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(54)名稱

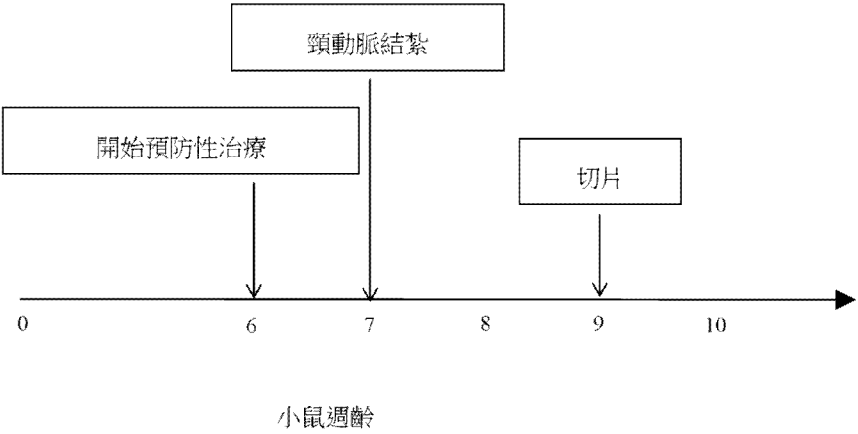
用於抑制血管平滑肌細胞增生之組成物與方法

(57)摘要

本揭露係提供藉由投予 ENPP1 藥劑或 ENPP3 藥劑於一對象中治療血管平滑肌細胞增生之組成物與方法，該對象不具有造成鈣化或骨化之病理疾病的外核苷酸焦磷酸酶磷酸二酯酶 1(ENPP1)缺乏。

The present disclosure provides compositions and methods for treating vascular smooth muscle cell proliferation in a subject that does not have a deficiency of ectonucleotide pyrophosphatase phosphodiesterase-1 (ENPP1) resulting in a pathological disease of calcification or ossification by administering an ENPP1 agent or an ENPP3 agent.

指定代表圖：



【圖1】

【發明摘要】

【中文發明名稱】 用於抑制血管平滑肌細胞增生之組成物與方法

【英文發明名稱】 COMPOSITIONS AND METHODS FOR INHIBITING
VASCULAR SMOOTH MUSCLE CELL
PROLIFERATION

【中文】

本揭露係提供藉由投予ENPP1藥劑或ENPP3藥劑於一對象中治療血管平滑肌細胞增生之組成物與方法，該對象不具有造成鈣化或骨化之病理疾病的外核苷酸焦磷酸酶磷酸二酯酶1(ENPP1)缺乏。

【英文】

The present disclosure provides compositions and methods for treating vascular smooth muscle cell proliferation in a subject that does not have a deficiency of ectonucleotide pyrophosphatase phosphodiesterase-1 (ENPP1) resulting in a pathological disease of calcification or ossification by administering an ENPP1 agent or an ENPP3 agent.

【指定代表圖】

圖1

【代表圖之符號簡單說明】

無

【特徵化學式】

無

【發明說明書】

【中文發明名稱】 用於抑制血管平滑肌細胞增生之組成物與方法

【英文發明名稱】 COMPOSITIONS AND METHODS FOR INHIBITING

 VASCULAR SMOOTH MUSCLE CELL

 PROLIFERATION

交互參照

【0001】 本申請書係聲請2020年5月27日申請的美國申請案第63/030,870號之優先權，其內容係以全文引用的方式併入本文中。

序列表

【0002】 本申請書係含有以ASCII電子型式提出的序列表且係以全文引用的方式併入。該2021年5月26所製作的ASCII副本係命名為4427-10102_sequence_ST25.txt且大小為340 kb。

【技術領域】

【0003】 本揭露係提供藉由投予ENPP1藥劑或ENPP3藥劑於一對象中治療血管平滑肌細胞增生之組成物與方法，該對象不具有造成鈣化或骨化之病理疾病的外核苷酸焦磷酸酶磷酸二酯酶1(ENPP1)缺乏。

【先前技術】

【0004】 肌內膜增生或肌內膜過度增生為一種特徵為血管壁的平滑肌細胞異常增生之複雜的病理過程。增生的平滑肌細胞遷移到內皮下區域並形成可能造成血管腔狹窄和阻塞的增生性病灶。

【0005】 動脈粥樣硬化和血管內膜過度增生促成心血管疾病(CVD)，其中動脈粥樣硬化造成初期原生血管狹窄而血管內膜過度增生則導致手術介入後的再狹窄發生。雖然支架減輕了選擇的冠狀動脈病灶中再狹窄的風險，但支架內再狹窄仍經常發生且常為棘手的臨床問題。儘管支架防止了血管成形術及後續收縮性重塑之後的立即血管回縮，但支架置入可能直接損傷血管壁並觸發血管內膜過度增生，其通常導致血管再狹窄，血管腔窄化。在具有冠狀動脈支架的病患中，血管內膜過度增生之發生和再發生的潛在機制仍未明。

【0006】 血管內膜過度增生亦為經皮冠狀動脈介入術，例如血管成形術後之再狹窄的主因。在繞道管道，例如靜脈和人工血管中的血管內膜過度增生大大地限制血管介入術之長遠的成功之路。血管內膜過度增生可能影響所有形式的人工血管，包括用於冠狀動脈和週邊動脈繞道的靜脈和人工血管，以及為了血液透析使用所製造的動靜脈瘻管(AVF)。

【0007】 全世界每年移植超過 1 百萬支的人工血管。高達 50%的這些移植植物，由於在吻合位置發生血管內膜過度增生，在手術後的前 18 個月內為失敗的。缺乏防止這些病理之治療為主要的問題並且尚未有效地解決。因此，對於防止及/或降低在各種臨床介入中的血管內膜過度增生之有效治療有其需求。

【發明內容】

【0008】 本揭露(至少部分)係以投予可溶性 ENPP1 或 ENPP3 可在不缺乏 ENPP1 蛋白活性或表現之一或二者的對象中抑制不欲的血管平滑肌細胞增生之意外發現為基礎。如在下列工作實例中所述，在不缺乏 ENPP1 表現或活性之野生型小鼠中組織損傷後，投予可溶性 ENPP1 或 ENPP3 抑制了血管平滑肌細胞增生。

【0009】 因此，在一方面，本揭露係提供在一具有組織損傷的對象中降低及/或防止血管平滑肌細胞增生惡化的方法。該方法係包括對該對象投予一治療上有效量之 ENPP1 或 ENPP3 藥劑，藉此降低及/或防止該對象中損傷位置之血管平滑肌細胞增生惡化。

【0010】 因此，在一方面，本揭露係提供在一具有組織損傷的對象中降低及/或防止血管平滑肌細胞增生惡化的方法。該方法係包括對該對象投予一治療上有效量之 ENPP1 或 ENPP3 藥劑，藉此降低及/或防止該對象中損傷位置之血管平滑肌細胞增生惡化。

【0011】 在某些具體實例中，該對象無 ENPP1 缺乏。

【0012】 在任何文中所述方法之某些具體實例中，該組織損傷為任何動脈或靜脈之損傷。動脈可為，例如冠狀動脈或頸動脈。

【0013】 在任何文中所述方法之某些具體實例中，該組織損傷係因為動脈中置入支架。在任何文中所述方法之某些具體實例中，該對象係處於發生再狹窄的風險中。在任何文中所述方法之某些具體實例中，該對象係患有再狹窄。在任何文中所述方法之某些具體實例中，該對象係患有動脈再狹窄。

【0014】 又在另外方面，本揭露之特色為於一需要手術的對象中降低及/或防止血管平滑肌細胞增生惡化的方法。該方法包括：向該對象投予一治療上有效量之 ENPP1 或 ENPP3 藥劑，藉此降低及/或防止該對象中手術位置之血管平滑肌細胞增生惡化。

【0015】 又在另外方面，本揭露之特色為於一需要手術的對象中降低及/或防止血管平滑肌細胞增生惡化的方法。該方法包括：向該對象投予一治療上有效量之 ENPP1 或 ENPP3 藥劑，藉此降低及/或防止該對象中手術位置之血管平滑肌細胞增生惡化。

【0016】 在某些具體實例中，任何文中所述的方法亦可包括偵測該對象中，例如在損傷位置或手術位置之血管平滑肌細胞增生的存在及/或測量其量。在某些具體實例中，此偵測及/或測量可在投予 ENPP1 藥劑或 ENPP3 藥劑之前，期間或之後進行。

【0017】 在任何文中所述方法之某些具體實例中，該 ENPP1 藥劑係包括保留酵素活性之 ENPP1 變體。

【0018】 在任何文中所述方法之某些具體實例中，該 ENPP3 藥劑係包括保留酵素活性之 ENPP3 變體。

【0019】 在任何文中所述方法之某些具體實例中，該藥劑(例如，ENPP1 藥劑或 ENPP3 藥劑)係在手術之前給藥。

【0020】 在任何文中所述方法之某些具體實例中，該藥劑(例如，ENPP1 藥劑或 ENPP3 藥劑)係在手術期間給藥。

【0021】 在任何文中所述方法之某些具體實例中，該藥劑(例如，ENPP1 藥劑或 ENPP3 藥劑)係在手術之後給藥。

【0022】 在任何文中所述方法之某些具體實例中，該藥劑(例如，ENPP1 藥劑或 ENPP3 藥劑)係在手術之前、手術期間或手術之後給藥。

【0023】 在某些具體實例中，任何文中所述的方法進一步係包括進行該手術。

【0024】 在任何文中所述方法之某些具體實例中，該手術係包括動脈繞道手術。

【0025】 在任何文中所述方法之某些具體實例中，該手術係包括置入動脈支架。

【0026】 在任何文中所述方法之某些具體實例中，該手術係包括血管成形術。

【0027】 在另外方面，本揭露係提供於一處於非手術組織損傷風險的對象中預防血管平滑肌細胞增生的方法。該方法係包括對該對象投予一治療上有效量的 ENPP1 或 ENPP3 藥劑，藉此於該對象之非手術組織損傷位置防止血管平滑肌細胞增生惡化或降低血管平滑肌細胞增生程度。在某些具體實例中，該非手術組織損傷係包括鈍力創傷。在某些具體實例中，該對象係處於下列任一風險：與不欲的平滑肌細胞增生有關的心血管病症、動脈粥樣硬化心血管病症、心肌梗塞、中風、發生冠狀動脈疾病。

【0028】 在另外方面，本揭露係提供於一處於非手術組織損傷風險的對象中預防血管平滑肌細胞增生的方法。該方法係包括向該對象投予一治療上有效量的 ENPP1 或 ENPP3 藥劑，藉此於該對象之非手術組織損傷位置防止血管平滑肌細胞增生惡化或降低血管平滑肌細胞增生程度。在某些具體實例中，該非手術組織損傷係包括鈍力創傷。在某些具體實例中，該對象係處於下列任一風險：與不欲的平滑肌細胞增生有關的心血管病症、動脈粥樣硬化心血管病症、心肌梗塞、中風、發生冠狀動脈疾病。

【0029】 在任何文中所述方法之某些具體實例中，該對象無 ENPP1 缺乏。

【0030】 在另外方面，本揭露之特色為用於治療患有心肌梗塞或中風之對象的方法。該方法係包括投予該對象一治療上有效量的 ENPP1 或 ENPP3 藥劑，藉此治療心肌梗塞或中風。

【0031】 在另外方面，本揭露之特色為於治療患有心肌梗塞或中風之對象的方法。該方法係包括向該對象投予一治療上有效量的 ENPP1 或 ENPP3 藥劑，藉此治療心肌梗塞或中風。

【0032】 又在另外方面，本揭露之特色為於一患有心肌梗塞或中風之對象中降低及/或防止血管平滑肌細胞增生惡化的方法。該方法係包括：向該對象投

予一治療上有效量的 ENPP1 或 ENPP3 藥劑，藉此降低及/或防止與該對象之心肌梗塞或中風有關的血管系統之血管平滑肌細胞增生惡化。

【0033】 又在另外方面，本揭露之特色為於一患有心肌梗塞或中風之對象中降低及/或防止血管平滑肌細胞增生惡化的方法。該方法係包括：向該對象投予一治療上有效量的 ENPP1 或 ENPP3 藥劑，藉此降低及/或防止與該對象之心肌梗塞或中風有關的血管系統之血管平滑肌細胞增生惡化。

【0034】 在任何文中所述方法之某些具體實例中，該對象無 ENPP1 缺乏。

【0035】 在任何文中所述方法之某些具體實例中，該對象並無罹患嬰兒泛發性動脈鈣化(GACI)或體染色體隱性低磷酸鹽佝僂症第 2 型(ARHR2)。

【0036】 在任何文中所述方法之某些具體實例中，該血管平滑肌細胞增生係位於該對象動脈壁的內膜層。

【0037】 在任何文中所述方法之某些具體實例中，該組織損傷係包括血管創傷。

【0038】 在任何文中所述方法之某些具體實例中，該手術係包括冠狀動脈介入術，例如手術刀切口或消融。

【0039】 在任何文中所述方法之某些具體實例中，該方法係包括在投予 ENPP1 藥劑或 ENPP3 藥劑的同時進行手術。

【0040】 在任何文中所述方法之某些具體實例中，該方法係包括在手術或血管介入術之前投予 ENPP1 藥劑或 ENPP3 藥劑。

【0041】 在任何文中所述方法之某些具體實例中，該方法係包括在投予 ENPP1 藥劑或 ENPP3 藥劑的同時進行手術，及視需要在手術後投予該藥劑。

【0042】 在任何文中所述方法之某些具體實例中，該方法係包括投予 ENPP1 藥劑或 ENPP3 藥劑，進行手術，及視需要在手術後投予該藥劑。

【0043】 在任何文中所述方法之某些具體實例中，該對象係患有心肌缺血。

【0044】 在任何文中所述方法之某些具體實例中，該 ENPP1 藥劑或 ENPP3 藥劑係在治療該心肌梗塞及/或該中風之後給藥。

【0045】 在任何文中所述方法之某些具體實例中，該 ENPP1 藥劑係包括一 ENPP1 多肽。

【0046】 在任何文中所述方法之某些具體實例中，該 ENPP1 藥劑係包括或為一編碼 ENPP1 多肽的核酸。

【0047】 在任何文中所述方法之某些具體實例中，該 ENPP1 藥劑係包括或為一包括編碼 ENPP1 多肽之核酸的病毒載體。

【0048】 在任何文中所述方法之某些具體實例中，該 ENPP3 藥劑係包括或為一 ENPP3 多肽。

【0049】 在任何文中所述方法之某些具體實例中，該 ENPP3 藥劑係包括或為一編碼 ENPP3 多肽核酸。

【0050】 在任何文中所述方法之某些具體實例中，該 ENPP3 藥劑係包括或為一包括編碼 ENPP3 多肽之核酸的病毒載體。

【0051】 在任何文中所述方法之某些具體實例中，該 ENPP1 多肽係包括 ENPP1 的胞外區。

【0052】 在任何文中所述方法之某些具體實例中，該 ENPP1 多肽係包括 ENPP1 的催化區。

【0053】 在任何文中所述方法之某些具體實例中，該 ENPP1 多肽係包括 SEQ ID NO：1 的胺基酸 99 至 925。

【0054】 在任何文中所述方法之某些具體實例中，該 ENPP3 多肽係包括 SEQ ID NO：7 的胺基酸 49 至 875。

【0055】 在任何文中所述方法之某些具體實例中，該 ENPP1 藥劑或 ENPP3 藥劑係包括一異源部分。在某些具體實例中，該異源部分為一異源蛋白。

【0056】 在任何文中所述方法之某些具體實例中，相對於無異源部分之 ENPP1 藥劑或 ENPP3 藥劑的半衰期，該異源部分增加了該 ENPP1 藥劑或 ENPP3 藥劑在哺乳動物中的半衰期。

