ser
                725                 730                 735

Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser Gly Ile
            740                 745                 750

Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln Ser
        755                 760                 765

Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys Tyr
    770                 775                 780

Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val Phe Asp
785                 790                 795                 800

Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln Lys
                805                 810                 815

Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe Phe
            820                 825                 830

Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His Cys
        835                 840                 845

Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp Asn
    850                 855                 860

Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu Glu
865                 870                 875                 880
```

```
Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile Thr
                885                 890                 895

Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile Leu
            900                 905                 910

Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp Leu Ile Asn
        915                 920                 925

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
    930                 935                 940

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
945                 950                 955                 960

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
                965                 970                 975

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
            980                 985                 990

His Asn Ala Lys Thr Lys Pro Arg  Glu Glu Gln Tyr Asn  Ser Thr Tyr
        995                 1000                1005

Arg Val  Val Ser Val Leu Thr  Val Leu His Gln Asp  Trp Leu Asn
    1010                1015                1020

Gly Lys  Glu Tyr Lys Cys Lys  Val Ser Asn Lys Ala  Leu Pro Ala
    1025                1030                1035

Pro Ile  Glu Lys Thr Ile Ser  Lys Ala Lys Gly Gln  Pro Arg Glu
    1040                1045                1050

Pro Gln  Val Tyr Thr Leu Pro  Pro Ser Arg Glu Glu  Met Thr Lys
    1055                1060                1065

Asn Gln  Val Ser Leu Thr Cys  Leu Val Lys Gly Phe  Tyr Pro Ser
    1070                1075                1080

Asp Ile  Ala Val Glu Trp Glu  Ser Asn Gly Gln Pro  Glu Asn Asn
    1085                1090                1095
```

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
1100 1105 1110

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
1115 1120 1125

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
1130 1135 1140

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
1145 1150 1155

<210> 29
<211> 1550
<212> PRT
<213> Artificial Sequence

<220>
<223> ENPP121-ALB Amino Acid Sequence

<220>
<221> SIGNAL
<222> (92)..(93)
<223> Cleavage position at the signal peptide sequence

<220>
<221> MISC_FEATURE
<222> (933)..(1550)
<223> Indicate albumin sequence

<400> 29

Met Glu Arg Asp Gly Cys Ala Gly Gly Gly Ser Arg Gly Gly Glu Gly
1 5 10 15

Gly Arg Ala Pro Arg Glu Gly Pro Ala Gly Asn Gly Arg Asp Arg Gly
20 25 30

Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala Ser
35 40 45

Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala
50 55 60

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

Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly Phe Thr Ala Gly
                85                  90                  95

Leu Lys Pro Ser Cys Ala Lys Glu Val Lys Ser Cys Lys Gly Arg Cys
            100                 105                 110

Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala Ala Cys Val Glu
        115                 120                 125

Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys Ile Glu Pro Glu
    130                 135                 140

His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu Lys Arg Leu Thr
145                 150                 155                 160

Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp Lys Gly Asp Cys
                165                 170                 175

Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp Val Glu
            180                 185                 190

Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro Ala Gly Phe Glu
        195                 200                 205

Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe Arg Ala Glu Tyr
    210                 215                 220

Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser Lys Leu Lys Lys
225                 230                 235                 240

Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr Lys Thr
                245                 250                 255

Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu Ser His
            260                 265                 270

Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala Ser Phe
```

```
        275                 280                 285

Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys Gly Glu
    290                 295                 300

Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly Thr Phe
305                 310                 315                 320

Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro Asp Ile
                325                 330                 335

Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Leu Ala
            340                 345                 350

Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His Phe Tyr
        355                 360                 365

Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr Gly Pro
    370                 375                 380

Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly Met Val
385                 390                 395                 400

Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg Cys Leu
                405                 410                 415

Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser Cys Lys
            420                 425                 430

Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn Ile Lys
        435                 440                 445

Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val Pro Asp
    450                 455                 460

Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu Ser Cys
465                 470                 475                 480

Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe Leu Pro
                485                 490                 495
```

```
Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu Thr Phe
            500                 505                 510

Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu Arg Lys
        515                 520                 525

Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser Asn Met
    530                 535                 540

Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys His Gly Ile Glu
545                 550                 555                 560

Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu
                565                 570                 575

Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn
            580                 585                 590

His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His Pro Lys Glu Val
        595                 600                 605

His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp Asn Leu
    610                 615                 620

Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe Gln Thr
625                 630                 635                 640

Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His Glu Thr
                645                 650                 655

Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr Ile Cys
            660                 665                 670

Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp Ile Leu
        675                 680                 685

Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser Phe Ser
    690                 695                 700

Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile Pro Leu
```

```
705                 710                 715                 720

Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val Ser
                725                 730                 735

Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser Gly Ile
            740                 745                 750

Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln Ser
        755                 760                 765

Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys Tyr
    770                 775                 780

Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val Phe Asp
785                 790                 795                 800

Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln Lys
                805                 810                 815

Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe Phe
            820                 825                 830

Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His Cys
        835                 840                 845

Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp Asn
    850                 855                 860

Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu Glu
865                 870                 875                 880

Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile Thr
                885                 890                 895

Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile Leu
            900                 905                 910

Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp Arg Ser Gly
        915                 920                 925
```

```
Ser Gly Gly Ser Met Lys Trp Val Thr Phe Leu Leu Leu Leu Phe Val
    930                 935                 940

Ser Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg Glu Ala His Lys
945                 950                 955                 960

Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys
                965                 970                 975

Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr
            980                 985                 990

Asp Glu His Ala Lys Leu Val Gln  Glu Val Thr Asp Phe  Ala Lys Thr
        995                 1000                1005

Cys Val  Ala Asp Glu Ser Ala  Ala Asn Cys Asp Lys  Ser Leu His
    1010                1015                1020

Thr Leu  Phe Gly Asp Lys Leu  Cys Ala Ile Pro Asn  Leu Arg Glu
    1025                1030                1035

Asn Tyr  Gly Glu Leu Ala Asp  Cys Cys Thr Lys Gln  Glu Pro Glu
    1040                1045                1050

Arg Asn  Glu Cys Phe Leu Gln  His Lys Asp Asp Asn  Pro Ser Leu
    1055                1060                1065

Pro Pro  Phe Glu Arg Pro Glu  Ala Glu Ala Met Cys  Thr Ser Phe
    1070                1075                1080

Lys Glu  Asn Pro Thr Thr Phe  Met Gly His Tyr Leu  His Glu Val
    1085                1090                1095

Ala Arg  Arg His Pro Tyr Phe  Tyr Ala Pro Glu Leu  Leu Tyr Tyr
    1100                1105                1110

Ala Glu  Gln Tyr Asn Glu Ile  Leu Thr Gln Cys Cys  Ala Glu Ala
    1115                1120                1125

Asp Lys  Glu Ser Cys Leu Thr  Pro Lys Leu Asp Gly  Val Lys Glu
```

```
    1130                1135                1140

Lys Ala  Leu Val Ser Ser Val  Arg Gln Arg Met Lys  Cys Ser Ser
    1145                1150                1155

Met Gln  Lys Phe Gly Glu Arg  Ala Phe Lys Ala Trp  Ala Val Ala
    1160                1165                1170

Arg Leu  Ser Gln Thr Phe Pro  Asn Ala Asp Phe Ala  Glu Ile Thr
    1175                1180                1185

Lys Leu  Ala Thr Asp Leu Thr  Lys Val Asn Lys Glu  Cys Cys His
    1190                1195                1200

Gly Asp  Leu Leu Glu Cys Ala  Asp Asp Arg Ala Glu  Leu Ala Lys
    1205                1210                1215

Tyr Met  Cys Glu Asn Gln Ala  Thr Ile Ser Ser Lys  Leu Gln Thr
    1220                1225                1230

Cys Cys  Asp Lys Pro Leu Leu  Lys Lys Ala His Cys  Leu Ser Glu
    1235                1240                1245

Val Glu  His Asp Thr Met Pro  Ala Asp Leu Pro Ala  Ile Ala Ala
    1250                1255                1260

Asp Phe  Val Glu Asp Gln Glu  Val Cys Lys Asn Tyr  Ala Glu Ala
    1265                1270                1275

Lys Asp  Val Phe Leu Gly Thr  Phe Leu Tyr Glu Tyr  Ser Arg Arg
    1280                1285                1290

His Pro  Asp Tyr Ser Val Ser  Leu Leu Leu Arg Leu  Ala Lys Lys
    1295                1300                1305

Tyr Glu  Ala Thr Leu Glu Lys  Cys Cys Ala Glu Ala  Asn Pro Pro
    1310                1315                1320

Ala Cys  Tyr Gly Thr Val Leu  Ala Glu Phe Gln Pro  Leu Val Glu
    1325                1330                1335
```

```
Glu Pro  Lys Asn Leu Val Lys  Thr Asn Cys Asp Leu  Tyr Glu Lys
    1340                1345                1350

Leu Gly  Glu Tyr Gly Phe Gln  Asn Ala Ile Leu Val  Arg Tyr Thr
    1355                1360                1365

Gln Lys  Ala Pro Gln Val Ser  Thr Pro Thr Leu Val  Glu Ala Ala
    1370                1375                1380

Arg Asn  Leu Gly Arg Val Gly  Thr Lys Cys Cys Thr  Leu Pro Glu
    1385                1390                1395

Asp Gln  Arg Leu Pro Cys Val  Glu Asp Tyr Leu Ser  Ala Ile Leu
    1400                1405                1410

Asn Arg  Val Cys Leu Leu His  Glu Lys Thr Pro Val  Ser Glu His
    1415                1420                1425

Val Thr  Lys Cys Cys Ser Gly  Ser Leu Val Glu Arg  Arg Pro Cys
    1430                1435                1440

Phe Ser  Ala Leu Thr Val Asp  Glu Thr Tyr Val Pro  Lys Glu Phe
    1445                1450                1455

Lys Ala  Glu Thr Phe Thr Phe  His Ser Asp Ile Cys  Thr Leu Pro
    1460                1465                1470

Glu Lys  Glu Lys Gln Ile Lys  Lys Gln Thr Ala Leu  Ala Glu Leu
    1475                1480                1485

Val Lys  His Lys Pro Lys Ala  Thr Ala Glu Gln Leu  Lys Thr Val
    1490                1495                1500

Met Asp  Asp Phe Ala Gln Phe  Leu Asp Thr Cys Cys  Lys Ala Ala
    1505                1510                1515

Asp Lys  Asp Thr Cys Phe Ser  Thr Glu Gly Pro Asn  Leu Val Thr
    1520                1525                1530

Arg Cys  Lys Asp Ala Leu Ala  Arg Ser Trp Ser His  Pro Gln Phe
```

1535 1540 1545

Glu Lys
1550

<210> 30
<211> 1147
<212> PRT
<213> Artificial Sequence

<220>
<223> ENPP121-NPP3-Fc sequence

<220>
<221> SIGNAL
<222> (95)..(96)
<223> Cleavage position at the signal peptide sequence

<220>
<221> MISC_FEATURE
<222> (921)..(1147)
<223> Indicate Fc sequence

<400> 30

Met Glu Arg Asp Gly Cys Ala Gly Gly Gly Ser Arg Gly Gly Glu Gly
1 5 10 15

Gly Arg Ala Pro Arg Glu Gly Pro Ala Gly Asn Gly Arg Asp Arg Gly
20 25 30

Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala Ser
35 40 45

Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala
50 55 60

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

Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly Phe Thr Ala Lys
85 90 95

Gln Gly Ser Cys Arg Lys Lys Cys Phe Asp Ala Ser Phe Arg Gly Leu
100 105 110

```
Glu Asn Cys Arg Cys Asp Val Ala Cys Lys Asp Arg Gly Asp Cys Cys
        115                 120                 125

Trp Asp Phe Glu Asp Thr Cys Val Glu Ser Thr Arg Ile Trp Met Cys
    130                 135                 140

Asn Lys Phe Arg Cys Gly Glu Arg Leu Glu Ala Ser Leu Cys Ser Cys
145                 150                 155                 160

Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys Cys Ala Asp Tyr Lys Ser
                165                 170                 175

Val Cys Gln Gly Glu Thr Ser Trp Leu Glu Glu Asn Cys Asp Thr Ala
            180                 185                 190

Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp Leu Pro Pro Val Ile Leu
        195                 200                 205

Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr Leu Tyr Thr Trp Asp Thr
    210                 215                 220

Leu Met Pro Asn Ile Asn Lys Leu Lys Thr Cys Gly Ile His Ser Lys
225                 230                 235                 240

Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Thr
                245                 250                 255

Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Asn
            260                 265                 270

Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser Leu Ser Ser Lys Glu
        275                 280                 285

Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro Met Trp Leu Thr Ala
    290                 295                 300

Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe Trp Pro Gly Ser Glu
305                 310                 315                 320
```

```
Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr Met Pro Tyr Asn Gly
                325                 330                 335

Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu Leu Lys Trp Leu Asp
            340                 345                 350

Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr Met Tyr Phe Glu Glu
        355                 360                 365

Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val Ser Ala Arg Val Ile
    370                 375                 380

Lys Ala Leu Gln Val Val Asp His Ala Phe Gly Met Leu Met Glu Gly
385                 390                 395                 400

Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn Ile Ile Leu Leu Ala
                405                 410                 415

Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys Met Glu Tyr Met Thr
            420                 425                 430

Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr Met Tyr Glu Gly Pro Ala
        435                 440                 445

Pro Arg Ile Arg Ala His Asn Ile Pro His Asp Phe Phe Ser Phe Asn
    450                 455                 460

Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg Lys Pro Asp Gln His
465                 470                 475                 480

Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys Arg Leu His Tyr Ala
                485                 490                 495

Lys Asn Val Arg Ile Asp Lys Val His Leu Phe Val Asp Gln Gln Trp
            500                 505                 510

Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys Gly Gly Gly Asn His
        515                 520                 525

Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala Ile Phe Leu Ala His
    530                 535                 540
```

```
Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu Pro Phe Glu Asn Ile
545                 550                 555                 560

Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg Ile Gln Pro Ala Pro
                565                 570                 575

Asn Asn Gly Thr His Gly Ser Leu Asn His Leu Leu Lys Val Pro Phe
            580                 585                 590

Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys Phe Ser Val Cys Gly
        595                 600                 605

Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu Asp Cys Phe Cys Pro His
    610                 615                 620

Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn Gln Met Leu Asn Leu
625                 630                 635                 640

Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val Asn Leu Pro Phe Gly
                645                 650                 655

Arg Pro Arg Val Leu Gln Lys Asn Val Asp His Cys Leu Leu Tyr His
            660                 665                 670

Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala Met Arg Met Pro Met Trp
        675                 680                 685

Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp Thr Ser Pro Leu Pro Pro
    690                 695                 700

Thr Val Pro Asp Cys Leu Arg Ala Asp Val Arg Val Pro Pro Ser Glu
705                 710                 715                 720

Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys Asn Ile Thr His Gly
                725                 730                 735

Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser Asp Ser Gln Tyr Asp
            740                 745                 750
```

```
Ala Leu Ile Thr Ser Asn Leu Val Pro Met Tyr Glu Glu Phe Arg Lys
        755                 760                 765

Met Trp Asp Tyr Phe His Ser Val Leu Leu Ile Lys His Ala Thr Glu
    770                 775                 780

Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile Phe Asp Tyr Asn Tyr
785                 790                 795                 800

Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr Lys His Leu Ala Asn
                805                 810                 815

Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val Val Leu Thr Ser Cys
            820                 825                 830

Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro Gly Trp Leu Asp Val
        835                 840                 845

Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn Val Glu Ser Cys Pro
    850                 855                 860

Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu Arg Phe Thr Ala His
865                 870                 875                 880

Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr Gly Leu Asp Phe Tyr
                885                 890                 895

Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu Gln Leu Lys Thr Tyr
            900                 905                 910

Leu Pro Thr Phe Glu Thr Thr Ile Asp Lys Thr His Thr Cys Pro Pro
        915                 920                 925

Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
    930                 935                 940

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
945                 950                 955                 960

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
                965                 970                 975
```

```
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
            980                 985                 990


Glu Glu Gln Tyr Asn Ser Thr Tyr  Arg Val Val Ser Val  Leu Thr Val
        995                 1000                1005


Leu His  Gln Asp Trp Leu Asn  Gly Lys Glu Tyr Lys  Cys Lys Val
    1010                1015                1020


Ser Asn  Lys Ala Leu Pro Ala  Pro Ile Glu Lys Thr  Ile Ser Lys
    1025                1030                1035


Ala Lys  Gly Gln Pro Arg Glu  Pro Gln Val Tyr Thr  Leu Pro Pro
    1040                1045                1050


Ser Arg  Glu Glu Met Thr Lys  Asn Gln Val Ser Leu  Thr Cys Leu
    1055                1060                1065


Val Lys  Gly Phe Tyr Pro Ser  Asp Ile Ala Val Glu  Trp Glu Ser
    1070                1075                1080


Asn Gly  Gln Pro Glu Asn Asn  Tyr Lys Thr Thr Pro  Pro Val Leu
    1085                1090                1095


Asp Ser  Asp Gly Ser Phe Phe  Leu Tyr Ser Lys Leu  Thr Val Asp
    1100                1105                1110


Lys Ser  Arg Trp Gln Gln Gly  Asn Val Phe Ser Cys  Ser Val Met
    1115                1120                1125


His Glu  Ala Leu His Asn His  Tyr Thr Gln Lys Ser  Leu Ser Leu
    1130                1135                1140


Ser Pro  Gly Lys
    1145


<210>  31
<211>  1542
<212>  PRT
<213>  Artificial Sequence
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<220>
<223> ENPP121-NPP3-Albumin sequence

<220>
<221> SIGNAL
<222> (95)..(96)
<223> Cleavage position at the signal peptide sequence

<220>
<221> MISC_FEATURE
<222> (935)..(1542)
<223> Indicate albumin sequence

<400> 31

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Met Glu Arg Asp Gly Cys Ala Gly Gly Gly Ser Arg Gly Gly Glu Gly
1               5                   10                  15


Gly Arg Ala Pro Arg Glu Gly Pro Ala Gly Asn Gly Arg Asp Arg Gly
            20                  25                  30


Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala Ser
        35                  40                  45


Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala
    50                  55                  60


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


Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly Phe Thr Ala Lys
                85                  90                  95


Gln Gly Ser Cys Arg Lys Lys Cys Phe Asp Ala Ser Phe Arg Gly Leu
            100                 105                 110


Glu Asn Cys Arg Cys Asp Val Ala Cys Lys Asp Arg Gly Asp Cys Cys
        115                 120                 125


Trp Asp Phe Glu Asp Thr Cys Val Glu Ser Thr Arg Ile Trp Met Cys
    130                 135                 140


Asn Lys Phe Arg Cys Gly Glu Arg Leu Glu Ala Ser Leu Cys Ser Cys
```

```
145                 150                 155                 160

Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys Cys Ala Asp Tyr Lys Ser
                165                 170                 175

Val Cys Gln Gly Glu Thr Ser Trp Leu Glu Glu Asn Cys Asp Thr Ala
            180                 185                 190

Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp Leu Pro Pro Val Ile Leu
        195                 200                 205

Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr Leu Tyr Thr Trp Asp Thr
    210                 215                 220

Leu Met Pro Asn Ile Asn Lys Leu Lys Thr Cys Gly Ile His Ser Lys
225                 230                 235                 240

Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Thr
                245                 250                 255

Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Asn