【0057】 在任何文中所述方法之某些具體實例中，該異源部分為一免疫球蛋白分子，例如 IgG1 之 Fc 區。在某些具體實例中，該免疫球蛋白為一人類免疫球蛋白。

【0058】 在任何文中所述方法之某些具體實例中，該異源部分為一白蛋白分子。

【0059】 在任何文中所述方法之某些具體實例中，該異源部分連接 ENPP1 多肽或 ENPP3 多肽之羧基端。

【0060】 在任何文中所述方法之某些具體實例中，該 ENPP1 藥劑或 ENPP3 藥劑係包括一連接子。

【0061】 在任何文中所述方法之某些具體實例中，該連接子隔開了 ENPP1 多肽或 ENPP3 多肽以及異源蛋白。

【0062】 在任何文中所述方法之某些具體實例中，該連接子係包括下列胺基酸序列：(GGGGS) n ，其中 n 為 1 至 10 的整數。

【0063】 在任何文中所述方法之某些具體實例中，該異源部分 ENPP1 藥劑或 ENPP3 藥劑係由皮下投予該對象。

【0064】 在任何文中所述方法之某些具體實例中，該 ENPP1 藥劑或 ENPP3 藥劑係由靜脈內投予該對象。

【0065】 又在另外方面，本揭露之特色為包括一血管支架；以及支架上的塗層之塗覆支架，該塗層係包括 ENPP1 藥劑；以及用於該 ENPP1 藥劑的載劑，其中該塗層係配置為以每天 1-10 $\mu\text{g/ml}$ 的速率從支架釋放該 ENPP1 藥劑。

【0066】 在任何文中所述的支架之某些具體實例中，該 ENPP1 藥劑之量，以塗層的總重量為基準，係介於 1 重量百分比(wt %)至 50wt %。

【0067】 在任何文中所述的支架之某些具體實例中，該 ENPP1 藥劑係由下列組成之群中選出：ENPP1、ENPP1-Fc、ENPP1-白蛋白及 ENPP1 mRNA。

【0068】 在任何文中所述的支架之某些具體實例中，該載劑不會與該 ENPP1 藥劑反應。

【0069】 在任何文中所述的支架之某些具體實例中，該載劑係包括物理上與 ENPP1 藥劑結合的聚合物載劑。

【0070】 在任何文中所述的支架之某些具體實例中，該載劑係包括化學上與 ENPP1 藥劑結合的聚合物載劑。

【0071】 在任何文中所述的支架之某些具體實例中，該載劑係包括生物可降解的聚合物載劑。

【0072】 在任何文中所述的支架之某些具體實例中，該載劑係包括非聚合物載劑。

【0073】 在任何文中所述的支架之某些具體實例中，該非聚合物載劑係由下列組成之群中選出：維生素 E、維生素 E 乙酸鹽、維生素 E 琥珀酸鹽、油酸、花生油和棉籽油。

【0074】 在任何文中所述方法之某些具體實例中，該載劑在體溫下為液體。在任何文中所述方法之某些具體實例中，該載劑在體溫下為固體。

【0075】 又在另外方面，本揭露之特色為於一具有組織損傷的對象中降低及/或防制血管平滑肌細胞增生惡化之方法，該方法係包括：將一塗覆 ENPP1 藥

劑的動脈支架植入接近該對象組織損傷的動脈中，其中該植入的支架係配置為以有效降低及/或防止該對象損傷位置之血管平滑肌細胞增生惡化的量釋放該 ENPP1 藥劑，其中該對象並無 ENPP1 缺乏，藉此在該對象損傷位置降低及/或防止血管平滑肌細胞增生惡化。

【0076】 在任何文中所述方法之某些具體實例中，組織損傷係包括動脈中置放支架。

【0077】 在任何文中所述方法之某些具體實例中，該組織損傷係由於先前在該動脈中置放非析出型動脈支架或由於先前置放析出該 ENPP1 以外之治療劑的析出型動脈支架。

【0078】 在任何文中所述方法之某些具體實例中，該對象係處於發生再狹窄的風險中。

【0079】 又在另外方面，本揭露之特色為於一具有需要手術之病症的對象中在手術位置降低及/或防止血管平滑肌細胞增生惡化的方法，該方法包括：將一塗覆 ENPP1 藥劑的動脈支架植入接近該對象手術位置的動脈中，其中該植入的支架係配置為以有效降低及/或防止血管平滑肌細胞增生惡化的量釋放該 ENPP1 藥劑，其中該對象並無 ENPP1 缺乏，藉此在該手術位置降低及/或防止血管平滑肌細胞增生惡化。

【0080】 在任何文中所述方法之某些具體實例中，該藥劑係在手術之前、手術期間及/或手術後投予該對象。

【0081】 在任何文中所述方法之某些具體實例中，進一步係包括進行該手術。

【0082】 在任何文中所述方法之某些具體實例中，該手術係包括動脈繞道手術。

【0083】 在任何文中所述方法之某些具體實例中，需要手術的病症係由於之前在該動脈中置放非析出型動脈支架。

【0084】 在任何文中所述方法之某些具體實例中，需要手術的病症係由於之前在該動脈中置入析出型動脈支架，而該析出型動脈支架係析出該 ENPP1 藥劑以外的治療劑。

【0085】 在任何文中所述方法之某些具體實例中，該手術係包括血管成形術。

【0086】 又在另外方面，本揭露之特色為於患有心肌梗塞或中風之對象中改善心肌梗塞或中風之方法，該方法包括：將一塗覆 ENPP1 藥劑的動脈支架植入該對象的動脈中，其中該植入的支架係配置為以有效改善心肌梗塞或中風的量釋放該 ENPP1 藥劑，藉此改善該心肌梗塞或中風。

【0087】 又在另外方面，本揭露之特色為用於患有心肌梗塞或中風之對象中降低及/或防止血管平滑肌細胞增生惡化的方法，該方法包括：將一塗覆 ENPP1 藥劑的動脈支架植入該對象的動脈中，其中該植入的支架係配置為以有效降低及/或防止與心肌梗塞或中風有關的血管系統之血管平滑肌細胞增生惡化的量釋放該 ENPP1 藥劑，藉此降低及/或防止與該對象之心肌梗塞或中風有關的血管系統之血管平滑肌細胞增生惡化。

【0088】 在任何文中所述方法之某些具體實例中，該對象無 ENPP1 缺乏。

【0089】 在任何文中所述方法之某些具體實例中，該 ENPP1 藥劑係包括一 ENPP1 多肽。

【0090】 在任何文中所述方法之某些具體實例中，該 ENPP1 藥劑為一編碼 ENPP1 多肽的核酸。

【0091】 在任何文中所述方法之某些具體實例中，該 ENPP1 藥劑係包括一病毒載體，而該病毒載體係包括一編碼 ENPP1 多肽之核酸。

【0092】 在任何文中所述方法之某些具體實例中，該 ENPP1 多肽係包括 ENPP1 的胞外區。

【0093】 在任何文中所述方法之某些具體實例中，該 ENPP1 多肽係包括 ENPP1 的催化區。

【0094】 在任何文中所述方法之某些具體實例中，該 ENPP1 多肽係包括 SEQ ID NO：1 的胺基酸 99 至 925。

【0095】 在任何文中所述方法之某些具體實例中，該 ENPP1 多肽係包括一異源蛋白。

【0096】 在任何文中所述方法之某些具體實例中，該異源蛋白係增加 ENPP1 多肽在哺乳動物中的循環半衰期。

【0097】 在任何文中所述方法之某些具體實例中，該異源蛋白為一免疫球蛋白分子之 Fc 區。

【0098】 在任何文中所述方法之某些具體實例中，該免疫球蛋白分子為一 IgG1 分子。

【0099】 在任何文中所述方法之某些具體實例中，該異源蛋白為一白蛋白分子。

【0100】 在任何文中所述方法之某些具體實例中，該異源蛋白連接 ENPP1 多肽羧基端。

【0101】 在任何文中所述方法之某些具體實例中，該 ENPP1 藥劑係包括一連接子。

【0102】 在任何文中所述方法之某些具體實例中，該連接子隔開了 ENPP1 多肽和異源蛋白。

【0103】 在任何文中所述方法之某些具體實例中，該連接子係包括下列胺基酸序列：(GGGGS) n ，其中 n 為 1 至 10 之整數。

【0104】 又在另外方面，本揭露之特色為於一具有組織損傷的對象中降低及/或防止血管平滑肌細胞增生惡化之方法，該方法包括：將一塗覆 ENPP3 藥劑的動脈支架植入接近該對象組織損傷位置的動脈中，其中該植入的支架係配置為以有效在該對象損傷位置降低及/或防止血管平滑肌細胞增生惡化的量釋放該 ENPP3 藥劑，藉此在該對象的損傷位置降低及/或防止血管平滑肌細胞增生惡化。

【0105】 在任何文中所述方法之某些具體實例中，該組織損傷係包括動脈損傷。

【0106】 在任何文中所述方法之某些具體實例中，該組織損傷係包括動脈內置入支架。

【0107】 在任何文中所述方法之某些具體實例中，該對象係處於發生再狹窄的風險中。

【0108】 又在另外方面，本揭露之特色為於具有需要手術之病症的對象中在手術位置降低及/或防止血管平滑肌細胞增生惡化的方法，該方法包括：將一塗覆 ENPP3 藥劑的動脈支架植入接近該對象手術位置的動脈中，其中該植入的支架係配置為以有效降低及/或防止血管平滑肌細胞增生惡化的量釋放該 ENPP3 藥劑，藉此降低及/或防止在該手術位置的血管平滑肌細胞增生惡化。

【0109】 在任何文中所述方法之某些具體實例中，該藥劑係在手術之前，手術期間及/或手術後投予該對象。

【0110】 在任何文中所述方法之某些具體實例中，進一步係包括進行該手術。

【0111】 在任何文中所述方法之某些具體實例中，該手術係包括動脈繞道手術。

【0112】 在任何文中所述方法之某些具體實例中，需要手術的病症係由於先前在該動脈中置入非析出型動脈支架所致。

【0113】 在任何文中所述方法之某些具體實例中，需要手術的病症係由於之前在該動脈中置放析出型動脈支架，而該析出型動脈支架係釋出該 ENPP3 藥劑以外的治療劑。

【0114】 在任何文中所述方法之某些具體實例中，該手術係包括血管成形術。

【0115】 又在另外方面，本揭露之特色為於患有心肌梗塞或中風之對象中改善心肌梗塞或中風之方法，該方法包括：將一塗覆 ENPP3 藥劑的動脈支架植入該對象的動脈中，其中該植入的支架係配置為以有效改善心肌梗塞或中風的量釋放該 ENPP3 藥劑，藉此改善該心肌梗塞或中風。

【0116】 又在另外方面，本揭露之特色為用於患有心肌梗塞或中風之對象中降低及/或防止血管平滑肌細胞增生惡化的方法，該方法包括：將一塗覆 ENPP3 藥劑的動脈支架植入該對象的動脈中，其中該植入的支架係配置為以有效降低及/或防止與心肌梗塞或中風有關的血管系統之血管平滑肌細胞增生惡化的量釋放該 ENPP3 藥劑，藉此降低及/或防止與該對象之心肌梗塞或中風有關的血管系統之血管平滑肌細胞增生惡化。

【0117】 在任何文中所述方法之某些具體實例中，該對象無 ENPP1 缺乏。

【0118】 在任何文中所述方法之某些具體實例中，該 ENPP3 藥劑係包括一 ENPP3 多肽。

【0119】 在任何文中所述方法之某些具體實例中，該 ENPP3 藥劑為一編碼 ENPP1 多肽的核酸。

【0120】 在任何文中所述方法之某些具體實例中，該 ENPP3 藥劑係包括一病毒載體，而該病毒載體係包括一編碼 ENPP3 多肽之核酸。

【0121】 在任何文中所述方法之某些具體實例中，該 ENPP3 多肽係包括一異源蛋白。

【0122】 在任何文中所述方法之某些具體實例中，該 ENPP3 多肽係包括 ENPP3 的胞外區。

【0123】 在任何文中所述方法之某些具體實例中，該 ENPP3 多肽係包括 ENPP3 的催化區。

【0124】 在任何文中所述方法之某些具體實例中，該 ENPP3 多肽係包括 SEQ ID NO：7 的 49-875 胺基酸。

【0125】 在任何文中所述方法之某些具體實例中，該 ENPP3 多肽係包括一異源蛋白。

【0126】 在任何文中所述方法之某些具體實例中，該異源蛋白係增加 ENPP3 多肽在哺乳動物中的循環半衰期。

【0127】 在任何文中所述方法之某些具體實例中，該異源蛋白為一免疫球蛋白分子之 Fc 區。

【0128】 在任何文中所述方法之某些具體實例中，該免疫球蛋白分子為一 IgG1 分子。

【0129】 在任何文中所述方法之某些具體實例中，該異源蛋白為一白蛋白分子。

【0130】 在任何文中所述方法之某些具體實例中，該異源蛋白連接 ENPP3 多肽羧基端。

【0131】 在任何文中所述方法之某些具體實例中，該 ENPP3 藥劑係包括一連接子。

【0132】 在任何文中所述方法之某些具體實例中，該連接子隔開了 ENPP3 多肽和異源蛋白。

【0133】 在任何文中所述方法之某些具體實例中，該連接子係包括下列胺基酸序列：(GGGGS) n ，其中 n 為 1 至 10 之整數。

【0134】 又在另外方面，本揭露之特色為包括一血管支架之塗層支架；以及支架上的塗層，該塗層係包括 ENPP3 藥劑；以及用於該 ENPP3 藥劑的載劑，其中該塗層係配置為以每天 1-10 $\mu\text{g/ml}$ 的速率從支架釋放該 ENPP3 藥劑。

【0135】 在任何文中所述方法之某些具體實例中，該 ENPP3 藥劑之量，以塗層的總重量為基準，係介於 1wt %至 50wt %。

【0136】 在任何文中所述方法之某些具體實例中，該 ENPP3 藥劑係由下列組成之群中選出：ENPP3、ENPP3-Fc、ENPP3-白蛋白及 ENPP3 mRNA。

【0137】 在任何文中所述方法之某些具體實例中，該載劑不會與該 ENPP3 藥劑反應。

【0138】 在任何文中所述方法之某些具體實例中，該載劑係包括物理上與 ENPP3 藥劑結合的聚合物載劑。

【0139】 在任何文中所述方法之某些具體實例中，該載劑係包括化學上與 ENPP3 藥劑結合的聚合物載劑。

【0140】 在任何文中所述方法之某些具體實例中，該載劑係包括生物可降解聚合物載劑。

【0141】 在任何文中所述方法之某些具體實例中，該載劑係包括非聚合物載劑。

【0142】 在任何文中所述方法之某些具體實例中該非聚合物載劑係由下列組成之群中選出：維生素 E、維生素 E 乙酸鹽、維生素 E 琥珀酸鹽、油酸、花生油和棉籽油。

【0143】 在任何文中所述方法之某些具體實例中，該載劑在體溫下為液體。

【0144】 在任何文中所述方法之某些具體實例中，該載劑在體溫下為固體。

【0145】 本揭露之其他特色和優點顯明於下列實施方式和申請專利範圍。

【圖式簡單說明】

【0146】 圖 1 係顯示頸動脈結紮前 WT 和 *ttw/ttw* 小鼠之預防性治療療法的概要圖。在頸動脈結紮前，將 WT 和 *ttw/ttw* 小鼠以 10 mg/kg 示例劑量的 ENPP1-Fc 每隔一天由皮下注射治療 7 天。對照組，WT 和 *ttw/ttw* 小鼠，以 pH 7.4 含有 tris 緩衝食鹽水的媒劑注射。然後將所有的小鼠在頸動脈結紮後 14 天解剖而小鼠大約為 9 個月大。

【0147】 圖 2A 係顯示頸動脈結紮和組織分析切片之概要圖。就結紮的頸動脈之形態測量，係採用緊鄰結紮位置的 5 μm 切片。每隻動物總計分析 12 片鄰近結紮位置的切片(每 25 μm)，跨距大約 250 μm 。計算各切片之中膜面積、內膜面積和內膜/中膜比率(I/M 比率)而代表性染色切片係如圖 2B 所示。