            260                 265                 270

Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser Leu Ser Ser Lys Glu
        275                 280                 285

Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro Met Trp Leu Thr Ala
    290                 295                 300

Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe Trp Pro Gly Ser Glu
305                 310                 315                 320

Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr Met Pro Tyr Asn Gly
                325                 330                 335

Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu Leu Lys Trp Leu Asp
            340                 345                 350

Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr Met Tyr Phe Glu Glu
        355                 360                 365
```

```
Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val Ser Ala Arg Val Ile
    370                 375                 380

Lys Ala Leu Gln Val Val Asp His Ala Phe Gly Met Leu Met Glu Gly
385                 390                 395                 400

Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn Ile Ile Leu Leu Ala
                405                 410                 415

Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys Met Glu Tyr Met Thr
            420                 425                 430

Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr Met Tyr Glu Gly Pro Ala
        435                 440                 445

Pro Arg Ile Arg Ala His Asn Ile Pro His Asp Phe Phe Ser Phe Asn
    450                 455                 460

Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg Lys Pro Asp Gln His
465                 470                 475                 480

Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys Arg Leu His Tyr Ala
                485                 490                 495

Lys Asn Val Arg Ile Asp Lys Val His Leu Phe Val Asp Gln Gln Trp
            500                 505                 510

Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys Gly Gly Gly Asn His
        515                 520                 525

Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala Ile Phe Leu Ala His
    530                 535                 540

Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu Pro Phe Glu Asn Ile
545                 550                 555                 560

Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg Ile Gln Pro Ala Pro
                565                 570                 575

Asn Asn Gly Thr His Gly Ser Leu Asn His Leu Leu Lys Val Pro Phe
```

```
            580                 585                 590

Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys Phe Ser Val Cys Gly
        595                 600                 605

Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu Asp Cys Phe Cys Pro His
    610                 615                 620

Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn Gln Met Leu Asn Leu
625                 630                 635                 640

Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val Asn Leu Pro Phe Gly
                645                 650                 655

Arg Pro Arg Val Leu Gln Lys Asn Val Asp His Cys Leu Leu Tyr His
            660                 665                 670

Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala Met Arg Met Pro Met Trp
        675                 680                 685

Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp Thr Ser Pro Leu Pro Pro
    690                 695                 700

Thr Val Pro Asp Cys Leu Arg Ala Asp Val Arg Val Pro Pro Ser Glu
705                 710                 715                 720

Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys Asn Ile Thr His Gly
                725                 730                 735

Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser Asp Ser Gln Tyr Asp
            740                 745                 750

Ala Leu Ile Thr Ser Asn Leu Val Pro Met Tyr Glu Glu Phe Arg Lys
        755                 760                 765

Met Trp Asp Tyr Phe His Ser Val Leu Leu Ile Lys His Ala Thr Glu
    770                 775                 780

Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile Phe Asp Tyr Asn Tyr
785                 790                 795                 800
```

```
Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr Lys His Leu Ala Asn
                805                 810                 815

Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val Val Leu Thr Ser Cys
            820                 825                 830

Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro Gly Trp Leu Asp Val
        835                 840                 845

Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn Val Glu Ser Cys Pro
    850                 855                 860

Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu Arg Phe Thr Ala His
865                 870                 875                 880

Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr Gly Leu Asp Phe Tyr
                885                 890                 895

Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu Gln Leu Lys Thr Tyr
            900                 905                 910

Leu Pro Thr Phe Glu Thr Thr Ile Gly Gly Gly Ser Gly Gly Gly Gly
        915                 920                 925

Ser Gly Gly Gly Gly Ser Met Lys Trp Val Thr Phe Leu Leu Leu Leu
    930                 935                 940

Phe Val Ser Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg Glu Ala
945                 950                 955                 960

His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His
                965                 970                 975

Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys
            980                 985                 990

Ser Tyr Asp Glu His Ala Lys Leu  Val Gln Glu Val Thr  Asp Phe Ala
        995                 1000                1005

Lys Thr  Cys Val Ala Asp Glu  Ser Ala Ala Asn Cys  Asp Lys Ser
```

```
    1010                1015                1020

Leu His  Thr Leu Phe Gly Asp  Lys Leu Cys Ala Ile  Pro Asn Leu
    1025                1030                1035

Arg Glu  Asn Tyr Gly Glu Leu  Ala Asp Cys Cys Thr  Lys Gln Glu
    1040                1045                1050

Pro Glu  Arg Asn Glu Cys Phe  Leu Gln His Lys Asp  Asp Asn Pro
    1055                1060                1065

Ser Leu  Pro Pro Phe Glu Arg  Pro Glu Ala Glu Ala  Met Cys Thr
    1070                1075                1080

Ser Phe  Lys Glu Asn Pro Thr  Thr Phe Met Gly His  Tyr Leu His
    1085                1090                1095

Glu Val  Ala Arg Arg His Pro  Tyr Phe Tyr Ala Pro  Glu Leu Leu
    1100                1105                1110

Tyr Tyr  Ala Glu Gln Tyr Asn  Glu Ile Leu Thr Gln  Cys Cys Ala
    1115                1120                1125

Glu Ala  Asp Lys Glu Ser Cys  Leu Thr Pro Lys Leu  Asp Gly Val
    1130                1135                1140

Lys Glu  Lys Ala Leu Val Ser  Ser Val Arg Gln Arg  Met Lys Cys
    1145                1150                1155

Ser Ser  Met Gln Lys Phe Gly  Glu Arg Ala Phe Lys  Ala Trp Ala
    1160                1165                1170

Val Ala  Arg Leu Ser Gln Thr  Phe Pro Asn Ala Asp  Phe Ala Glu
    1175                1180                1185

Ile Thr  Lys Leu Ala Thr Asp  Leu Thr Lys Val Asn  Lys Glu Cys
    1190                1195                1200

Cys His  Gly Asp Leu Leu Glu  Cys Ala Asp Asp Arg  Ala Glu Leu
    1205                1210                1215
```

```
Ala Lys  Tyr Met Cys Glu Asn  Gln Ala Thr Ile Ser  Ser Lys Leu
    1220                1225                1230

Gln Thr  Cys Cys Asp Lys Pro  Leu Leu Lys Lys Ala  His Cys Leu
    1235                1240                1245

Ser Glu  Val Glu His Asp Thr  Met Pro Ala Asp Leu  Pro Ala Ile
    1250                1255                1260

Ala Ala  Asp Phe Val Glu Asp  Gln Glu Val Cys Lys  Asn Tyr Ala
    1265                1270                1275

Glu Ala  Lys Asp Val Phe Leu  Gly Thr Phe Leu Tyr  Glu Tyr Ser
    1280                1285                1290

Arg Arg  His Pro Asp Tyr Ser  Val Ser Leu Leu Leu  Arg Leu Ala
    1295                1300                1305

Lys Lys  Tyr Glu Ala Thr Leu  Glu Lys Cys Cys Ala  Glu Ala Asn
    1310                1315                1320

Pro Pro  Ala Cys Tyr Gly Thr  Val Leu Ala Glu Phe  Gln Pro Leu
    1325                1330                1335

Val Glu  Glu Pro Lys Asn Leu  Val Lys Thr Asn Cys  Asp Leu Tyr
    1340                1345                1350

Glu Lys  Leu Gly Glu Tyr Gly  Phe Gln Asn Ala Ile  Leu Val Arg
    1355                1360                1365

Tyr Thr  Gln Lys Ala Pro Gln  Val Ser Thr Pro Thr  Leu Val Glu
    1370                1375                1380

Ala Ala  Arg Asn Leu Gly Arg  Val Gly Thr Lys Cys  Cys Thr Leu
    1385                1390                1395

Pro Glu  Asp Gln Arg Leu Pro  Cys Val Glu Asp Tyr  Leu Ser Ala
    1400                1405                1410

Ile Leu  Asn Arg Val Cys Leu  Leu His Glu Lys Thr  Pro Val Ser
```

```
    1415                1420                1425

Glu His  Val Thr Lys Cys Cys  Ser Gly Ser Leu Val  Glu Arg Arg
    1430                1435                1440

Pro Cys  Phe Ser Ala Leu Thr  Val Asp Glu Thr Tyr  Val Pro Lys
    1445                1450                1455

Glu Phe  Lys Ala Glu Thr Phe  Thr Phe His Ser Asp  Ile Cys Thr
    1460                1465                1470

Leu Pro  Glu Lys Glu Lys Gln  Ile Lys Lys Gln Thr  Ala Leu Ala
    1475                1480                1485

Glu Leu  Val Lys His Lys Pro  Lys Ala Thr Ala Glu  Gln Leu Lys
    1490                1495                1500

Thr Val  Met Asp Asp Phe Ala  Gln Phe Leu Asp Thr  Cys Cys Lys
    1505                1510                1515

Ala Ala  Asp Lys Asp Thr Cys  Phe Ser Thr Glu Gly  Pro Asn Leu
    1520                1525                1530

Val Thr  Arg Cys Lys Asp Ala  Leu Ala
    1535                1540
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<210> 32
<211> 92
<212> PRT
<213> Artificial Sequence

<220>
<223> ENPP121GLK Protein Export Signal Sequence

<400> 32

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1               5                   10                  15

Gly Arg Ala Pro Arg Glu Gly Pro Ala Gly Asn Gly Arg Asp Arg Gly
            20                  25                  30

Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala Ser
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35 40 45

Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala
50 55 60

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

Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly
85 90

<210> 33
<211> 623
<212> PRT
<213> Artificial Sequence

<220>
<223> Albumin Sequence

<400> 33

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Met
1 5 10 15

Lys Trp Val Thr Phe Leu Leu Leu Leu Phe Val Ser Gly Ser Ala Phe
20 25 30

Ser Arg Gly Val Phe Arg Arg Glu Ala His Lys Ser Glu Ile Ala His
35 40 45

Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile
50 55 60

Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys
65 70 75 80

Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu
85 90 95

Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys
100 105 110

Leu Cys Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala Asp

```
        115                 120                 125

Cys Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His
    130                 135                 140

Lys Asp Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala Glu
145                 150                 155                 160

Ala Met Cys Thr Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly His
                165                 170                 175

Tyr Leu His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
            180                 185                 190

Leu Leu Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys
        195                 200                 205

Ala Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val
    210                 215                 220

Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys Ser
225                 230                 235                 240

Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala
                245                 250                 255

Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr Lys
            260                 265                 270

Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly Asp
        275                 280                 285

Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met Cys
    290                 295                 300

Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys Cys Asp Lys
305                 310                 315                 320

Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val Glu His Asp Thr
                325                 330                 335
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Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp Phe Val Glu Asp Gln
            340                 345                 350

Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Thr
        355                 360                 365

Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Asp Tyr Ser Val Ser Leu
    370                 375                 380

Leu Leu Arg Leu Ala Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys Cys
385                 390                 395                 400

Ala Glu Ala Asn Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu Phe
                405                 410                 415

Gln Pro Leu Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys Asp
            420                 425                 430

Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val
        435                 440                 445

Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu
    450                 455                 460

Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu Pro
465                 470                 475                 480

Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile Leu
                485                 490                 495

Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His Val
            500                 505                 510

Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe Ser
        515                 520                 525

Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys Ala Glu
    530                 535                 540

Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu Lys Glu Lys
```

545 550 555 560

Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val Lys His Lys Pro
565 570 575

Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met Asp Asp Phe Ala Gln
580 585 590

Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp Lys Asp Thr Cys Phe Ser
595 600 605

Thr Glu Gly Pro Asn Leu Val Thr Arg Cys Lys Asp Ala Leu Ala
610 615 620

<210> 34
<211> 227
<212> PRT
<213> Artificial Sequence

<220>
<223> Human IgG Fc domain, Fc

<400> 34

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
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Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65 70 75 80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85 90 95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile

```
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

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

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

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys
225
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<210> 35
<211> 618
<212> PRT
<213> Artificial Sequence

<220>
<223> Albumin Sequence

<400> 35

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Met Lys Trp Val Thr Phe Leu Leu Leu Leu Phe Val Ser Gly Ser Ala
1               5                   10                  15

Phe Ser Arg Gly Val Phe Arg Arg Glu Ala His Lys Ser Glu Ile Ala
            20                  25                  30

His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu
```

```
        35                  40                  45

Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala
    50                  55                  60

Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala
            100                 105                 110

Asp Cys Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala
    130                 135                 140

Glu Ala Met Cys Thr Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly
145                 150                 155                 160

His Tyr Leu His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys
            180                 185                 190

Cys Ala Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly
        195                 200                 205

Val Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys
    210                 215                 220

Ser Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr
                245                 250                 255
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```
Lys Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met
        275                 280                 285

Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys Cys Asp
    290                 295                 300

Lys Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val Glu His Asp
305                 310                 315                 320

Thr Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp Phe Val Glu Asp
                325                 330                 335

Gln Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Thr Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Asp Tyr Ser Val Ser
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Glu Ala Asn Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu
385                 390                 395                 400

Phe Gln Pro Leu Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys
                405                 410                 415

Asp Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu
            420                 425                 430

Val Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu
    450                 455                 460

Pro Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile
```

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465                 470                 475                 480

Leu Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His
                485                 490                 495

Val Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu Lys Glu
    530                 535                 540

Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met Asp Asp Phe Ala
                565                 570                 575

Gln Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp Lys Asp Thr Cys Phe
            580                 585                 590

Ser Thr Glu Gly Pro Asn Leu Val Thr Arg Cys Lys Asp Ala Leu Ala
        595                 600                 605

Arg Ser Trp Ser His Pro Gln Phe Glu Lys
    610                 615


<210>  36
<211>  16
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  ENPP2 Signal Peptide

<400>  36

Leu Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly Phe Thr Ala
1               5                   10                  15


<210>  37
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<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Signal Sequence ENPP7

<400> 37

Met Arg Gly Pro Ala Val Leu Leu Thr Val Ala Leu Ala Thr Leu Leu
1 5 10 15

Ala Pro Gly Ala
20

<210> 38
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Signal sequence ENPP7

<400> 38

Met Arg Gly Pro Ala Val Leu Leu Thr Val Ala Leu Ala Thr Leu Leu
1 5 10 15

Ala Pro Gly Ala Gly Ala
20

<210> 39
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<223> Signal Sequence ENPP1-2-1

<400> 39