【0148】 圖 3 係顯示血管分布的組織分析。由左至右分別係顯示來自 WT 小鼠/媒劑治療，WT 小鼠/ENPP1-Fc 治療，*ttw/ttw* 小鼠/媒劑治療以及 *ttw/ttw* 小鼠/ENPP1-Fc 治療，距離綁紮處 100 μm (上方)或 200 μm (下方)的代表性染色切片。以 Van Gieson 溶液染色彈性膠原纖維並從血管腔(L)區分出內(IEL)和外彈性膜層(EEL)。在 WT 小鼠中，頸動脈結紮造成內膜過度增生，導致內腔窄化，其中

接近結紮處較為嚴重(100 μm)而較遠離的阻塞較不嚴重(200 μm)。相反的，在 *ttw/ttw* 小鼠中，內膜過度增生的程度似乎增加，在 200 μm 的內腔中幾乎完全阻塞。WT 和 *ttw/ttw* 小鼠二者在 ENPP1-Fc 給藥後顯示血管平滑肌細胞(VSMC)增生下降。以 ENPP1-Fc 治療後 VSMC 增生的下降效應在 *ttw/ttw* 小鼠中更明顯，但令人意外的，在 WT 小鼠中亦看到 VSMC 增生降低。看來即使在不具有 ENPP1 缺乏的 WT 小鼠中，投予 ENPP1-Fc 亦大大地降低 VSMC 增生。經 ENPP1-Fc 治療的 *ttw/ttw* 小鼠和 WT 小鼠顯示內膜過度增生比經媒劑治療的小鼠少很多。此項顯示在頸動脈結紮之前和之後投予 ENPP1-Fc 保護並反轉內膜過度增生。

【0149】 圖 4A-C 和 D-F 係顯示型態測量學定性結果。圖 4G 係顯示血管分布的組織學分析。切片係以如同上述之方式染色。測量外和內彈性膜層以及腔緣之圓周以便定量中膜(M)和內膜(I)面積。投予 ENPP1-Fc 防止 WT-和 *ttw/ttw*-小鼠頸動脈結紮後之內膜增生。ENPP1-Fc 治療係在頸動脈結紮前 7 天開始，及在頸動脈結紮後 14 天(A-C)或 21 天(D-F)採集左頸動脈的連續切片。進行中膜(A&D)和內膜(B&E)面積之形態測量學定量，並計算 I/M 比率(C&F)。數值係以平均 $\pm$ SEM 表示，各組 $n \geq 9$ ，* $p < 0.05$ ，** $p < 0.01$ ，*** $p < 0.001$ (單因子 ANOVA 多組比較，接著包法隆尼事後檢定(Bonferroni's post hoc test))。

【0150】 介於中外膜層和內膜層之間的中膜面積仍為不變的(圖 4A)。在媒劑治療的 WT 小鼠中，相對於 ENPP1-Fc 治療的 WT 小鼠，內腔周圍的內膜面積顯示統計上顯著性增加(圖 4B)。同樣的，在媒劑治療的 *ttw/ttw* 小鼠中，相對於 ENPP1-Fc 治療的 *ttw/ttw* 小鼠，內腔周圍的內膜面積顯示統計上顯著性增加(圖 4B)。在內膜面積和比率上，ENPP1-Fc-治療的 *ttw/ttw* 小鼠與 ENPP1-Fc 治療的 WT 小鼠相似，其中結果亦為統計上顯著的(圖 4C)。

【0151】 圖 5(A-C)係顯示在 WT-和 *ttw/ttw*-小鼠中頸動脈結紮後，治療性投予 ENPP1-Fc 抑制了內膜增生。圖 5D 係顯示血管分布的組織學分析。切片係

以如同上述之方式染色。ENPP1-Fc 治療係在頸動脈結紮後 7 天開始，並在頸動脈結紮後 14 天採集左頸動脈的連續切片。進行中膜(A)和內膜(B)面積之形態測量學定量，並計算 I/M 比率(C)。數值係以平均 $\pm$ SEM 表示，WT 為 $n=7$ ，媒劑治療的 *ttw/ttw* 或 rhENPP1-治療的 *ttw/ttw*-小鼠為 $n=10$ ，* $p<0.05$ ，** $p<0.01$ ，*** $p<0.001$ (單因子 ANOVA 多組比較，接著包法隆尼事後檢定(Bonferroni's post hoc test))。

【0152】 當血管內膜過度增生確實存在時，於結紮後 7 天開始評估 ENPP1-Fc 的治療效用。在所有的小鼠組別中，外膜層和內膜層之間的中膜面積仍為不變的(圖 5A)。相較於媒劑治療的 *ttw/ttw*-小鼠，在 ENPP1-Fc 治療的 *ttw/ttw*-小鼠中，於結紮後 7 天開始 ENPP1-Fc 的治療性治療造成內膜面積顯著下降(圖 5B, $p<0.05$)，然而在 ENPP1-Fc 治療的和媒劑治療的 WT-小鼠之間觀察到下降的傾向。相較於媒劑治療的 WT-和 *ttw/ttw*-小鼠，ENPP1-Fc 治療的 WT-和 *ttw/ttw*-小鼠二者之 I/M 比率顯著下降(圖 5C，二者 $p<0.05$)。

【0153】 圖 6A-C 係顯示用於測定 *ttw/ttw*-和 WT-小鼠之治療性治療的最佳起點和設計之中膜面積、內膜面積和 I/M 比率圖式。就最佳起點之測定，係評估結紮 7、10 和 14 天的 *ttw/ttw*-小鼠之中膜(A)和內膜(B)面積體以及 I/M 比率(C)。以這些數據為基準，於 7 週大的小鼠中進行 *ttw/ttw* 和 WT-小鼠之頸動脈結紮且於頸動脈結紮後 7 天開始(8 週大時)，當頸動脈結紮的 *ttw/ttw*-小鼠的血管中內膜過度增生確實存在時，投予 ENPP1-Fc(10 mg/kg，皮下，每隔一天)或媒劑(TBS，pH7.4)，且相較於 14 天結紮的 *ttw/ttw*-小鼠亦具顯著差異(就內膜面積和 I/M 比率 $p<0.001$ ，B 和 C)。數值係以平均 $\pm$ SEM 表示，* $p<0.05$ ，*** $p<0.001$ (單因子 ANOVA 多組比較，接著包法隆尼事後檢定(Bonferroni's post hoc test))。

【0154】 圖 7 係顯示組織學切片，其係指出 *ttw/ttw*-小鼠在頸動脈結紮 21 天後內膜頸動脈組織之降解。結紮 21 天的 *ttw/ttw*-小鼠頸動脈組織學分析(彈性

van Gieson 染色)。切片係從距離小鼠的結紮點 200、150、100 和 50 μm 處所採集，其顯示內膜面積和彈性纖維降解(圖 7A)。將結紮 21 天的 *ttw/ttw*-小鼠頸動脈的正 TUNEL 染色與來自 WT-小鼠距離結紮處大約 300 μm 尾端的頸動脈之負染色(圖 7B)相比較。負對照：進行無 TUNEL 酵素染色；正對照：使用 I 級 DNA 酶 I 降解 DNA。

【0155】 圖 8 係顯示預防性和治療性投予 ENPP1-Fc 在 WT-和 *ttw/ttw*-小鼠頸動脈結紮後內膜增生上之比較。預防性 ENPP1-Fc 治療係在頸動脈結紮前 7 天開始，而治療性 ENPP1-Fc 治療係在頸動脈結紮後 7 天開始。在頸動脈結紮後 14 天採集所有動物左頸動脈的連續切片。進行中膜(A)和內膜(B)面積之形態學測量定量，並計算 I/M 比例(C)。數值係以平均 $\pm$ SEM 表示，各組 $n \geq 8$ ，* $p < 0.05$ ，*** $p < 0.001$ (單因子 ANOVA 多組比較，接著包法隆尼事後檢定(Bonferroni's post hoc test))。

【0156】 圖9A為在無塗覆支架的存在下經歷再狹窄之動脈橫切面。內皮12通常係作為平滑肌細胞層14和動脈腔20之間的固體屏障。內皮12中的小裂口16可能暴露平滑肌細胞14，然後平滑肌細胞14可能遷移入動脈腔20並過度增生變成團塊18，其可能部分或完全堵塞動脈腔20，即使在處置60，例如血管成形術期間，在動脈10中置入無塗覆支架21用以保持動脈腔20通暢。圖9B為含有塗層支架22之動脈10的橫切面。該支架係具有含載劑以及生物活性化合物，例如抑制及/或防止再狹窄的ENPP1藥劑65之塗層24。藉由使用具有此塗層24的支架，可能減低或消除顯示圖9A中所示的內皮12中之裂口16。另外，消除或實質上降低了如圖9A所示之由平滑肌細胞14增生所產生的團塊18。

【實施方式】

定義

【0157】 除非另有定義，否則文中所用的所有技術和科學術語係具有熟習本揭露所屬技術之一般技術者正常理解的相同意義。雖然類似或等同文中所述的方法和材料可用於施行或試驗本揭露，但較佳的方法和材料係如所述。

【0158】 為了明確起見，「*ENPP1*」和「*ENPP1*」係指相同的蛋白且在文中可交換使用。如文中所述，術語「*ENPP1* 蛋白」和「*ENPP1* 多肽」係指由 *ENPP1* 基因所編碼的外核苷酸焦磷酸酶/磷酸二酯酶-1 蛋白，其能裂解 ATP 產生 PP_i 且亦降低軟組織中的異位性鈣化。

【0159】 *ENPP1* 蛋白為一種第 II 型跨膜糖蛋白且裂解各種基質，包括核苷酸和核苷酸糖類的磷酸二酯鍵以及核苷酸和核苷酸糖類的焦磷酸鍵。*ENPP1* 蛋白具有一跨膜區和可溶性胞外區。胞外區進一步細分為體介素 (somatomedin) B 區、催化區和核酸酶區。野生型 *ENPP1* 的序列和結構係詳述於 Braddock 等人之 PCT 申請公開案號 WO 2014/126965 中，該案係以全文引用的方式併入本文中。

【0160】 *ENPP1* 多肽如文中所用係包括具有 *ENPP1* 酵素活性之多肽，保留 *ENPP1* 酵素活性的 *ENPP1* 變體，*ENPP1* 片段或 *ENPP1* 變體，包括如下文所述具有 *ENPP1* 酵素活性之刪除變體。

【0161】 *ENPP3* 多肽如文中所用係包括具有酵素活性之多肽，保留酵素活性的 *ENPP3* 變體，*ENPP3* 片段或 *ENPP3* 變體，包括如下文所述具有酵素活性之刪除變體。

【0162】 某些 *ENPP1* 和 *ENPP3* 多肽、突變體或其突變體片段的實例先前已揭示於國際 PCT 申請公開案號 WO/2014/126965-Braddock 等人，WO/2016/187408-Braddock 等人，WO/2017/087936-Braddock 等人，以及 WO2018/027024-Braddock 等人中，其全部係以全文引用的方式併入本文中。

【0163】 如文中所用有關 ENPP1 多肽或 ENPP3 多肽之「*酵素性活化*」，或有關 ENPP1 多肽或 ENPP3 多肽之「*酵素活性*」係定義為具有將 ATP 水解成 AMP 和 PP_i 及/或 AP3a 水解成 ADP 和 AMP 的活性。NPP1 和 NPP3 容易地將 ATP 水解成 AMP 和 PP_i 。使用 ATP 作為基質測定 NPP1 之穩態米開勒斯-曼登酵素常數(Michaelis-Menten enzymatic constant)。可藉由 HPLC 的酵素反應分析驗證 NPP1 裂解 ATP，並藉由使用 ATP、AMP 和 ADP 標準，確認基質和反應產物的身份。ATP 基質在 NPP1 存在下隨時間降解，伴隨酵素性產物 AMP 堆積。使用各種濃度的 ATP 基質，在 ATP 的存在下衍生出 NPP1 的最初速率速度，並將該數據擬合一曲線，衍生酵素速率常數。在生理 pH 時，NPP1 的動力學速率常數為 $K_m=144\ \mu\text{M}$ 及 $k_{cat}=7.8\ \text{s}^{-1}$ 。

【0164】 如文中所用術語「*血漿焦磷酸鹽(PP_i)量*」係指存在動物血漿中焦磷酸鹽的量。在特定的具體實例中，動物係包括大鼠、小鼠、貓、狗、人類、牛和馬。必須測量血漿中的 PP_i 而非血清中的 PP_i 係因為從血小板釋放。有數種測量 PP_i 的方法，其中一種係藉由酵素分析使用帶有修飾的尿苷-二磷酸葡萄糖(UDPG)焦磷酸化酶(Lust & Seegmiller, 1976, *Clin. Chim. Acta* 66 : 241-249; Cheung & Suhadolnik, 1977, *Anal. Biochem.* 83 : 61-63)。

【0165】 典型地，在健康人類對象中血漿 PP_i 量之範圍係從 $1\ \mu\text{M}$ 至約 $3\ \mu\text{M}$ ，在某些案例中係介於 $1-2\ \mu\text{M}$ 。血漿中正常的 ENPP1 量係指在健康對象中維持正常的血漿焦磷酸鹽(PP_i)之量所需要的 ENPP1 蛋白量。健康人類中正常 PP_i 量係相當於 $2-3\ \mu\text{M}$ 。具有 ENPP1 缺乏之對象展現低 PP_i 量，其範圍從低於正常量至少 10%，低於正常量至少 20%，低於正常量至少 30%，低於正常量至少 40%，低於正常量至少 50%，低於正常量至少 60%，低於正常量至少 70%，低於正常量至少 80% 及其組合。在罹患 GACI 的病患中發現 PP_i 量係低於 $1\ \mu\text{M}$ 且在某些案例中係低於可偵測量。在罹患 PXE 的病患中， PP_i 量係低於 $0.5\ \mu\text{M}$ (*Arterioscler*

Thromb Vasc Biol. 2014 Sep;34(9) : 1985-9; Braddock et al., *Nat Commun.* 2015; 6 : 10006.)。

【0166】 如文中所用，術語「*PP_i*」係指焦磷酸鹽。

【0167】 如文中所用，術語「改變」、「缺陷」、「變異」或「突變」係指影響所編碼之多肽功能、活性、表現(轉錄或轉譯)或構型的細胞中基因之突變，包括錯義和無義突變、插入、刪除、移碼和過早終止。

【0168】 如文中所用，術語「*ENPP1* 前驅蛋白」係指在 *ENPP1* N-端帶有其訊號肽序列之 *ENPP1* 多肽。在蛋白水解後，訊號序列從 *ENPP1* 裂解出，提供 *ENPP1* 蛋白。可用於本揭露內的訊號肽序列包括，但不限於，白蛋白訊號肽序列、天青殺素(Azurocidin)訊號肽序列、*ENPP1* 訊號肽序列、*ENPP2* 訊號肽序列、*ENPP7* 訊號肽序列及/或 *ENPP5* 訊號肽序列。

【0169】 如文中所用，術語「*ENPP3* 前驅蛋白」係指在 *ENPP3* N-端帶有其訊號肽序列之 *ENPP3* 多肽。在蛋白水解後，訊號序列從 *ENPP3* 裂解出，提供 *ENPP3* 蛋白。可用於本揭露內的訊號肽序列包括，但不限於，白蛋白訊號肽序列、天青殺素訊號肽序列、*ENPP1* 訊號肽序列、*ENPP2* 訊號肽序列、*ENPP7* 訊號肽序列及/或 *ENPP5* 訊號肽序列。