Met Glu Arg Asp Gly Cys Ala Gly Gly Gly Ser Arg Gly Gly Glu Gly
1 5 10 15

Gly Arg Ala Pro Arg Glu Gly Pro Ala Gly Asn Gly Arg Asp Arg Gly
20 25 30

Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala Ser

35 40 45

Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala
50 55 60

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

Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly Phe Thr Ala
85 90 95

<210> 40
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> exENPP3

<400> 40

Leu Leu Val Ile Met Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg
1 5 10 15

Lys

<210> 41
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Signal Sequence ENPP5

<400> 41

Met Thr Ser Lys Phe Leu Leu Val Ser Phe Ile Leu Ala Ala Leu Ser
1 5 10 15

Leu Ser Thr Thr Phe Ser
20

<210> 42
<211> 3255
<212> DNA

<213> Artificial Sequence

<220>
<223> Azurocidin-ENPP1-FC Nucleotide sequence

<220>
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<222> (72)..(73)
<223> Nucleotide sequence of signal peptide

<400> 42
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cggaccttcg gcaactgtag atgtgacgcc gcttgcgtgg aactgggcaa ctgctgcctg 180

gactaccaag agacatgcat cgagcccgag cacatctgga cctgcaacaa gttcagatgc 240

ggcgagaagc ggctgaccag atctctgtgc gcctgctctg acgactgcaa ggacaagggc 300

gactgctgca tcaactactc ctctgtgtgc cagggcgaga agtcctgggt tgaagaaccc 360

tgcgagtcca tcaacgagcc tcagtgtcct gccggcttcg agacacctcc tactctgctg 420

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atctccaagc tgaagaagtg cggcacctac accaagaaca tgaggcctgt gtaccctacc 540

aagacattcc ccaaccacta ctccatcgtg accggcctgt atcctgagag ccacggcatc 600

atcgacaaca agatgtacga ccccaagatg aacgcctcct tcagcctgaa gtccaaagag 660

aagttcaacc ccgagtggta taagggcgag cctatctggg tcaccgctaa gtaccaggga 720

ctgaagtctg gcaccttctt ttggcctggc tccgacgtgg aaatcaacgg catcttcccc 780

gacatctata agatgtacaa cggctccgtg cctttcgagg aacgcattct ggctgttctg 840

cagtggctgc agctgcctaa ggatgagagg cctcacttct acaccctgta cctggaagaa 900

cctgactcct ccggccactc ttatggccct gtgtcctctg aagtgatcaa ggccctgcag 960

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tgcctgaacc tgatcctgat ctccgaccac ggcatggaac aggggagctg caagaagtac 1080

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gccagactga ggccttctga tgtgcctgac aagtactact ccttcaacta cgagggaatc 1200

gcccggaacc tgtcctgcag agagcctaac cagcacttca agccctacct gaagcacttt 1260

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cctgagaaca actacaagac aacccctcct gtgctggaca gcgacggctc attcttcctg 3120

tactctaagc tgacagtgga caagtcccgg tggcagcaag gcaatgtgtt ttcctgctct 3180

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aaatgatagc tcgag 3255

<210> 43
<211> 4404
<212> DNA
<213> Artificial Sequence

<220>
<223> Azurocidin-ENPP1-Albumin Nucleotide sequence

<400> 43
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aactgtagat gtgacgccgc ttgcgtggaa ctgggcaact gctgcctgga ctaccaagag 180

acatgcatcg agcccgagca catctggacc tgcaacaagt tcagatgcgg cgagaagcgg 240

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aactactcct ctgtgtgcca gggcgagaag tcctgggttg aagaaccctg cgagtccatc 360

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ggcttcagag ccgagtacct gcatacttgg ggaggcctgc tgccagtgat ctccaagctg 480

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cggaacgata gcttctccac cgaggacttc agcaactgcc tgtaccagga tttcagaatc 1920

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agcttctacc agcagcggaa agaacctgtg tccgatatcc tgaagctgaa aacccatctg 2520

ccaaccttca gccaagagga cctgatcaac atgaagtggg tgaccttcct gctgctgctg 2580

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tttcgttgtg gagagaccag attagaggcc agcctttgct cttgttcaga tgactgtttg 360

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gaagaaaact gtgacacagc ccagcagtct cagtgcccag aagggtttga cctgccacca 480

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atgccaaata tcaataaact gaaaacatgt ggaattcatt caaaatacat gagagctatg 600

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tatcaaggtt taaaagccgc tacctacttt tggcccggat cagaagtggc tataaatggc 840

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<212> DNA
<213> Artificial Sequence

<220>
<223> ENPP1 Nucleotide sequence

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<213> Artificial Sequence

<220>
<223> Linker

<220>
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<222> (0)..(15)
<223> The sequence can be anywhere from 0 to 15 amino acids

<400> 57

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<210> 58
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 58

Asp Ser Ser Ser Glu Glu Lys Phe Leu Arg Arg Ile Gly Arg Phe Gly
1 5 10 15

<210> 59
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 59

Glu Glu Glu Glu Glu Glu Glu Pro Arg Gly Asp Thr
1 5 10

<210> 60
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<212> PRT
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<220>
<223> Linker

<400> 60

Ala Pro Trp His Leu Ser Ser Gln Tyr Ser Arg Thr
1 5 10

<210> 61
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 61

Ser Thr Leu Pro Ile Pro His Glu Phe Ser Arg Glu
1 5 10

<210> 62
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 62

Val Thr Lys His Leu Asn Gln Ile Ser Gln Ser Tyr
1 5 10

<210> 63
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<212> PRT
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<220>
<223> Linker

<220>
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<223> The sequence can be anywhere from 1 to 15 amino acids

<400> 63

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<210> 64
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<220>
<223> Linker

<400> 64

Gly Gly Ser Gly Gly Ser
1   5

<210> 65
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 65

Arg Ser Gly Ser Gly Gly Ser
1   5

<210> 66
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<212> PRT
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<220>
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<400> 66

Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp
1 5 10 15

<210> 67
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 67

Leu Val Ile Met Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5 10 15

<210> 68
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 68

Val Ile Met Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5 10 15

<210> 69
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 69

Ile Met Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5 10

<210> 70
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 70

Met Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1   5   10

<210> 71
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 71

Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1   5   10

<210> 72
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 72

Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1   5   10

<210> 73
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 73

Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1   5   10

<210> 74
<211> 9
<212> PRT

<213> Artificial Sequence

<220>
<223> Linker

<400> 74

Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5

<210> 75
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 75

Gly Leu Gly Leu Gly Leu Arg Lys
1 5

<210> 76
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 76

Leu Gly Leu Gly Leu Arg Lys
1 5

<210> 77
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 77

Gly Leu Gly Leu Arg Lys
1 5

<210> 78

<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 78

Leu Gly Leu Arg Lys
1 5

<210> 79
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<400> 79

Gly Leu Arg Lys
1

<210> 80
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<220>
<221> MISC_FEATURE
<222> (1)..(15)
<223> The sequence can be anywhere from 1 to 15 amino acids

<400> 80

Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys
1 5 10 15

<210> 81
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Linker

<220>
<221> MISC_FEATURE
<222> (1)..(15)
<223> The sequence can be anywhere from 1 to 15 amino acids

<400> 81

Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp
1 5 10 15

<210> 82
<211> 1063
<212> PRT
<213> Artificial Sequence

<220>
<223> Soluble NPP1-Fc fuion protein sequence

<220>
<221> MISC_FEATURE
<222> (837)..(1063)
<223> Indicate Fc sequence

<400> 82

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

Lys Gly Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala
20 25 30

Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys
35 40 45

Ile Glu Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu
50 55 60

Lys Arg Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp
65 70 75 80

Lys Gly Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys
85 90 95

Ser Trp Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro

```
            100                 105                 110

Ala Gly Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe
        115                 120                 125

Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser
    130                 135                 140

Lys Leu Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr
145                 150                 155                 160

Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr
                165                 170                 175

Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met
            180                 185                 190

Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp
        195                 200                 205

Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys
    210                 215                 220

Ser Gly Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile
225                 230                 235                 240

Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu
                245                 250                 255

Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg
            260                 265                 270

Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His
        275                 280                 285

Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val
    290                 295                 300

Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu
305                 310                 315                 320
```

```
His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln
                325                 330                 335

Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val
            340                 345                 350

Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser
        355                 360                 365

Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg
    370                 375                 380

Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys
385                 390                 395                 400

His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu
                405                 410                 415

Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro
            420                 425                 430

Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val
        435                 440                 445

Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys
    450                 455                 460

His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu
465                 470                 475                 480

Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His
                485                 490                 495

Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His
            500                 505                 510

Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro
        515                 520                 525

Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu
```

```
    530                 535                 540

Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile
545                 550                 555                 560

Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu
                565                 570                 575

Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser
            580                 585                 590

Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn
        595                 600                 605

Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe
    610                 615                 620

Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn
625                 630                 635                 640

Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn
                645                 650                 655

Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro
            660                 665                 670

Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu
        675                 680                 685

Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly
    690                 695                 700

Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn
705                 710                 715                 720

Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro
                725                 730                 735

Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr
            740                 745                 750
```

```
Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His
        755                 760                 765

Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser
    770                 775                 780

Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val
785                 790                 795                 800

Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val
                805                 810                 815

Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu
            820                 825                 830

Asp Leu Ile Asn Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
        835                 840                 845

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
    850                 855                 860

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
865                 870                 875                 880

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
                885                 890                 895

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
            900                 905                 910

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
        915                 920                 925

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
    930                 935                 940

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
945                 950                 955                 960