【0170】 如文中所用，術語「天青殺素(Azurocidin)訊號肽序列」係指衍生自人類天青殺素的訊號肽。天青殺素，亦稱為陽離子抗微生物蛋白 *CAP37* 或肝素結合蛋白(HBP)，為一種在人類中由 *AZU1* 基因所編碼的蛋白。編碼天青殺素訊號肽的核苷酸序列(MTRLTVLALLAGLLASSRA(SE ID NO : 42)與 *NPP1* 或 *NPP3* 基因的核苷酸序列融合，其在編碼時產生 *ENPP1* 前驅蛋白或 *ENPP* 前驅蛋白(*Optimized signal peptides for the development of high expressing CHO cell lines*, Kober et al., *Biotechnol Bioeng.* 2013 Apr;110(4) : 1164-73)。

【0171】 術語「*ENPP1-Fc 結構*」係指 ENPP1 重組融合及/或化學接合(包括共價和非共價接合二者)一 IgG 分子(較佳地，人類 IgG)的 FcR 結合區。在特定的具體實例中，ENPP1 的 C-端係與 FcR 結合區的 N-端融合或接合。

【0172】 如文中所用，術語「*ENPP3-Fc 結構*」係指 ENPP3 重組融合及/或化學接合(包括共價和非共價接合二者)一 IgG 分子(較佳地，人類 IgG)的 FcR 結合區。在特定的具體實例中，ENPP3 的 C-端係與 FcR 結合區的 N-端融合或接合。

【0173】 如文中所用，術語「*Fc*」係指人類 IgG(免疫球蛋白)Fc 結構域。IgG 的亞型，例如 IgG1、IgG2、IgG3 和 IgG4 可考量用作為 Fc 結構域。「*Fc 區*或*Fc 多肽*」為 IgG 分子之部分，其係關於藉由木瓜酶消化 IgG 分子所得到的可結晶片段。Fc 區係包括藉由雙硫鍵連結之 IgG 分子二條重鏈的 C-端半邊。其不具有抗原結合活性，但含有碳水化合物部分及補體和 Fc 受體，包括 FcRn 受體的結合位置。Fc 片段係含有整個第二恆定區 CH2 (根據 Kabat 編號系統，人類 IgG1 的 231-340 殘基)和第三恆定區 CH3(341-447 殘基)。術語「*IgG 絞鏈-Fc 區*」或「*絞鏈-Fc 片段*」係指一 IgG 分子之區域，其係由 Fc 區(231-447 殘基)和從 Fc 區的 N 端延伸之絞鏈(216-230 殘基)所組成。術語「*恆定區*」係指相對於免疫球蛋白之其他部分(含有抗原結合位的可變區)，其係具有更保守胺基酸序列之免疫球蛋白部分。恆定區含有重鏈的 CH1、CH2 和 CH3 區以及輕鏈的 CHL 區。

【0174】 如文中所用，術語「*功能等同變體*」係關於實質上與 ENPP1 或 ENPP3 序列(如上定義)同源以及分別保存 ENPP1 或 ENPP3 之酵素和生物活性的多肽。用於測定一變體是否保存天然 ENPP1 或 ENPP3 之生物活性的方法已廣為熟習技術者周知並且包括任何在該申請書之實驗部分所用的分析。特言之，本揭露係涵蓋藉由病毒載體所遞送的 ENPP1 或 ENPP3 之功能等同變體。ENPP1 或 ENPP3 之功能等同變體為實質上分別與天然 ENPP1 或 ENPP3 同源的多肽。

詞語「實質上同源」係關於就上述 ENPP1 或 ENPP3 序列而言，當該蛋白序列具有分別至少 80%，至少 85%，至少 90%，至少 91%，至少 92%，至少 93%，至少 94%，至少 95%，至少 96%，至少 97%，至少 98%或至少 99%之相同度且就酵素活性而言仍保留至少 50%，55%，60%，70%，80%或 90%之野生型 ENPP1 或 ENPP3 蛋白活性的蛋白序列。

【0175】 二多肽間的相同度係使用電腦演算法和廣為熟習本項技術者周知的方法所測。雖然亦可使用其他類似的演算法，但二種胺基酸序列間的相同性較佳地係使用 BLASTP 演算法來測定(*BLAST Manual, Altschul, S., et al., NCBI NLM NIH Bethesda, Md. 20894, Altschul, S., et al., J. Mol. Biol. 215 :403-410 (1990)*)。使用 BLAST 和 BLAST 2.0，以文中所述的參數，測定序列相同性百分比。用於進行 BLAST 分析的軟體可經由國家生物技術資訊中心公開取得。

【0176】 ENPP1 或 ENPP3 之「功能等同變體」可藉由置換負責分別用來製造 ENPP1 或 ENPP3 之宿主細胞中密碼子優先性的多核苷酸內的核苷酸來獲得。此「密碼子優化」可經由併入密碼子頻率表的電腦演算法，例如威斯康辛州麥迪遜的威斯康辛大學 Package Version 9.0, Genetics Computer Group 所提供用於密碼子優先性之「Human high.cod」來測定。就酵素活性而言，預期 ENPP1 或 ENPP3 多肽之變體係保留至少 50%、55%、60%、70%、80%或 90%野生型 ENPP1 或 ENPP3 蛋白之活性。

【0177】 如文中所用，術語「野生型」係指分離自天然生成來源的基因或基因產物。野生型基因在一群族中為最常觀察到且因此被任意地設計人類 NPP1 或 NPP3 基因之「正常」或「野生型」形式。相反的，術語「功能上等同物」係指當相較於野生型基因或基因產物時，在序列及/或功能性質上展現修飾作用(亦即，特性改變)之 NPP1 或 NPP3 基因或基因產物。天然生成的突變體可經分離；

這些突變體可藉由在相較於野生型基因或基因產物時，其具有特性改變(包括核酸序列改變)之事實來鑑別。

【0178】 術語「大約」如文中所用當係指一可測量數值，例如量、暫時的持續時間等等，係表示涵蓋與所指的數值相差+20%或+10%，更佳地+5%，甚佳地+1%及又更佳地+0.1%之變化，因而變化係適合進行所揭示的方法。

【0179】 如文中所定義，術語「對象」、「個體」或「病患」係指哺乳動物，較佳地人類。

【0180】 如文中所定義，術語「部分(*moiety*)」係指可共價或非共價連接 ENPP1 或 ENPP3 蛋白且具有賦予其所連接的蛋白所欲性質之能力的化學組份或生物分子。例如，術語「部分」可指一以胜肽為目標的鍵，例如聚天門冬胺酸或聚麩胺酸(的 4-20 個連續 asp 或 glu 殘基)或延長 ENPP1 或 ENPP3 多肽之半衰期的分子。某些半衰期延長部分之實例包括 Fc、白蛋白、運鐵蛋白、聚乙二醇(PEG)、高胺基酸聚合物(HAP)、脯胺酸-丙胺酸-絲胺酸(PAS)、類彈性蛋白胜肽(ELP)和類明膠蛋白(GLK)。

【0181】 如文中所定義，詞語「中膜面積」為介於動脈之外彈性層和內彈性層之間的面積。

【0182】 如文中所定義，詞語「內膜面積」和該內膜面積為介於該內彈性層和動脈腔之間的面積。

【0183】 如文中所定義，詞語「外彈性層」係指緊接在動脈中層之平滑肌外側的彈性結締組織層。

【0184】 如文中所定義，詞語「內彈性層」係指形成血管中膜之最外側部分的彈性組織層。

【0185】 如文中所定義，詞語「內腔」係指血管的內部，例如動脈、靜脈或微血管中的主要空間，經由該空間發生血流。

【0186】 如文中所定義，詞語「*手術*」係指涉及藉由手術刀切開或射頻消融或冷凍消融或雷射消融造成組織損傷之冠狀動脈介入術的侵入性醫療過程。

【0187】 如文中所定義，詞語「*組織損傷*」係指在經皮冠狀動脈介入術，例如裝支架或血管成形術之後，血管平滑肌之增生或增生發作和遷移，最終造成動脈壁增厚並降低動脈腔空間並產生再狹窄。

【0188】 如文中所定義，詞語「*缺乏 NPPI*」或「*ENPP1 缺乏*」係指在 ENPP1 蛋白或編碼該蛋白之基因上具有喪失功能突變，導致泛發性動脈鈣化 (GACI) 之診斷，或處於發生或罹患體染色體隱性低磷酸鹽佝僂症第 2 型 (ARHR2) 之診斷的風險。

【0189】 如文中所定義，詞語「*血管創傷*」係指血管—將血液帶至末端的動脈，或將血液帶回心臟的靜脈之損傷。血管損傷亦可能由侵入性處置過程所造成，例如經皮穿腔冠狀動脈血管成形術及血管繞道手術。

【0190】 如文中所定義，詞語「*意外創傷*」係指血管，例如由於運用體力當血管被擠壓或拉伸時發生的動脈鈍性損傷，或當血管被刺破、撕裂或切斷時發生的穿透性損傷。鈍性損傷係發生在身體變化，例如拳擊期間，而穿透性損傷係由於尖銳物品例如刀子或子彈傷口所發生。創傷和損傷可能由不同的因素所造成，例如放射線、病毒感染、產生免疫複合物和高脂血症。

【0191】 如文中所定義，詞語「*再狹窄*」係指狹窄的再發生。狹窄係指血管窄化，導致血流受限。再狹窄通常係關於動脈或其他大血管變窄，接受治療清除阻塞且後續再度變窄。再狹窄一般係藉由使用一或多種的超音波、X 光、電腦斷層 (CT)、核子造影、光學造影或對比強化影像或免疫組織化學偵測來偵測。

【0192】 如文中所定義，詞語「*肌內膜增生*」係指發生在一個體之動脈壁內膜的血管平滑肌細胞增生。

【0193】 如文中所用，術語「治療」係定義為：以治癒、療癒、減輕、緩解、改變、補救、改善、改良或影響疾病或病症、該疾病或病症之徵候，或發生疾病或病症之可能性為目的，將可溶性 NPP1(單獨或與另外的醫藥劑組合)施用於或投予具有該疾病或病症，該疾病或病症之徵候或可能發生該疾病或病症的病患，或將治療劑施用於或投予一從病患分離出的組織或細胞株(例如，診斷或活體外應用)。以藥物基因學領域的知識為基礎，此等治療可經特別量身訂製或修改。

【0194】 如文中所用，術語「防止」或「降低」係指若尚未發生則無病症或疾病發展，或若已有發生該病症或疾病則為無進一步病症或疾病。亦考量防止某些或所有與該病症或疾病有關的徵候之能力。

【0195】 如文中所用，術語「降低或防止肌內膜或血管內膜增生」係指可溶性 NPP1 在投予後降低組織損傷位置之增生血管平滑肌細胞程度，藉此降低動脈壁增厚並防止動脈再狹窄發生或降低其程度的能力。

【0196】 如文中所用，術語「冠狀動脈介入術」係指手術或非手術過程，例如包括用來清除阻塞並恢復血液流至阻塞血管之氣球血管成形術，支架之血管成形術，旋磨術或切割氣球導管插入術。

【0197】 如文中所用，術語「非手術組織損傷」係指在創傷事件期間持續至組織或血管的損傷，其係包括(但不限於)涉及使用鈍力或尖銳物品例如刀子之肢體衝突，機械性損傷例如從高處落下，由於重型機具之工作場所受傷或交通工具受傷，例如車禍。

【0198】 如文中所用，術語「非手術組織損傷位置」係指發生組織損傷的位置，其包括(但不限於)腦、脊椎、冠狀動脈和週邊動脈。

【0199】 如文中所用，術語「手術位置」係指由於血管創傷或意外創傷發生組織損傷之動脈區域。

【0200】 如文中所用，術語「*ENPP1* 片段」係指以蛋白形式或以編碼該蛋白之核酸形式投予之 *ENPP1* 蛋白的片段或一部分，或具有至少 *ENPP1* 催化區之全長 *NPP1* 的活性子序列。

【0201】 如文中所用，術語「*ENPP1* 藥劑」如文中所用係指 *ENPP1* 多肽或融合蛋白或包括至少催化區之 *ENPP1* 片段其能藉由裂解腺苷三磷酸(ATP)製造血漿焦磷酸鹽(Ppi)，或多核苷酸例如編碼 *ENPP1* 多肽或融合蛋白或包括至少催化區之 *ENPP1* 片段其能藉由酵素裂解 ATP 製造 Ppi 之 cDNA 或 RNA，或載體，例如含有編碼彼等之多核苷酸的病毒載體。

【0202】 如文中所用，術語「支架」係指置放在血管內的管狀支撐物、管子或幫助療癒或緩解阻塞或防止通道窄化的管子。支架一般而言係包括金屬(例如：不鏽鋼、鈷合金、鎳-鈦合金、錳合金、鋁合金、鉑合金、鎢合金)或聚合物(例如：聚矽氧)製造的可擴展網線。

【0203】 如文中所用，術語「血管支架」係指置放在哺乳動物的動脈或靜脈內的管狀支撐物用以幫助療癒或緩解動脈通道阻塞或防止動脈通道窄化。

【0204】 如文中所用，術語「塗覆支架」或「析出支架」係指塗覆上治療分子，例如蛋白、化學化合物或核酸，在植入位置逐漸從支架表面(內部或外部)析出，藉此提供治療舒緩之支架。治療分子，例如 *ENPP1* 藥劑或 *ENPP3* 藥劑可直接與金屬支架結合，且某些係與基質聚合物結合，其可用作為藥物儲池用以確保在部署期間藥物滯留及均勻分布在支架上。塗覆在支架上的聚合物類型、組成和設計主宰著在原位植入後數周或數月的期間內藥物釋放持續時間之釋出動力學。塗層物質可分類為有機與無機，生物可分解與非生物可分解，以及合成或天然生成物質。

【0205】 如文中所用，術語「塗層」係指，用於與 *ENPP1* 藥劑或 *ENPP3* 藥劑結合塗覆在支架上之包括聚合物載劑的組成物。該塗層可以包括懸浮於聚

合基質中的 ENPP1 藥劑或 ENPP3 藥劑之噴霧或乾膜形式來塗覆。聚合物載劑為足可提供聚合物基質或支撐 ENPP1 藥劑或 ENPP3 藥劑之量。聚合物較佳地不會與 ENPP1 藥劑或 ENPP3 藥劑反應，亦即當二者混合時無化學反應發生。

【0206】 如文中所用，術語「*溶劑*」係根據其最廣泛理解的定義來加以定義並包括在室溫或 20°C 至 40°C 時可將載劑(聚合物)和 ENPP1 藥劑或 ENPP3 藥劑完全或部分溶解其中形成塗層組成物的任何物質。無菌的再蒸餾水為較佳的溶劑。

【0207】 如文中所用，術語「*損傷位置*」係指其中由於一或多種脂質、膽固醇、鈣和各種類型的細胞，例如平滑肌細胞和血小板堆積，而使血流或脊髓液狹縮的血管分布的區域。損傷位置通常係藉由使用心導管檢查術來鑑別。在心導管檢查期間，係經由一塑膠導引鞘(一種插入手臂或腿之血管內的短中空管)插入一稱為導管的長窄管子。在 x 光機的輔助下，經由血管將該導管導引至冠狀動脈。經由該導管注射顯影劑及當顯影劑移動通過心室、瓣膜和主要血管時產生 x-光影像(冠狀動脈血管攝影)。使用顯影劑的數位照片來鑑別冠狀動脈中窄化或阻塞位置。在某些情況下可進行另外的造影法，稱為血管內超音波(IVUS)和血流儲備分數(FFR)伴隨心導管檢查，用以得到詳細的血管壁影像。

【0208】 如文中所用「*植入位置*」係指在血管分布中 ENPP1 或 ENPP3 塗覆支架植入的區域。本發明之塗覆支架可置入組織損傷位置的中心，緊鄰組織損傷位置或距離組織損傷位置中心 200 μm 內的任一側。

【0209】 如文中所用，術語「*心肌梗塞*」係指由於在動脈的內壁形成斑塊，造成心臟血流下降並由於缺乏氧供給而損害心肌，發生心肌永久性損傷。MI 的症候群包括從左臂移到頸部之胸痛、呼吸短促、盜汗、噁心、嘔吐、心跳異常、焦慮、疲勞、虛弱、壓力、憂鬱和其他因子。