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
```

965 970 975

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
980 985 990

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
995 1000 1005

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
1010 1015 1020

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
1025 1030 1035

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
1040 1045 1050

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
1055 1060

<210> 83
<211> 3180
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence of solube NPP1-Fc

<400> 83
ttcaccgccg gactgaagcc cagctgcgcc aaagaagtga agtcctgcaa gggccggtgc 60

ttcgagcgga ccttcggcaa ctgcagatgc gacgccgcct gtgtggaact gggcaactgc 120

tgcctggact accaggaaac ctgcatcgag cccgagcaca tctggacctg caacaagttc 180

agatgcggcg agaagcggct gaccagatcc ctgtgtgcct gcagcgacga ctgcaaggac 240

aagggcgact gctgcatcaa ctacagcagc gtgtgccagg gcgagaagtc ctgggtggaa 300

gaaccctgcg agagcatcaa cgagccccag tgccctgccg gcttcgagac acctcctacc 360

ctgctgttca gcctggacgg ctttcgggcc gagtacctgc acacatgggg aggcctgctg 420

cccgtgatca gcaagctgaa gaagtgcggc acctacacca agaacatgcg gcccgtgtac 480

cccaccaaga ccttccccaa ccactactcc atcgtgaccg gcctgtaccc cgagagccac 540

ggcatcatcg acaacaagat gtacgacccc aagatgaacg ccagcttcag cctgaagtcc 600

aaagagaagt tcaaccccga gtggtataag ggcgagccca tctgggtcac cgccaagtac 660

cagggcctga aaagcggcac attcttttgg cccggcagcg acgtggaaat caacggcatc 720

ttccccgaca tctataagat gtacaacggc agcgtgccct tcgaggaacg gatcctggct 780

gtgctgcagt ggctgcagct gcccaaggat gagcggcccc acttctacac cctgtacctg 840

gaagaacctg acagcagcgg ccacagctac ggccctgtgt ccagcgaagt gatcaaggcc 900

ctgcagcggg tggacggcat ggtgggaatg ctgatggacg gcctgaaaga gctgaacctg 960

cacagatgcc tgaacctgat cctgatcagc gaccacggca tggaacaggg atcctgcaag 1020

aagtacatct acctgaacaa gtacctgggc gacgtgaaga acatcaaagt gatctacggc 1080

ccagccgcca gactgaggcc tagcgacgtg cccgacaagt actacagctt caactacgag 1140

ggaatcgccc ggaacctgag ctgcagagag cccaaccagc acttcaagcc ctacctgaag 1200

cacttcctgc ccaagcggct gcacttcgcc aagagcgaca gaatcgagcc cctgaccttc 1260

tacctggacc cccagtggca gctggccctg aatcccagcg agagaaagta ctgcggcagc 1320

ggcttccacg gctccgacaa cgtgttcagc aacatgcagg ccctgttcgt gggctacgga 1380

cccggcttta agcacggcat cgaggccgac accttcgaga acatcgaggt gtacaatctg 1440

atgtgcgacc tgctgaatct gacccctgcc cccaacaatg gcacccacgg cagcctgaac 1500

catctgctga agaaccccgt gtacacccct aagcacccca aagaggtgca ccccctggtg 1560

cagtgcccct tcaccagaaa ccccagagac aacctgggct gtagctgcaa ccccagcatc 1620

ctgcccatcg aggacttcca gacccagttc aacctgaccg tggccgagga aaagatcatc 1680

aagcacgaga cactgcccta cggcagaccc cgggtgctgc agaaagagaa caccatctgc 1740

ctgctgagcc agcaccagtt catgagcggc tactcccagg acatcctgat gcccctgtgg 1800

accagctaca ccgtggaccg gaacgacagc ttctccaccg aggatttcag caactgcctg 1860

taccaggatt tccggatccc cctgagcccc gtgcacaagt gcagcttcta caagaacaac 1920

accaaggtgt cctacggctt cctgagccct ccccagctga acaagaacag ctccggcatc 1980

tacagcgagg ccctgctgac taccaacatc gtgcccatgt accagagctt ccaagtgatc 2040

tggcggtact tccacgacac cctgctgcgg aagtacgccg aagaacggaa cggcgtgaac 2100

gtggtgtccg gcccagtgtt cgacttcgac tacgacggca gatgtgacag cctggaaaat 2160

ctgcggcaga aaagaagagt gatccggaac caggaaattc tgatccctac ccacttcttt 2220

atcgtgctga caagctgcaa ggataccagc cagacccccc tgcactgcga gaacctggat 2280

accctggcct tcatcctgcc tcaccggacc gacaacagcg agagctgtgt gcacggcaag 2340

cacgacagct cttgggtgga agaactgctg atgctgcacc gggccagaat caccgatgtg 2400

gaacacatca ccggcctgag cttttaccag cagcggaaag aacccgtgtc cgatatcctg 2460

aagctgaaaa cccatctgcc caccttcagc caggaagatg acaagaccca cacttgcccc 2520

ccctgcccag ctcctgaact gctgggagga ccctctgtgt tcctgttccc cccaaagccc 2580

aaggacaccc tgatgatctc taggaccccc gaagtcactt gcgtcgtcgt cgacgtgtcc 2640

cacgaggacc ctgaagtcaa gttcaactgg tacgtcgacg gtgtcgaagt ccacaacgcc 2700

aagaccaagc ccagggaaga acagtacaac tctacctacc gcgtcgtcag cgtcctgacc 2760

gtcctgcacc aggactggct gaacggaaag gaatacaagt gcaaggtgtc caacaaggcc 2820

ctgcctgccc ccatcgaaaa gaccatctct aaggccaagg gacagccccg cgaaccccag 2880

gtctacaccc tgccaccctc tagggaagaa atgaccaaga accaggtgtc cctgacctgc 2940

ctggtcaagg gattctaccc ctctgacatc gccgtcgaat gggaatctaa cggacagccc 3000

gaaaacaact acaagaccac ccccccctgtc ctggactctg acggatcatt cttcctgtac 3060

tctaagctga ctgtcgacaa gtctaggtgg cagcagggaa acgtgttctc ttgctctgtc 3120

atgcacgaag ccctgcacaa ccactacacc cagaagtctc tgtctctgtc ccccggaaag 3180

<210> 84
<211> 1060
<212> PRT
<213> Artificial Sequence

<220>
<223> Soluble NPP1-(GLK)-Fc fusion protein sequence

<220>
<221> MISC_FEATURE
<222> (4)..(830)
<223> beginning and end of NPP1

<220>
<221> MISC_FEATURE
<222> (834)..(1060)
<223> Fc sequence

<400> 84

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Gly Leu Lys Pro Ser Cys Ala Lys Glu Val Lys Ser Cys Lys Gly Arg
1               5                  10                  15

Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala Ala Cys Val
            20                  25                  30

Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys Ile Glu Pro
        35                  40                  45

Glu His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu Lys Arg Leu
    50                  55                  60

Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp Lys Gly Asp
65                  70                  75                  80

Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp Val
                85                  90                  95

Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro Ala Gly Phe
            100                 105                 110

Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe Arg Ala Glu
        115                 120                 125

Tyr Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser Lys Leu Lys
    130                 135                 140

Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr Lys
145                 150                 155                 160

Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu Ser
                165                 170                 175

His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala Ser
            180                 185                 190

Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys Gly
        195                 200                 205
```

```
Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly Thr
    210                 215                 220

Phe Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro Asp
225                 230                 235                 240

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

Ala Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His Phe
            260                 265                 270

Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr Gly
        275                 280                 285

Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly Met
    290                 295                 300

Val Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg Cys
305                 310                 315                 320

Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser Cys
                325                 330                 335

Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn Ile
            340                 345                 350

Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val Pro
        355                 360                 365

Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu Ser
    370                 375                 380

Cys Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe Leu
385                 390                 395                 400

Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu Thr
                405                 410                 415

Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu Arg
            420                 425                 430
```

```
Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser Asn
        435                 440                 445

Met Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys His Gly Ile
    450                 455                 460

Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp
465                 470                 475                 480

Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu
                485                 490                 495

Asn His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His Pro Lys Glu
            500                 505                 510

Val His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp Asn
        515                 520                 525

Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe Gln
    530                 535                 540

Thr Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His Glu
545                 550                 555                 560

Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr Ile
                565                 570                 575

Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp Ile
            580                 585                 590

Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser Phe
        595                 600                 605

Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile Pro
    610                 615                 620

Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val
625                 630                 635                 640
```

```
Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser Gly
                645                 650                 655

Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln
            660                 665                 670

Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys
        675                 680                 685

Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val Phe
    690                 695                 700

Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln
705                 710                 715                 720

Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe
                725                 730                 735

Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His
            740                 745                 750

Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp
        755                 760                 765

Asn Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu
    770                 775                 780

Glu Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile
785                 790                 795                 800

Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile
                805                 810                 815

Leu Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp Leu Ile
            820                 825                 830

Asn Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
        835                 840                 845

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
    850                 855                 860
```

```
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
865                 870                 875                 880

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
                885                 890                 895

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
            900                 905                 910

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
        915                 920                 925

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
    930                 935                 940

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
945                 950                 955                 960

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
                965                 970                 975

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
            980                 985                 990

Glu Trp Glu Ser Asn Gly Gln Pro  Glu Asn Asn Tyr Lys  Thr Thr Pro
        995                 1000                1005

Pro Val  Leu Asp Ser Asp Gly  Ser Phe Phe Leu Tyr  Ser Lys Leu
    1010                1015                1020

Thr Val  Asp Lys Ser Arg Trp  Gln Gln Gly Asn Val  Phe Ser Cys
    1025                1030                1035

Ser Val  Met His Glu Ala Leu  His Asn His Tyr Thr  Gln Lys Ser
    1040                1045                1050

Leu Ser  Leu Ser Pro Gly Lys
    1055                1060
```

<210> 85
<211> 1057
<212> PRT
<213> Artificial Sequence

<220>
<223> Soluble NPP1-Fc fusion protein sequence

<220>
<221> MISC_FEATURE
<222> (1)..(827)
<223> beginning and end of NPP1

<220>
<221> MISC_FEATURE
<222> (831)..(1057)
<223> Fc sequence

<400> 85

Pro Ser Cys Ala Lys Glu Val Lys Ser Cys Lys Gly Arg Cys Phe Glu
1 5 10 15

Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala Ala Cys Val Glu Leu Gly
20 25 30

Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys Ile Glu Pro Glu His Ile
35 40 45

Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu Lys Arg Leu Thr Arg Ser
50 55 60

Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp Lys Gly Asp Cys Cys Ile
65 70 75 80

Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp Val Glu Glu Pro
85 90 95

Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro Ala Gly Phe Glu Thr Pro
100 105 110

Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe Arg Ala Glu Tyr Leu His
115 120 125

Thr Trp Gly Gly Leu Leu Pro Val Ile Ser Lys Leu Lys Lys Cys Gly

```
    130                 135                 140

Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr Lys Thr Phe Pro
145                 150                 155                 160

Asn His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly Ile
                165                 170                 175

Ile Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala Ser Phe Ser Leu
            180                 185                 190

Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys Gly Glu Pro Ile
        195                 200                 205

Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly Thr Phe Phe Trp
    210                 215                 220

Pro Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro Asp Ile Tyr Lys
225                 230                 235                 240

Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Leu Ala Val Leu
                245                 250                 255

Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His Phe Tyr Thr Leu
            260                 265                 270

Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr Gly Pro Val Ser
        275                 280                 285

Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly Met Val Gly Met
    290                 295                 300

Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg Cys Leu Asn Leu
305                 310                 315                 320

Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser Cys Lys Lys Tyr
                325                 330                 335

Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn Ile Lys Val Ile
            340                 345                 350
```

```
Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val Pro Asp Lys Tyr
        355                 360                 365

Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu Ser Cys Arg Glu
    370                 375                 380

Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe Leu Pro Lys Arg
385                 390                 395                 400

Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu Thr Phe Tyr Leu
                405                 410                 415

Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu Arg Lys Tyr Cys
            420                 425                 430

Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser Asn Met Gln Ala
        435                 440                 445

Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys His Gly Ile Glu Ala Asp
    450                 455                 460

Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Asn
465                 470                 475                 480

Leu Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His Leu
                485                 490                 495

Leu Lys Asn Pro Val Tyr Thr Pro Lys His Pro Lys Glu Val His Pro
            500                 505                 510

Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp Asn Leu Gly Cys
        515                 520                 525

Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe Gln Thr Gln Phe
    530                 535                 540

Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His Glu Thr Leu Pro
545                 550                 555                 560

Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr Ile Cys Leu Leu
```

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                565                 570                 575

Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp Ile Leu Met Pro
            580                 585                 590

Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser Phe Ser Thr Glu
        595                 600                 605

Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile Pro Leu Ser Pro
    610                 615                 620

Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val Ser Tyr Gly
625                 630                 635                 640

Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser Gly Ile Tyr Ser
                645                 650                 655

Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln Ser Phe Gln
            660                 665                 670

Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys Tyr Ala Glu
        675                 680                 685

Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val Phe Asp Phe Asp
    690                 695                 700

Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln Lys Arg Arg
705                 710                 715                 720

Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe Phe Ile Val
                725                 730                 735

Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His Cys Glu Asn
            740                 745                 750

Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp Asn Ser Glu
        755                 760                 765

Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu Glu Leu Leu
    770                 775                 780
```

```
Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile Thr Gly Leu
785                 790                 795                 800


Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile Leu Lys Leu
                805                 810                 815


Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp Leu Ile Asn Asp Lys
            820                 825                 830


Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
        835                 840                 845


Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
    850                 855                 860


Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
865                 870                 875                 880


Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
                885                 890                 895


Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
            900                 905                 910


Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
        915                 920                 925


Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
    930                 935                 940


Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
945                 950                 955                 960


Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
                965                 970                 975


Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
            980                 985                 990


Ser Asn Gly Gln Pro Glu Asn Asn  Tyr Lys Thr Thr Pro  Pro Val Leu
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995 1000 1005

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
1010 1015 1020

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
1025 1030 1035

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
1040 1045 1050

Ser Pro Gly Lys
1055

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<211> 1058
<212> PRT
<213> Artificial Sequence

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<222> (2)..(828)
<223> beginning and end of NPP1

<220>
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Ala Pro Ser Cys Ala Lys Glu Val Lys Ser Cys Lys Gly Arg Cys Phe
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Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala Ala Cys Val Glu Leu
20 25 30

Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys Ile Glu Pro Glu His
35 40 45

Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu Lys Arg Leu Thr Arg
50 55 60

```
Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp Lys Gly Asp Cys Cys
65                  70                  75                  80

Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp Val Glu Glu
                85                  90                  95

Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro Ala Gly Phe Glu Thr
            100                 105                 110

Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe Arg Ala Glu Tyr Leu
        115                 120                 125

His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser Lys Leu Lys Lys Cys
    130                 135                 140

Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr Lys Thr Phe
145                 150                 155                 160

Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly
                165                 170                 175

Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala Ser Phe Ser
            180                 185                 190

Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys Gly Glu Pro
        195                 200                 205

Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly Thr Phe Phe
    210                 215                 220

Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro Asp Ile Tyr
225                 230                 235                 240

Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Leu Ala Val
                245                 250                 255

Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His Phe Tyr Thr
            260                 265                 270
```

```
Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr Gly Pro Val
        275                 280                 285

Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly Met Val Gly
    290                 295                 300

Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg Cys Leu Asn
305                 310                 315                 320

Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser Cys Lys Lys
                325                 330                 335

Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn Ile Lys Val
            340                 345                 350

Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val Pro Asp Lys
        355                 360                 365

Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu Ser Cys Arg
    370                 375                 380

Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe Leu Pro Lys
385                 390                 395                 400

Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu Thr Phe Tyr
                405                 410                 415

Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu Arg Lys Tyr
            420                 425                 430

Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser Asn Met Gln
        435                 440                 445

Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys His Gly Ile Glu Ala
    450                 455                 460

Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu
465                 470                 475                 480

Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His
                485                 490                 495
```

```
Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His Pro Lys Glu Val His
            500                 505                 510

Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp Asn Leu Gly
        515                 520                 525

Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe Gln Thr Gln
    530                 535                 540

Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His Glu Thr Leu
545                 550                 555                 560

Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr Ile Cys Leu
                565                 570                 575

Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp Ile Leu Met
            580                 585                 590

Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser Phe Ser Thr
        595                 600                 605

Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile Pro Leu Ser
    610                 615                 620

Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val Ser Tyr
625                 630                 635                 640

Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser Gly Ile Tyr
                645                 650                 655

Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln Ser Phe
            660                 665                 670

Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys Tyr Ala
        675                 680                 685

Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val Phe Asp Phe
    690                 695                 700
```

```
Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln Lys Arg
705                 710                 715                 720


Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe Phe Ile
                725                 730                 735


Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His Cys Glu
            740                 745                 750


Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp Asn Ser
        755                 760                 765


Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu Glu Leu
    770                 775                 780


Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile Thr Gly
785                 790                 795                 800


Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile Leu Lys
                805                 810                 815


Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp Leu Ile Asn Asp
            820                 825                 830


Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
        835                 840                 845


Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
    850                 855                 860


Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
865                 870                 875                 880


Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
                885                 890                 895


Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
            900                 905                 910


Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
        915                 920                 925
```

```
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
    930                 935                 940

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
945                 950                 955                 960

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
                965                 970                 975

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
            980                 985                 990

Glu Ser Asn Gly Gln Pro Glu Asn  Asn Tyr Lys Thr Thr  Pro Pro Val
        995                 1000                1005

Leu Asp  Ser Asp Gly Ser Phe  Phe Leu Tyr Ser Lys  Leu Thr Val
    1010                1015                1020

Asp Lys  Ser Arg Trp Gln Gln  Gly Asn Val Phe Ser  Cys Ser Val
    1025                1030                1035

Met His  Glu Ala Leu His Asn  His Tyr Thr Gln Lys  Ser Leu Ser
    1040                1045                1050

Leu Ser  Pro Gly Lys
    1055
```