【0210】 如文中所用術語「**心肌缺血**」係指特徵為心組織的血供應下降，導致胸痛或狹心症之心肌症狀，心肌梗塞為此缺血的終點，其由於缺乏血液供應而造成心組織壞死。冠狀動脈疾病(CAD)被視為常見的心肌缺血原因。

【0211】 如文中所用術語「**鈍力創傷**」係指由撞擊、受傷或身體攻擊或高速撞擊所導致之身體部分的物理性創傷。鈍性創傷可能導致瘀傷、擦傷、撕裂傷及/或骨折。如文中所用術語「**非手術組織損傷**」或「**穿透性創傷**」係指當一物體，例如子彈或刀子進入身體組織，製造一開放性傷口時所發生的身體部分之創傷。

【0212】 如文中所用術語「**手術刀切口**」係指使用尖銳物體，例如手術刀在手術操作期間在組織中所製造的切口。切口為在身體組織中所製造的切口用以暴露其下的組織、骨骼，使得手術過程得以進行。

【0213】 如文中所用術語「**消融**」係指移除或破壞身體部分或組織或其功能。消融可藉由手術、荷爾蒙、藥物、射頻、熱來進行。

【0214】 如文中所用，術語「**有效量**」係指藥劑的量(例如，NPP1 融合物或 NPP3 融合多肽)，其相較於未接受此量之對應對象，係足以提供改善症狀、病症、疾病，或提供降低症狀、病症或疾病之惡化或加重。有效量亦可能產生治療、療癒、防止或改善症狀、疾病或病症。此術語在其範圍內亦包括有效增進正常生理功能之量。

【0215】 如文中所用，術語「**多肽**」係指由胺基酸殘基所組成的聚合物，相關的天然生成結構變體，及經由肽鍵連接之其合成的非天然生成類似物。

【0216】 如文中所用術語「**分離的**」係指改變或從其自然狀態移除。例如，自然存在活的動物中的核酸或多肽並非「**分離的**」，但部分或完全從其天然狀態之共存物質中分開的相同核酸或多肽即為「**分離的**」。分離的核酸或蛋白可

能以實質上純化的形式存在或可能存在於非天然環境，例如，舉例而言，宿主細胞。

【0217】 如文中所用「*實質上純化的*」係指基本上無其他組份。例如，實質上純化的多肽為一種已從在天然發生狀態下一般與其相結合的其他組份中分離出之多肽。非限定實例包括 95%純度，99%純度，99.5%純度，99.9%純度和100%純度。

【0218】 如文中所用術語「*寡核苷酸*」或「*多核苷酸*」為長度範圍從至少2個，在特定具體實例中至少8、15或25個核苷酸之核酸，但可能高達50、100、1000或5000個核苷酸長或特異性與多核苷酸雜交的化合物。

【0219】 如文中所用，術語「*醫藥組成物*」或「*組成物*」係指至少一種可用本揭露內的化合物與一醫藥上可接受載劑之混合物。醫藥組成物係幫助化合物投予病患。本項技術中存有多種投予化合物的技術，包括(但不限於)皮下、靜脈內、口服、氣霧、吸入、直腸、陰道、經皮、鼻內、頰內、舌下、非經腸、鞘內、胃內、眼、肺和局部給藥。

【0220】 如文中所用，術語「*醫藥上可接受*」係指不會消除化合物的生物活性或性質之載劑或稀釋劑，且相對為無毒的，亦即該物質可投予一個體而不會造成不欲的生物效應或以有害的方式與包含在組成物中的任何組份，例如磷酸緩衝食鹽水(PBS)交互作用。

【0221】 如文中所用，術語「*病理性鈣化*」係指鈣鹽異常沉澱在身體的軟組織，分泌和排泄通道上，造成其硬化。其有二種類型，發生在瀕死和死亡組織之營養不良性鈣化，以及升高的胞外鈣量(高鈣血症)，超過細胞和組織的體內平衡能力之轉移性鈣化。鈣化可能涉及細胞以及胞外基質組份，例如基底膜之膠原蛋白和動脈壁的彈性纖維。某些有鈣化傾向的實例包括：胃黏膜-胃的上皮內襯、腎和肺、角膜、體動脈和肺靜脈。

【0222】 如文中所用，術語「*病理性骨化*」係指其中骨骼出現在非骨骼系統的組織和通常不會顯現成骨性質之結締組織中的病理症狀。依照受影響組織的性質，骨化係分成三類，軟骨內骨化為發生在軟骨中並取代軟骨的骨化。膜內骨化為發生在結締組織並取代結締組織之骨化。化生性骨化為在正常的軟體結構中發展骨性物質；亦稱為異位性骨化。

【0223】 如文中所用，「*降低鈣化*」係藉由使用非侵入性方法，如 X-光、微 CT 和 MRI 來觀察。降低鈣化亦藉由使用放射線造影以 ^{99m}Tc -交磷酸鹽 (^{99m}PYP) 吸收來推斷。小鼠中鈣化的存在係經由事後解剖藉由微電腦斷層掃描和取自心臟、主動脈和腎臟的組織切片及使用染劑，例如蘇木精和伊紅 (Hematoxylin and Eosin (H&E)) 及茜素紅 (Alizarin red) 並藉由下列由 Braddock 等人所建立的方法來評估 (Nature Communications volume 6, Article number : 10006 (2015))。

【0224】 「*低量的 PP_i* 」係指其中該對象具有低於或等於 2%-5% 之正常血漿焦磷酸鹽 (PP_i) 量的狀況。在健康的人類對象中正常的血漿 PP_i 量為大約 1.8 至 2.6 μM 。(Arthritis and Rheumatism, Vol. 22, No. 8 (August 1979))

【0225】 如文中所用術語「*異位性鈣化*」係指特徵為病理性鈣鹽堆積在組織或骨骼生長在軟組織中之症狀。

【0226】 如文中所用術語「*軟組織之異位性鈣化*」係指不適當的生物礦化，典型地係由發生在軟組織中的磷酸鈣、羥磷灰石、草酸鈣和磷酸八鈣所組成，導致喪失硬化的軟組織。「動脈鈣化」係指發生在動脈和心瓣膜中的異位性鈣化，導致動脈硬化及/或窄化。動脈鈣化係與動脈粥樣硬化斑塊負荷有關並增加心肌梗塞的風險，增加週邊血管疾病的缺血事件，以及增加血管成形術後剝離的風險。

【0227】 如文中所用，術語「靜脈鈣化」係指發生在靜脈中降低靜脈彈性及限制血流的異位性鈣化，其然後可能導致血壓增加和冠狀動脈缺損。

【0228】 如文中所用，術語「血管鈣化」係指礦物病理性沉積在血管系統中。其係具有各種形式，包括內膜鈣化和中膜鈣化，但亦可能在心臟瓣膜中發現。血管鈣化係與動脈粥樣硬化、糖尿病、特定的遺傳症狀和腎疾病，尤其是CKD有關。具有血管鈣化的病患處於較高的不良心血管事件風險中。血管鈣化影響廣泛的各種病患。特發性嬰兒動脈鈣化為一種其中新生兒動脈鈣化之罕見的血管鈣化形式。

【0229】 如文中所用，術語「腦鈣化」(BC)係指非特異性神經病理學，其中發生鈣和其他礦物沉積在血管壁和組織薄壁組織，導致神經元死亡和膠樣變性。腦鈣化通常係與各種慢性和急性腦病症有關，包括唐氏症，路易氏體疾病、阿茲海默症、帕金森氏症、血管失智症、腦腫瘤、和各種內分泌症狀。心臟組織鈣化係指鈣(可能包括其他礦物質)沉降堆積在心臟組織中，例如主動脈組織和冠狀動脈組織。

【0230】 術語「腺相關病毒載體」、「AAV載體」、「腺相關病毒」、「AAV病毒」、「AAV病毒體」和「AAV病毒顆粒」和「AAV顆粒」如在文中可交換使用，係指由至少一種 AAV 殼體蛋白(較佳地特定 AAV 血清型之所有的殼體蛋白)及一般體包裹的重組病毒基因體所組成的病毒顆粒。該顆粒係包括一具有異源多核苷酸之重組病毒基因體，該異源多核苷酸係包括一編碼人類 ENPP1 或人類 ENPP3 之序列或其功能上同等物)及一至少包括一側邊有 AAV 末端反向重複序列之啟動子的轉錄調節區。該顆粒典型地係指「AAV載體顆粒」或「AAV載體」。

【0231】 如文中所用，術語「載體」係指能運送已與其連接的另外核酸之核酸分子。在某些具體實例中，載體為一質體，亦即環形雙股 DNA 環，於其中

可連接另外的 DNA 片段。在某些具體實例中，該載體為一病毒載體，其中另外的核苷酸序列可綁紮至該病毒體。在某些具體實例中，此等載體能在將其導入其中的宿主細胞中自主複製(例如，具有細菌複製源的細菌載體和游離基因組哺乳動物載體)。在其他的具體實例中，該等載體(例如，非游離基因組哺乳動物載體)係在導入宿主細胞後整合至該宿主細胞的基因體中，且因此跟隨宿主基因體複製。再者，特定的載體(表現載體)能主導與其操作上連接的基因表現。

【0232】 如文中所用，術語「*重組的宿主細胞*」(或簡言之「*宿主細胞*」)，如文中所用，係指其內已導入一外生性核酸及/或重組載體的細胞。應了解，「*重組的宿主細胞*」和「*宿主細胞*」不僅係指特定對象細胞亦指此一細胞的繼代。因為由於突變或環境影響在後代中可能發生特定的修飾作用，因此，此繼代事實上可能不會與親代細胞相同，但仍包括在如文中所用之術語「*宿主細胞*」的範圍內。

【0233】 術語「*重組的病毒基因體*」，如文中所用，係指一 AAV 基因體，其中至少一外來的表現匣多核苷酸係插入到天然生成的 AAV 基因體中。根據本揭露，AAV 的基因體典型地係包括同側作用 5' 和 3' 末端反向重復序列(ITR)和一表現匣。

【0234】 術語「*表現匣*」，如文中所用，係指帶有一系列指定核酸元件之重組產生的或合成的核酸結構，其能讓特定核酸在目標細胞中轉錄。根據本揭露，AAV 載體之重組病毒基因體的表現匣係包括操作上連接一編碼 ENPP1 或 ENPP3 之核苷酸序列的轉錄調節區或其功能上的同等物。

【0235】 術語「*轉錄調節區*」，如文中所用，係指能調節一或多種基因表現的核酸片段。根據本揭露，該轉錄調節區係包括一啟動子及視需要一增強子。

【0236】 術語「*啟動子*」，如文中所用，係指位於多核苷酸序列上游，用於控制一或多個多核苷酸轉錄的核酸片段，且其係藉由 DNA-依賴的 RNA 聚合

酶結合位、轉錄起始位和任何其他 DNA 序列的存在由結構上辨識，其包括(但不限於)轉錄因子結合位、抑制子和活化蛋白結合位，以及任何其他本項技術中直接或間接用於調節啟動子之轉錄量的已知核苷酸序列。任何種類的啟動子可用於本揭露中，包括誘導型啟動子、組成型啟動子和組織特異性啟動子。

【0237】 術語「*增強子*」，如文中所用，係指與轉錄因子結合，用以增加基因轉錄的 DNA 序列元素。增強子的實例可為(不限於)RSV 增強子、CMV 增強子、HCR 增強子等。在另外的具體實例中，該增強子為一肝特異性增強子，更佳地，肝調控區增強子(HCR)。

【0238】 術語「*操作上連接*」，如文中所用，係指啟動子序列與感興趣多核苷酸之功能關係和位置(例如，若其影響序列的轉錄，則啟動子或增強子係操作上連接一編碼序列)。一般而言，操作上連接的啟動子係與該感興趣序列相連。然而，增強子不一定要與感興趣序列相連來控制其表現。在另外的具體實例中，啟動子和編碼 ENPP1 或 ENPP3 的核苷酸序列或其功能上的同等物。

【0239】 術語「*有效量*」係指無毒但足量的編碼 ENPP1 或 ENPP3 之病毒載體用以提供所欲的生物結果。該結果可能為降低及/或緩解疾病的跡象、徵候或原因，或任何其他所欲的生物系統之改變。

【0240】 術語「*Cap 蛋白*」，如文中所用，係指具有至少一天然 AAV Cap 蛋白活性之多肽(例如 VP1、VP2、VP3)。Cap 蛋白之功能活性的實例包括引發殼體形成的能力，幫助單股 DNA 堆積，幫助 AAV DNA 包裹入殼體(亦即包被)，與細胞受體結合及幫助病毒體進入宿主細胞。原則上，任何的 Cap 蛋白皆可用於本揭露的內文中。

【0241】 術語「*殼體(capsid)*」，如文中所用，係指將病毒基因體包裹在其中的結構。殼體係由數種蛋白製成的寡聚結構次單元所組成。例如，AAV 具有一藉由三種殼體蛋白：VP1、VP2 和 VP3 交互作用所形成的二十面體殼體。

【0242】 術語「*Rep* 蛋白」，如文中所用，係指具有至少一種天然 AAV *Rep* 蛋白之功能活性的多肽(例如，*Rep* 40、52、68、78)。*Rep* 蛋白之「功能活性」為與蛋白生理功能有關的任何活性，其係包括經由辨識幫助 DNA 複製，結合和切割 DNA 複製的 AAV 源以及 DNA 螺旋酶活性。

【0243】 術語「腺相關病毒 *ITR*」或「AAV *ITR*」，如文中所用，係指存在腺相關病毒基因體之 DNA 股二端的末端反向重複序列。*ITR* 序列為 AAV 基因體高效增殖所需。這些序列的另外屬性為其形成髮夾(hairpin)的能力。此特性歸因於其自身促發，允許導引酶-依賴的第二 DNA 股合成。修飾這些 *ITR* 序列的方法已為本項技術所知(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)。

【0244】 術語「組織特異性」啟動子為僅在特定類型的分化細胞或組織中具有活性。典型地，組織特異性啟動子的下游基因在對其具特異性的組織中比在任何其他組織具有更高程度活性。於該情況下，在任何其特異性組織以外的組織中，可能有極少或實質上無啟動子活性。

【0245】 術語「誘導型啟動子」，如文中所用，係指例如藉由應用化學誘導劑生理上或發生上調節的啟動子。例如，其可為一四環素-誘導的啟動子，美服培酮(mifepristone)(RU-486)-誘導的啟動子及諸如此類。

【0246】 術語「組成型啟動子」，如文中所用，係指其活性在一生物體的所有細胞中，或在最發展階段期間係維持在相對恆定量的啟動子，與細胞環境

幾乎無關。在另外的具體實例中，轉錄調節區讓 ENPPI 得以組成性表現。組成型啟動子之實例包括(不限於)勞司氏肉瘤病毒(RSV)LTR 啟動子(視需要帶有 RSV 增強子)，巨細胞病毒(CMV)啟動子(視需要帶有 CMV 增強子)，SV40 啟動子，二氫葉酸還原酶啟動子， β -肌動蛋白啟動子，磷酸甘油酯激酶(PGK)啟動子和 EF1a 啟動子(Boshart M, et al., Cell 1985; 41 : 521-530)。

【0247】 術語「多腺苷酸化訊號」，如文中所用，係指媒介多腺苷酸延伸與 mRNA 的 3' 端連接之核酸序列。適合的多腺苷酸化訊號包括(不限於)SV40 早期多腺苷酸化訊號、SV40 晚期多腺苷酸化訊號、HSV 胸苷激酶多腺苷酸化訊號、魚精蛋白(protamine)基因多腺苷酸化訊號、腺病毒 5 E1b 多腺苷酸化訊號、牛生長激素多腺苷酸化訊號、人類變體生長激素多腺苷酸化訊號及諸如此類。

【0248】 術語「訊號肽」，如文中所用，係指於蛋白轉譯期間，在感興趣初生蛋白之胺基端結合的胺基酸殘基序列(長度範圍 10-30 個殘基)。訊號肽係藉由訊號識別顆粒(SRP)辨識並在轉運後於內質網藉由訊號肽酶裂解(Lodish et al., 2000, Molecular Cell Biology, 4th edition)。

【0249】 如文中所用，術語「免疫回應」或「免疫反應」係指宿主的免疫系統對入侵(感染)病原生物的抗原，或對導入或表現的外來蛋白之反應。免疫反應一般為體液性或局部的；由 B 細胞所製造的抗體與抗原組合成抗原-抗體複合物，用以不活化或中和抗原。當人類蛋白注射至小鼠模型系統中時常觀察到免疫反應。一般而言，係在導入外來抗原之前藉由注射免疫抑制劑，使小鼠模型系統具免疫耐受，以確保較佳的存活力。

【0250】 如文中所用，術語「免疫抑制」為使用免疫抑制藥物蓄意降低宿主免疫系統之活化或效力，用以促進對外來抗原，例如外來蛋白、骨髓和組織移植之免疫耐受性。免疫抑制藥物之非限定實例包括抗-CD4(GK1.5)抗體、環磷醯胺 (Cyclophosphamide)、硫唑嘌呤 (Azathioprine)(Imuran)、黴酚酸酯

(Mycophenolate mofetil)(Cellcept)、環孢素(Cyclosporine)(Neoral, Sandimmune, Gengraf)、氨甲蝶呤(Methotrexate)(Rheumatrex)、來氟米特(Leflunomide)(Arava)、環磷醯胺(Cytosan)和苯丁酸氮芥(Chlorambucil)(Leukeran)。

【0251】 範圍：整個本揭露，本揭露的各種方面可以一範圍的模式呈現。應了解，範圍模式之說明僅為方便和簡潔起見且不應理解為刻板限制本揭露之範圍。因此，一範圍的描述應視為特定揭示所有可能的子範圍以及在該範圍內的個別數值。例如，一範圍之描述，例如從 1 至 6 應視為特意揭示子範圍，例如從 1 至 3，從 1 至 4，從 1 至 5，從 2 至 4，從 2 至 6，從 3 至 6 等，以及該範圍內的個別數字，例如 1、2、2.7、3、4、5、5.3 和 6。

治療方法

【0252】 本揭露係關於投予 ENPP1 或 ENPP3 藥劑，其係包括投予 sNPP1 和 sNPP3 多肽及其融合蛋白於一對象，以及投予編碼此等多肽的核酸。此等多肽之序列包括(不限於)下列。

序列

SEQ ID NO : 1 - ENPP1 胺基酸序列 - 野生型

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	
		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					

SEQ ID No : 2 -天青殺素-ENPP1-FC

MTRLTVLALLAGLLASSRA**APSCAKEVKSCKGRCFERTFGNCRCDAAACVELGNCCLDYQETCIE
PEHIWTCNKFRCEKRLTRSLCACSDCKDKGDCINYSVCQGEKSWVEEPCESINEPQCPAGFE
TPPTLLFSLDGFRAEYLHTWGGLLPVISKLKCKGTYTKNMRPVYPTKTFPNHYSIVTGLYPESHGI
IDNKMYDPKMNASFSLKSKEKFNPEWYKGEPWVTAKYQGLKSGTFFWPGSDVEINGIFPDIYKMY
NGSVPFEERILAVLQWLQLPKDERPHFYTLYLEEPDSSGHSYGPVSSEVIKALQRVDGMVGMMLMDG
LKELNLHRCNLNLIISDHGMEQGSCKKYIYLNKYLGDVKNIKVIYGPAARLRPSDVPDKYYSFNYE
GIARNLSCREPQNQHFQPKYLFKFLPKRLHFAKSDRIEPLTFYLDLPQWQLALNPSEKRYCGSGFHGSD
NVFSNMQALFVGYPGFKHGIEADTFENIEVYNLMCDLLNLTAPNNGTHGSLNHLLKNPVYTPKH

PKEVHPLVQCPFTRNPRDNLGCSCNPSILPIEDFQTQFNLTVAEEKI IKHETLPYGRPRVLQKENT
ICLLSQHQFMSGYSQDILMPLWTSYTVDRNDSFSTEDFSNCLYQDFRIPLSPVHKCSFYKNNTKVS
YGFLSPPQLNKNSSGIYSEALLTTNIVPMYQSFQVIWRYFHDTLRLKYAEERNGVNVVSGPVFDFD
YDGRCDLENLRQKRRVIRNQEILIPHTFFIVLTSCKDTSQTPLHCENLDTLAFILPHRTDNSESC
VHGKHDSSWVEELMLHRARITDVEHITGLSFYQQRKEPVSDILKLKTHLPTFSQEDLINDKTHTC
PPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR
EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEM
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFS
CSVMHEALHNHYTQKSLSLSPGK

單底線-天青殺素訊號序列，雙底線-ENPP1 序列的起點和末端，粗黑字體殘基
-Fc 序列，**係指訊號序列的裂解點。

SEQ ID No : 3 - 天青殺素-ENPP1-Alb

MTRLTVLALLAGLLASSRA**APSCAKEVKSCKGRCFERTFGNCRCDAAACVELGNCCLDYQETCIE
PEHIWTCNKFRGCEKRLTRSLCACSDCKDKGDCCINYSVCQGEKSWVEEPCESINEPQCPAGFE
TPPTLLFSLDGFRAEYLHTWGGLLPVISLKKCGTYTKNMRPVYPTKTFPNHYSIVTGLYPESHGI
IDNKMYDPKMNASFSLKSKEKFNPEWYKGEPiWVTAKYQGLKSGTFFWPGSDVEINGIFPDIYKMY
NGSVPFEERILAVLQWLQLPKDERPHFYTLYLEEPDSSGHSYGPVSSEVIKALQRVDGMVGMMLMDG
LKEINLHRCNLNLIISDHGMEQGSCKKYIYLNKYLGDVKNIKVIYGPAARLRPSDVPDKYYSFNYE
GIARNLSCREPNQHFQPYLKHFLPKRLHFAKSDRIEPLTFYLDLPQWQLALNPSEKCYGSGFHGSD
NVFSNMQALFVGYPGFKHGIEADTFENIEVYNLMCDLLNLTAPANNNGTHGSLNHLNKNPVYTPKH
PKEVHPLVQCPFTRNPRDNLGCSCNPSILPIEDFQTQFNLTVAEEKI IKHETLPYGRPRVLQKENT
ICLLSQHQFMSGYSQDILMPLWTSYTVDRNDSFSTEDFSNCLYQDFRIPLSPVHKCSFYKNNTKVS
YGFLSPPQLNKNSSGIYSEALLTTNIVPMYQSFQVIWRYFHDTLRLKYAEERNGVNVVSGPVFDFD
YDGRCDLENLRQKRRVIRNQEILIPHTFFIVLTSCKDTSQTPLHCENLDTLAFILPHRTDNSESC
VHGKHDSSWVEELMLHRARITDVEHITGLSFYQQRKEPVSDILKLKTHLPTFSQEDLINMKWVTF
LLLLFVSGSAFSGVFRREAHKSEIAHRYNDLGEQHFKGLVLIAFSQYLQKCSYDEHAKLVQEVTD
FAKTCVADESAANCDKSLHTLFGDKLCAIPNLRENYGELADCTKQEPERNECFLOHKDDNPSLPP
FERPEAEAMCTSFKENPTTFMGHYLHEVARRHPYFYAPELLYYAEQYNEILTQCCAEADKESCLTP
KLDGVKEKALVSSVRQRMKCSSMQKGERAFKAWAVARLSQTFPNADFAEITKLATDLTKVNKECC
HGDILLECADDRAE LAKYMCENQATISSKLQTCCKPLKKAHCLSEVEHDTMPADLPAIAADFVED
QEVCKNYAEAKDVLGTFLYEYSRRHPDYSVSLLLRLAKKYEATLEKCCAEANPPACYGTVLAEFQ
PLVEEPKNLVKTNCDLYEKLGEYGFQNAILVRYTQKAPQVSTPTLVEAARNLGRVGTCKCTLPEDQ
RLPCVEDYLSAILNRVCLLHEKTPVSEHVTKCCSGSLVERRPCFSALTVDETYVPKEFKAEFTTFH
SDICTLPEKEKQIKKQTALAEVLVHKPKATAEQLKTMDDFAQFLDTCKKAADKDTCFSTEGPNLV
TRCKDALARSWSHPPQFEK

單底線-天青殺素訊號序列，雙底線-ENPP1 序列的起點和末端，粗黑字體殘基-
白蛋白序列，**係指訊號序列的裂解點。

SEQ ID No : 4 - 天青殺素-ENPP1

MTRLTVLALLAGLLASSRA**APSCAKEVKSCKGRCFERTFGNCRCDAAACVELGNCCLDYQETCIE
PEHIWTCNKFRGCEKRLTRSLCACSDCKDKGDCCINYSVCQGEKSWVEEPCESINEPQCPAGFE
TPPTLLFSLDGFRAEYLHTWGGLLPVISLKKCGTYTKNMRPVYPTKTFPNHYSIVTGLYPESHGI
IDNKMYDPKMNASFSLKSKEKFNPEWYKGEPiWVTAKYQGLKSGTFFWPGSDVEINGIFPDIYKMY
NGSVPFEERILAVLQWLQLPKDERPHFYTLYLEEPDSSGHSYGPVSSEVIKALQRVDGMVGMMLMDG
LKEINLHRCNLNLIISDHGMEQGSCKKYIYLNKYLGDVKNIKVIYGPAARLRPSDVPDKYYSFNYE
GIARNLSCREPNQHFQPYLKHFLPKRLHFAKSDRIEPLTFYLDLPQWQLALNPSEKCYGSGFHGSD
NVFSNMQALFVGYPGFKHGIEADTFENIEVYNLMCDLLNLTAPANNNGTHGSLNHLNKNPVYTPKH
PKEVHPLVQCPFTRNPRDNLGCSCNPSILPIEDFQTQFNLTVAEEKI IKHETLPYGRPRVLQKENT
ICLLSQHQFMSGYSQDILMPLWTSYTVDRNDSFSTEDFSNCLYQDFRIPLSPVHKCSFYKNNTKVS
YGFLSPPQLNKNSSGIYSEALLTTNIVPMYQSFQVIWRYFHDTLRLKYAEERNGVNVVSGPVFDFD

YDGRCDSELENLRQKRRVIRNQEILIPTHFFIVLTSCKDTSQTAPSCAKEVKSCKGRCFERTFGNCR
CDAACVELGNCCLDYQETCIEPEHIWTCNKFRCEKRLTRSLCACSDDCDKGDCCINYSVCQGE
KSWVEEPCESINEPQCPAGFETPPTLLFSLDGFRAEYLHTWGGLLPVISKLKKCGTYTKNMRPVYP
TKTFPNHYSIVTGLYPESHGIIIDNKMYDPKMNASFSLKSKEKFNPEWYKGEPWVTAKYQGLKSGT
FFWPGSDVEINGIFPDIYKMYNGSVPFEEERILAVLQWLQLPKDERPHFYTLYLEEPDSSGHSYGPV
SSEVIKALQQRVDGMVGMMDGLKELNLHRCNLNLIISDHGMEQGSCKKYIYLNKYLGDVKNIKVIY
GPAARLRPSDVPDKYYSFNYEGIARNLSCREPNQHFKPYLKHFLPKRLHFAKSDRIEPLTFYLDPO
WQLALNPSEKRYCGSGFHGSDNVFSNMQALFVGYPGPGFKHGIEADTFENIEVYNLMCDLLNLTPAP
NNGTHGSLNHLNKNPVYTPKHPKEVHPLVQCPFTRNPRDNLGCSCNPSILPIEDFQTQFNLTVAEE
KIIKHETLPYGRPRVLQKENTICLLSQHQFMSGYSQDILMPLWTSYTVDRNDSFSTEDFSNCLYQD
FRIPSPVHKCSFYKNNTKVSYGFLSPPQLNKNSSGIYSEALLTTNIVPMYQSFQVIWRYFHDTLL
RKYAEERNGVNVVSGPVDFDYDGRCDSELENLRQKRRVIRNQEILIPTHFFIVLTSCKDTSQTPLH
CENLDTLAFILPHRTDNSESCVHGKHDSSWVEELLMLHRARITDVEHITGLSFYQQRKEPVSDILK
LKTHLPTFSQED

單底線 – 天青殺素訊號序列，雙底線 – ENPP1 序列的起點和末端，**係指訊號序
列的裂解點。

SEQ ID NO : 5 - ENPP2 胺基酸序列 – 野生型

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															

SEQ. ID NO : 6 - ENPP3 的胞外區：

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	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 胺基酸序列：

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				385			
Tyr	Met	Thr	Asp	Tyr	Phe	Pro	Arg	Ile	Asn	Phe	Phe	Tyr	Met	Tyr	Glu
				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						

SEQ ID No : 8 - 天青殺素-ENPP3-FC

MTRLTVLALLAGLLASSRA*AKQGSCRKKCFDASFRGLENCRCDVACKDRGDCCWDFEDTCVEST
RIWMCNKFRCGETRLEASLCSCSDDCLQRKDCCADYKSVCOGETSWLEENCDDTAQQSQCPGFDLP
PVILFSMDGFRAEYLYTWDTLMPNINKLKTCGIHSKYMRAMYPTKTFPNHYTIVTGLYPESHGIID
NNMYDVNLNKNFSLSSKEQNNPAWWHGQPMNLTAMYQGLKAATYFWPGSEVAINGSFPSIYMPYNG
SVPFEERISTLLKWLDLPKAERPRFYTMFYFEEPSSGHAGGPVSARVIKALQVVDHAFGMLMEGLK
QRNLHNCVNIILLADHGMDQTYCNKMEYMTDYFPRINFFYMYEGPAPRIRAHNI PHDFFSFNSEEI
VRNLSCRKPDQHFKPYLTPDLPKRLHYAKNVRIDKVHLFVDQQWLAVRSKSNNTNCGGGNHGYNNEF
RSMEAIFLAHGPSFKEKTEVEPFENIEVYNLMCDLLRIQPAPNNGTHGSLNHLLKVPFYEP SHAEE
VSKFSVCGFANPLPTESLDCFCPHLQNSTQLEQVNQMLNLTQEEITATVKVNLFPGRPRVLQKNVD
HCLLYHREYVSGFGKAMRMPMWSSYTPVQLGDTSPLPPTVPDCLRADVRVPPSESQKCSFYLDKN
ITHGFLYPPASNRTSDSQYDALITSNLVPMYEEFRKMWDYFHSVLLIKHATERNGVNVVSGPIFDY
NYDGHFDAPDEITKHLANTDVPIPTHYFVVLTSCKNKSHTPENCPGWLDVLPFIIPHRPTNVESCP
EGKPEALWVEERFTAHIARVRDVELLTGLDFYQDKVQPVSEILQLKTYLPTFETI**DKTHTCPCP**
APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVM
HEALHNYHTQKSLSLSPGK

單底線 –天青殺素訊號序列，雙底線–ENPP1 序列的起點和末端，粗黑字體殘基 -Fc 序列，**係指訊號序列的裂解點。

SEQ ID No : 9 - 天青殺素-ENPP3-白蛋白

MTRLTVLALLAGLLASSRA**AKQGSCRKKCFDASFRGLENCRCDVACKDRGDCCWDFEDTCVEST
RIWMCNKFRCGETRLEASLCSCSDDCLQRKDCCADYKSVQCGETSWLEENCDDTAQQSQCEGFDLP
PVILFSMDGFRAEYLYTWDTLMPNINKLKTCGIHSKYMRAMYPTKTFPNHYTIVTGLYPESHGIIID
NNMYDVNLNKNFSLSSKEQNNPAWWHGQPMNLTAMYQGLKAATYFWPGSEVAINGSFPSIYMPYNG
SVPFEERISTLLKWLDLPAERPRFYTMYYEFPDSSGHAGGPVSARVIKALQVVDHAFGMLMEGLK
QRNLHNCVNIILLADHGMDQTYCNKMEYMTDYFPRINFFYMYEGPAPRIRAHNI PHDFFSFNSEEI
VRNLSCRKPDQHF KPYP LTPDL PKRLHYAKNVRIDKVHLFVDQQWLAVRSKSNNTNCGGGNHGYNNEF
RSMEAI FLAHGPS FKEKTEVEPFENIEVYNLMCDLLRIQPAPNNGTHGSLNHLLKVPFYEPSHAE
VSKFSVCGFANPLPTESLDCFCPHLQNSTQLEQVNQMLNLTQEEITATVKVNL PFGRRV LQKNVD
HCLLYHREYVSGFGKAMRMPMWSSYTVPQLGDTSP LPPTVPDCLRADVRVPPSESQKCSFY LADKN
ITHGFLYP PASNRTSDSQYDALITSNLVPMYEEFRKMWDYFHSVLLIKHATERNGVNVSGPIFDY
NYDGHF DAPDEITKHLANTDVPIPTHYFVVLTSCKNKSHTPENCPGWLDVLPFIIPHRPTNVESCP
EGKPEALWVEERFTAHIARVRDV ELLTGLDFYQDKVQPVSEILQLKTYLPTFETTI**IMKWVTFLLLL**
FVSGSAFSRGVFRREAHKSEIAHRYNDLGEQHFKGLVLIAFSQYLQKCSYDEHAKLVQEVTDFAKT
CVADESAANCDKSLHTLFGDKLCAIPNLRENYGELADCCTKQEPERNECF LQHKDDNP SLPPFERP
EAEAMCTSFKENPTTFMGHYLHEVARRHYPFYAPELLYAEQYNEILTQCCAEADKESCLTPKLDG
VKEKALVSSVRQRMKCSSMQKFGERAFKAWAVARLSQTFPNADFAEITKLATDLTKVNKECCHGDL
LECADDRAELAKYMCENQATISSKLQTCCKPLLKKAHCLSEVEHDTMPADLP AIAADFVEDQEV
KNYAEAKDVFLGTFLYEYSRRHPDYSVSLLLRLAKYEATLEKCCAEANPPACYGTVLAEFQPLVE
EPKNLVKTNC DLYEKLGEYGFQNAILVRYTQKAPQVSTPTLVEAARNLGRVGTKCCTLPEDQRLPC
VEDYLSAILNRVCLLHEKTPVSEHVTKCCSGSLVERRPCFSALTVDETYVPKEFKAETFTFHS DIC
TLPEKEKQIKQTALAE LVKHKPKATAEQLKTVMD DFAQFLDTCCKAADKDTCFSTEGPNLVTRCK
DALARSWSHPQFEK

單底線 –天青殺素訊號序列，雙底線–ENPP1 序列的起點和末端，粗黑字體殘基-白蛋白序列，**係指訊號序列的裂解點。

SEQ ID No : 10 - 天青殺素-ENPP3

MTRLTVLALLAGLLASSRA**AKQGSCRKKCFDASFRGLENCRCDVACKDRGDCCWDFEDTCVEST
RIWMCNKFRCGETRLEASLCSCSDDCLQRKDCCADYKSVQCGETSWLEENCDDTAQQSQCEGFDLP
PVILFSMDGFRAEYLYTWDTLMPNINKLKTCGIHSKYMRAMYPTKTFPNHYTIVTGLYPESHGIIID
NNMYDVNLNKNFSLSSKEQNNPAWWHGQPMNLTAMYQGLKAATYFWPGSEVAINGSFPSIYMPYNG
SVPFEERISTLLKWLDLPAERPRFYTMYYEFPDSSGHAGGPVSARVIKALQVVDHAFGMLMEGLK
QRNLHNCVNIILLADHGMDQTYCNKMEYMTDYFPRINFFYMYEGPAPRIRAHNI PHDFFSFNSEEI
VRNLSCRKPDQHF KPYP LTPDL PKRLHYAKNVRIDKVHLFVDQQWLAVRSKSNNTNCGGGNHGYNNEF
RSMEAI FLAHGPS FKEKTEVEPFENIEVYNLMCDLLRIQPAPNNGTHGSLNHLLKVPFYEPSHAE
VSKFSVCGFANPLPTESLDCFCPHLQNSTQLEQVNQMLNLTQEEITATVKVNL PFGRRV LQKNVD
HCLLYHREYVSGFGKAMRMPMWSSYTVPQLGDTSP LPPTVPDCLRADVRVPPSESQKCSFY LADKN
ITHGFLYP PASNRTSDSQYDALITSNLVPMYEEFRKMWDYFHSVLLIKHATERNGVNVSGPIFDY
NYDGHF DAPDEITKHLANTDVPIPTHYFVVLTSCKNKSHTPENCPGWLDVLPFIIPHRPTNVESCP
EGKPEALWVEERFTAHIARVRDV ELLTGLDFYQDKVQPVSEILQLKTYLPTFETTI

單底線 –天青殺素訊號序列，雙底線–ENPP3 序號的起點和末端，**係指訊號序列的裂解點。

SEQ. ID NO : 11 - ENPP4 胺基酸序列 – 野生型

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

420

Ser Val Pro Arg Pro Phe Ser Arg

435

Asp Pro Leu Ile Gly

450

425

Leu Gln Leu Gln Glu

440

430

Asp Asp Asp

445

SEQ. ID NO : 12 - ENPP51 胺基酸序列

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	

SEQ. ID NO : 13 - ENPP51 – ALB 胺基酸序列 :

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

Lys

單底線：訊號肽序列；雙底線：NPP1 的起點和末端；**=訊號肽序列的裂解位置；粗黑字體殘基係指白蛋白序列。。

SEQ. ID NO : 14 - ENPP5-NPP3-Fc 序列

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	<u>Thr</u>	<u>Thr</u>	<u>Ile</u>	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

單底線：訊號肽序列；雙底線：NPP33 的起點和末端；**=訊號肽序列的裂解位置；粗黑字體殘基係指白蛋白序列。

SEQ. ID NO : 15- ENPP5-NPP3-白蛋白序列

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						
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						
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						
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	<u>Thr</u>	<u>Thr</u>	<u>Ile</u>	<u>Gly</u>	
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						
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						
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	

單底線：訊號肽序列；雙底線：NPP3 的起點和末端；**=訊號肽序列的裂解位置；粗黑字體殘基係指白蛋白序列。

SEQ. ID NO : 16 - ENPP5 蛋白輸出訊號序列

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 - ENPP51-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	
	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
Val Ser Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser		
	725	730
Leu Glu Asn Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile		
	740	745
Leu Ile Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr		
	755	760
Ser Gln Thr Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile		
	775	780
Leu Pro His Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His		
785	790	795
Asp Ser Ser Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile		
	805	810
Thr Asp Val Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys		
	820	825
Glu Pro Val Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe		
	835	840
Ser <u>Gln Glu Asp</u> 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
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val		
	885	890
Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp		
	900	905
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr		
	915	920
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
Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg		
	965	970
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys		
	980	985
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	

單底線：訊號肽序列；雙底線：NPP3 的起點和末端；**=訊號肽序列的裂解位置；粗黑字體殘基係指 Fc 序列。

SEQ. ID NO : 18 - ENPP71-Fc 胺基酸序列

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	<u>Gln</u>	<u>Glu</u>	<u>Asp</u>	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							

單底線：訊號肽序列；雙底線：NPP1 的起點和末端；**=訊號肽序列的裂解位置；粗黑字體殘基係指 Fc 序列。

SEQ. ID NO : 19 - ENPP71 (缺少 NPP1 N-端 GLK)胺基酸序列：

Met	Arg	Gly	Pro	Ala	Val	Leu	Leu	Thr	Val	Ala	Leu	Ala	Thr	Leu	Leu
1			5			10			15						
<u>Ala</u>	<u>Pro</u>	<u>Gly</u>	<u>Ala</u>	<u>Gly</u>	<u>Ala</u>	**Pro		Ser	Cys	<u>Ala</u>	<u>Lys</u>	<u>Glu</u>	<u>Val</u>	<u>Lys</u>	<u>Ser</u>
			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
Lys Leu Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr		
	165	170
Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr		
	180	185
Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met		
	195	200
Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp		
	210	215
Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys		
225	230	235
Ser Gly Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile		
	245	250
Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu		
	260	265
Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg		
	275	280
Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His		
	290	295
Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val		
305	310	315
Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu		
	325	330
His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln		
	340	345
Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val		
	355	360
Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser		
	370	375
Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg		
385	390	395
Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys		
	405	410
His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu		
	420	425
Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro		
	435	440
Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val		
	450	455
Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys		
465	470	475
His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu		
	485	490
Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His		
	500	505
Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His		
	515	520
Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro		
	530	535
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	<u>Gln</u>	<u>Glu</u>	
		835					840						845			

Asp
單底線：訊號肽序列；雙底線：NPP3 的起點和末端；**=訊號肽序列的裂解位置。

SEQ. ID NO : 20 -ENPP71(缺少 NPP1 N-端 GLK) – Fc 胺基酸序列：

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	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	<u>Gln</u>	<u>Glu</u>	
		835					840					845				
<u>Asp</u>	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

單底線：訊號肽序列；雙底線：NPP1 的起點和末端；**=訊號肽序列的裂解位置；粗黑字體殘基係指 Fc 序列。

SEQ. ID NO : 21 - ENPP71 (缺少 NPP1 N-端 GLK) – ALB 胺基酸序列

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	<u>Arg</u>	<u>Ser</u>	<u>Gly</u>	<u>Ser</u>	<u>Gly</u>	<u>Gly</u>	<u>Ser</u>	<u>Met</u>	<u>Lys</u>	<u>Trp</u>	<u>Val</u>	<u>Thr</u>	<u>Phe</u>	<u>Leu</u>	<u>Leu</u>	
	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	Gln	Lys	Phe	Gly	Glu	Arg	Ala	Phe	Lys	Ala	Trp	Ala	Val	Ala	Arg
1085	Leu	Ser	Gln	Thr	Phe	Pro	Asn	Ala	Asp	Phe	Ala	Glu	Ile	Thr	Lys
1100	Leu	Ala	Thr	Asp	Leu	Thr	Lys	Val	Asn	Lys	Glu	Cys	Cys	His	Gly
1115	Asp	Leu	Leu	Glu	Cys	Ala	Asp	Asp	Arg	Ala	Glu	Leu	Ala	Lys	Tyr
1130	Met	Cys	Glu	Asn	Gln	Ala	Thr	Ile	Ser	Ser	Lys	Leu	Gln	Thr	Cys
1145	Cys	Asp	Lys	Pro	Leu	Leu	Lys	Lys	Ala	His	Cys	Leu	Ser	Glu	Val
1160	Glu	His	Asp	Thr	Met	Pro	Ala	Asp	Leu	Pro	Ala	Ile	Ala	Ala	Asp
1175	Phe	Val	Glu	Asp	Gln	Glu	Val	Cys	Lys	Asn	Tyr	Ala	Glu	Ala	Lys
1190	Asp	Val	Phe	Leu	Gly	Thr	Phe	Leu	Tyr	Glu	Tyr	Ser	Arg	Arg	His
1205	Pro	Asp	Tyr	Ser	Val	Ser	Leu	Leu	Leu	Arg	Leu	Ala	Lys	Lys	Tyr
1220	Glu	Ala	Thr	Leu	Glu	Lys	Cys	Cys	Ala	Glu	Ala	Asn	Pro	Pro	Ala
1235	Cys	Tyr	Gly	Thr	Val	Leu	Ala	Glu	Phe	Gln	Pro	Leu	Val	Glu	Glu
1250	Pro	Lys	Asn	Leu	Val	Lys	Thr	Asn	Cys	Asp	Leu	Tyr	Glu	Lys	Leu
1265	Gly	Glu	Tyr	Gly	Phe	Gln	Asn	Ala	Ile	Leu	Val	Arg	Tyr	Thr	Gln
1280	Lys	Ala	Pro	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Ala	Ala	Arg
1295	Asn	Leu	Gly	Arg	Val	Gly	Thr	Lys	Cys	Cys	Thr	Leu	Pro	Glu	Asp
1310	Gln	Arg	Leu	Pro	Cys	Val	Glu	Asp	Tyr	Leu	Ser	Ala	Ile	Leu	Asn
1325	Arg	Val	Cys	Leu	Leu	His	Glu	Lys	Thr	Pro	Val	Ser	Glu	His	Val
1340	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	Ala	Glu	Thr	Phe	Thr	Phe	His	Ser	Asp	Ile	Cys	Thr	Leu	Pro	Glu
1385	Lys	Glu	Lys	Gln	Ile	Lys	Lys	Gln	Thr	Ala	Leu	Ala	Glu	Leu	Val
1400	Lys	His	Lys	Pro	Lys	Ala	Thr	Ala	Glu	Gln	Leu	Lys	Thr	Val	Met
1415	Asp	Asp	Phe	Ala	Gln	Phe	Leu	Asp	Thr	Cys	Cys	Lys	Ala	Ala	Asp
1430	Lys	Asp	Thr	Cys	Phe	Ser	Thr	Glu	Gly	Pro	Asn	Leu	Val	Thr	Arg
1445	Cys	Lys	Asp	Ala	Leu	Ala	Arg	Ser	Trp	Ser	His	Pro	Gln	Phe	Glu
1460															

Lys

單底線：訊號肽序列；雙底線：NPP1 的起點和末端；**=訊號肽序列的裂解位置；粗黑字體殘基係指白蛋白序列。

SEQ. ID NO : 22 - ENPP7-NPP3-Fc 序列：

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	<u>Phe</u>	<u>Glu</u>	<u>Thr</u>	<u>Thr</u>	<u>Ile</u>	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														

單底線：訊號肽序列；雙底線：NPP3 的起點和末端；**=訊號肽序列的裂解位置；粗黑字體殘基係指 Fc 序列。

SEQ. ID NO : 23 - ENPP71-白蛋白

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	<u>Gln</u>	
		835					840					845				
<u>Glu</u>	<u>Asp</u>	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

單底線：訊號肽序列；雙底線：NPP3 的起點和末端；**=訊號肽序列的裂解位置；粗黑字體殘基係指 Fc 序列。

SEQ. ID NO : 24 - ENPP7-NPP3-白蛋白

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						
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						
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	
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Cys	Asp	Lys	Ser	Leu	His	Thr	Leu	Phe	Gly	Asp	Lys	Leu	Cys	Ala	Ile	
945					950					955						
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								

單底線：訊號肽序列；雙底線：NPP3 的起點和末端；**=訊號肽序列的裂解位置；粗黑字體殘基係指白蛋白序列。

SEQ. ID NO : 25 - ENPP7-ENPP3-白蛋白

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	<u>Pro</u>	<u>Glu</u>	<u>Val</u>	<u>Thr</u>	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	Asn	Leu	Val	Lys	Thr	Asn	Cys	Asp	Leu	Tyr	Glu	Lys	Leu	Gly	Glu
1310	Tyr	Gly	Phe	Gln	Asn	Ala	Ile	Leu	Val	Arg	Tyr	Thr	Gln	Lys	Ala
1325	Pro	Gln	Val	Ser	Thr	Pro	Thr	Leu	Val	Glu	Ala	Ala	Arg	Asn	Leu
1340	Gly	Arg	Val	Gly	Thr	Lys	Cys	Cys	Thr	Leu	Pro	Glu	Asp	Gln	Arg
1355	Leu	Pro	Cys	Val	Glu	Asp	Tyr	Leu	Ser	Ala	Ile	Leu	Asn	Arg	Val
1370	Cys	Leu	Leu	His	Glu	Lys	Thr	Pro	Val	Ser	Glu	His	Val	Thr	Lys
1385	Cys	Cys	Ser	Gly	Ser	Leu	Val	Glu	Arg	Arg	Pro	Cys	Phe	Ser	Ala
1400	Leu	Thr	Val	Asp	Glu	Thr	Tyr	Val	Pro	Lys	Glu	Phe	Lys	Ala	Glu
1415	Thr	Phe	Thr	Phe	His	Ser	Asp	Ile	Cys	Thr	Leu	Pro	Glu	Lys	Glu
1430	Lys	Gln	Ile	Lys	Lys	Gln	Thr	Ala	Leu	Ala	Glu	Leu	Val	Lys	His
1445	Lys	Pro	Lys	Ala	Thr	Ala	Glu	Gln	Leu	Lys	Thr	Val	Met	Asp	Asp
1460	Phe	Ala	Gln	Phe	Leu	Asp	Thr	Cys	Cys	Lys	Ala	Ala	Asp	Lys	Asp
1475	Thr	Cys	Phe	Ser	Thr	Glu	Gly	Pro	Asn	Leu	Val	Thr	Arg	Cys	Lys
1490	Asp	Ala	Leu	Ala											
1505															

單底線：訊號肽序列；雙底線：NPP3 的起點和末端；**=訊號肽序列的裂解位置；粗黑字體殘基係指白蛋白序列。

SEQ. ID NO : 26 - ENPP71 胺基酸序列

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	<u>Gln</u>	<u>Glu</u>	<u>Asp</u>													
	850															

單底線：訊號肽序列；雙底線：NPP1 的起點和末端；**=訊號肽序列的裂解位置。

SEQ. ID NO : 27 - ENPP121 胺基酸序列

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	<u>Gly</u>	
				85					90					95		

<u>Leu</u>	<u>Lys</u>	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	<u>Gln</u>	<u>Glu</u>	<u>Asp</u>				
		915					920					925				

單底線：訊號肽序列；雙底線：NPP1 的起點和末端；**=訊號肽序列的裂解位置。

SEQ. ID. NO : 28 - ENPP121-Fc 胺基酸序列

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	<u>Leu</u>	
65					70				75						80	
Phe	Thr	Phe	Ala	Val	Gly	Val	Asn	Ile	Cys	Leu	Gly**	Phe	Thr	Ala	<u>Gly</u>	
				85					90					95		
<u>Leu</u>	<u>Lys</u>	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 385	Ser	Ser	Glu	Val	Ile 390	Lys	Ala	Leu	Gln	Arg 395	Val	Asp	Gly	Met	Val 400
Gly	Met	Leu	Met	Asp 405	Gly	Leu	Lys	Glu	Leu	Asn 410	Leu	His	Arg	Cys 415	Leu
Asn	Leu	Ile	Leu	Ile 420	Ser	Asp	His	Gly	Met 425	Glu	Gln	Gly	Ser	Cys 430	Lys
Lys	Tyr	Ile 435	Tyr	Leu	Asn	Lys	Tyr 440	Leu	Gly	Asp	Val	Lys	Asn	Ile	Lys
Val 450	Ile	Tyr	Gly	Pro	Ala	Ala 455	Arg	Leu	Arg	Pro	Ser	Asp	Val	Pro	Asp
Lys 465	Tyr	Tyr	Ser	Phe	Asn 470	Tyr	Glu	Gly	Ile	Ala	Arg	Asn	Leu	Ser	Cys 480
Arg	Glu	Pro	Asn	Gln 485	His	Phe	Lys	Pro	Tyr 490	Leu	Lys	His	Phe	Leu	Pro
Lys	Arg	Leu	His 500	Phe	Ala	Lys	Ser	Asp 505	Arg	Ile	Glu	Pro	Leu	Thr	Phe
Tyr	Leu	Asp 515	Pro	Gln	Trp	Gln	Leu 520	Ala	Leu	Asn	Pro	Ser	Glu	Arg	Lys
Tyr 530	Cys	Gly	Ser	Gly	Phe	His 535	Gly	Ser	Asp	Asn	Val	Phe	Ser	Asn	Met
Gln 545	Ala	Leu	Phe	Val	Gly 550	Tyr	Gly	Pro	Gly	Phe	Lys	His	Gly	Ile	Glu 560
Ala	Asp	Thr	Phe	Glu 565	Asn	Ile	Glu	Val	Tyr 570	Asn	Leu	Met	Cys	Asp	Leu 575
Leu	Asn	Leu	Thr 580	Pro	Ala	Pro	Asn	Asn 585	Gly	Thr	His	Gly	Ser	Leu	Asn
His	Leu	Leu 595	Lys	Asn	Pro	Val	Tyr 600	Thr	Pro	Lys	His	Pro	Lys	Glu	Val
His 610	Pro	Leu	Val	Gln	Cys	Pro 615	Phe	Thr	Arg	Asn	Pro	Arg	Asp	Asn	Leu
Gly 625	Cys	Ser	Cys	Asn	Pro 630	Ser	Ile	Leu	Pro	Ile	Glu	Asp	Phe	Gln	Thr 640
Gln	Phe	Asn	Leu	Thr 645	Val	Ala	Glu	Glu	Lys	Ile	Ile	Lys	His	Glu	Thr 655
Leu	Pro	Tyr	Gly 660	Arg	Pro	Arg	Val	Leu	Gln 665	Lys	Glu	Asn	Thr	Ile	Cys
Leu	Leu	Ser 675	Gln	His	Gln	Phe	Met 680	Ser	Gly	Tyr	Ser	Gln	Asp	Ile	Leu
Met 690	Pro	Leu	Trp	Thr	Ser	Tyr 695	Thr	Val	Asp	Arg	Asn	Asp	Ser	Phe	Ser
Thr 705	Glu	Asp	Phe	Ser	Asn 710	Cys	Leu	Tyr	Gln	Asp	Phe	Arg	Ile	Pro	Leu 720
Ser	Pro	Val	His 725	Lys	Cys	Ser	Phe	Tyr	Lys 730	Asn	Asn	Thr	Lys	Val	Ser 735
Tyr	Gly	Phe	Leu 740	Ser	Pro	Pro	Gln	Leu	Asn 745	Lys	Asn	Ser	Ser	Gly	Ile
Tyr	Ser	Glu	Ala 755	Leu	Leu	Thr	Thr 760	Asn	Ile	Val	Pro	Met	Tyr	Gln	Ser
Phe 770	Gln	Val	Ile	Trp	Arg	Tyr 775	Phe	His	Asp	Thr	Leu	Leu	Arg	Lys	Tyr
Ala 785	Glu	Glu	Arg	Asn	Gly 790	Val	Asn	Val	Val	Ser	Gly	Pro	Val	Phe	Asp 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	<u>Gln</u>	<u>Glu</u>	<u>Asp</u>	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		

單底線：訊號肽序列；雙底線：NPP1 的起點和末端；**=訊號肽序列的裂解位置；粗黑字體殘基係指 Fc 序列。

SEQ. ID NO : 29 - ENPP121-ALB 胺基酸序列：

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	<u>Leu</u>	
65					70					75					80	
Phe	Thr	Phe	Ala	Val	Gly	Val	Asn	Ile	Cys	Leu	Gly**	Phe	Thr	Ala	<u>Gly</u>	
				85					90					95		
<u>Leu</u>	<u>Lys</u>	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	<u>Gln</u>	<u>Glu</u>	<u>Asp</u>	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														

單底線：訊號肽序列；雙底線：NPP1 的起點和末端；**=訊號肽序列的裂解位置；粗黑字體殘基係指白蛋白序列。

SEQ. ID NO : 30 - ENPP121-NPP3-Fc 序列

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	
<u>Gln</u>	<u>Gly</u>	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

單底線：訊號肽序列；雙底線：NPP1 的起點和末端；**=訊號肽序列的裂解位置；粗黑字體殘基係指 Fc 序列。

SEQ. ID NO : 31 - ENPP121-NPP3-白蛋白序列

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	<u>Pro</u>	<u>Thr</u>	<u>Phe</u>	<u>Glu</u>	<u>Thr</u>	<u>Thr</u>	<u>Ile</u>	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	Pro	Glu	Asp	Gln	Arg	Leu	1390	Pro	Cys	Val	Glu	Asp	1395	Tyr	Leu	Ser	Ala
1400	Ile	Leu	Asn	Arg	Val	Cys	1405	Leu	Leu	His	Glu	Lys	1410	Thr	Pro	Val	Ser
1415	Glu	His	Val	Thr	Lys	Cys	1420	Cys	Ser	Gly	Ser	Leu	1425	Val	Glu	Arg	Arg
1430	Pro	Cys	Phe	Ser	Ala	Leu	1435	Thr	Val	Asp	Glu	Thr	1440	Tyr	Val	Pro	Lys
1445	Glu	Phe	Lys	Ala	Glu	Thr	1450	Phe	Thr	Phe	His	Ser	1455	Asp	Ile	Cys	Thr
1460	Leu	Pro	Glu	Lys	Glu	Lys	1465	Gln	Ile	Lys	Lys	Gln	1470	Thr	Ala	Leu	Ala
1475	Glu	Leu	Val	Lys	His	Lys	1480	Pro	Lys	Ala	Thr	Ala	1485	Glu	Gln	Leu	Lys
1490	Thr	Val	Met	Asp	Asp	Phe	1495	Ala	Gln	Phe	Leu	Asp	1500	Thr	Cys	Cys	Lys
1505	Ala	Ala	Asp	Lys	Asp	Thr	1510	Cys	Phe	Ser	Thr	Glu	1515	Gly	Pro	Asn	Leu
1520	Val	Thr	Arg	Cys	Lys	Asp	1525	Ala	Leu	Ala			1530				
1535							1540										

單底線：訊號肽序列；雙底線：NPP3 的起點和末端；**=訊號肽序列的裂解位置；粗黑字體殘基係指白蛋白序列。

SEQ. ID NO : 32 - ENPP121GLK 蛋白輸出訊號序列

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 – 白蛋白序列

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 –人類 IgG Fc 結構域，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 –白蛋白序列

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	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 訊號肽

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

SEQ. ID NO : 37 - 訊號序列 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 – 訊號序列 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 - 訊號序列 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

SEQ. ID NO : 40 - exENPP3

Leu Leu Val Ile Met Ser Leu Gly Leu Gly Leu Gly Leu Arg
1 5 10 15
Lys

SEQ. ID NO : 41 - 訊號序列 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 – 訊號序列– 天青殺素

Met Thr Arg Leu Thr Val Leu Ala Leu Leu Ala Gly Leu Leu Ala Ser

Ser Arg Ala

SEQ. ID NO : 43 – 連接子

Asp Ser Ser

SEQ. ID NO : 44 - 連接子

Glu Ser Ser

SEQ. ID NO : 45 -連接子

Arg Gln Gln

SEQ. ID NO : 46 - 連接子

Lys Arg

SEQ. ID NO : 47 - 連接子

(Arg)_m ; m=0-15

SEQ. ID NO : 48 - 連接子

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

SEQ. ID NO : 49 - 連接子

Glu Glu Glu Glu Glu Glu Glu Pro Arg Gly Asp Thr
1 5 10

SEQ. ID NO : 50 – 連接子

Ala Pro Trp His Leu Ser Ser Gln Tyr Ser Arg Thr
1 5 10

SEQ. ID NO : 51 - 連接子

Ser Thr Leu Pro Ile Pro His Glu Phe Ser Arg Glu
1 5 10

SEQ. ID NO : 52 - 連接子

Val Thr Lys His Leu Asn Gln Ile Ser Gln Ser Tyr
1 5 10

SEQ. ID NO : 53 - 連接子

(Glu)_m; m=1-15

SEQ. ID NO : 54 - 連接子

Leu Ile Asn

SEQ. ID NO : 55 - 連接子

Gly Gly Ser Gly Gly Ser
1 5

SEQ. ID NO : 56 - 連接子

Arg Ser Gly Ser Gly Gly Ser
1 5

SEQ. ID NO : 57 - 連接子

(Asp)_m ; m=1-15
1

SEQ. ID NO : 58 - 連接子

Leu Val Ile Met Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5 10 15

SEQ. ID NO : 59 - 連接子

Val Ile Met Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5 10 15

SEQ. ID NO : 60 - 連接子

Ile Met Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5 10

SEQ. ID NO : 61 - 連接子

Met Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5 10

SEQ. ID NO : 62 - 連接子

Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5 10

SEQ. ID NO : 63 - 連接子

Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5 10

SEQ. ID NO : 64 - 連接子

Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5 10

SEQ. ID NO : 65 - 連接子

Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5

SEQ. ID NO : 66 - 連接子

Gly Leu Gly Leu Gly Leu Arg Lys
1 5

SEQ. ID NO : 67 - 連接子

Leu Gly Leu Gly Leu Arg Lys
1 5

SEQ. ID NO : 68 - 連接子

Gly Leu Gly Leu Arg Lys
1 5

SEQ. ID NO : 69 - 連接子

Leu Gly Leu Arg Lys
1 5

SEQ. ID NO : 70 - 連接子

Gly Leu Arg Lys

1

SEQ. ID NO : 71 - 連接子

Leu Arg Lys

1

SEQ. ID NO : 72 - 連接子

Arg Lys

1

SEQ. ID NO : 73 - 連接子

(Lys)_m; m=0-15

1

SEQ. ID NO : 74 - 連接子

D_m; m=1-15

SEQ. ID NO : 75 - 連接子

(GGGS)_n; n=1-10

SEQ. ID NO : 76 - ENPP3 核苷酸序列

atggaatcta	cgttgacttt	agcaacggaa	caacctgtta	agaagaacac	tcttaagaaa	60
tataaaatag	cttgcatgtt	tcttcttgct	ttgctggtga	tcatgtcact	tggattaggc	120
ctggggcctt	gactcaggaa	actggaaaag	caaggcagct	gcaggaagaa	gtgctttgat	180
gcatcattta	gaggactgga	gaactgccgg	tgtgatgtgg	catgtaaaga	ccgaggtgat	240
tgctgctggg	attttgaa	cacctgtgtg	gaatcaactc	gaatatggat	gtgcaataaa	300
tttcgtttgt	gagagaccag	attagaggcc	agcctttgct	cttgttcaga	tgactgtttg	360
cagaggaaa	attgctgtgc	tgactataag	agtgtttgcc	aaggagaaac	ctcatggctg	420
gaagaaaact	gtgacacagc	ccagcagctc	cagtgccccag	aagggtttga	cctgccacca	480
gttatcttgt	tttctatgga	tggatttaga	gctgaatatt	tatacacatg	ggatacttta	540
atgccaaata	tcaataaact	gaaaacatgt	ggaattcatt	caaaatacat	gagagctatg	600
tatcctacca	aaaccttccc	aatcattac	accattgtca	cgggcttgta	tccagagtca	660
catggcatca	ttgacaataa	tatgtatgat	gtaaatctca	acaagaattt	ttcactttct	720
tcaaaggaac	aaaataatcc	agcctgggtg	catgggcaac	caatgtggct	gacagcaatg	780
tatcaagggt	taaaagccgc	tacctacttt	tggcccggat	cagaagtggc	tataaatggc	840
tcctttccct	ccatatacat	gccttacaac	ggaagtgtcc	catttgaaga	gaggatttct	900
acactgttaa	aatggctgga	cctgccc aaa	gctgaaagac	ccaggtttta	taccatgtat	960
tttgaagaac	ctgattcctc	tggacatgca	ggtggaccag	tcagtgccag	agtaattaaa	1020
gccttacagg	tagtagatca	tgcttttggg	atgttgatgg	aaggcctgaa	gcagcggaat	1080
ttgcacaact	gtgtcaatat	caccttctg	gctgaccatg	gaatggacca	gacttattgt	1140
aacaagatgg	aatacatgac	tgattatttt	cccagaataa	acttcttcta	catgtacgaa	1200
gggcctgccc	ccgcgcatcc	agctcataat	atacctcatg	acttttttag	ttttaattct	1260
gaggaaattg	ttagaaacct	cagttgccga	aaacctgatc	agcatttcaa	gccctatttg	1320
actcctgatt	tgccaaagcg	actgcactat	gccaagaacg	tcagaatcga	caaagtcat	1380
ctctttgtgg	atcaacagtg	gctggctggt	aggagtaa	caaatacaaa	ttgtggagga	1440
ggcaaccatg	gttataacaa	tgagtttagg	agcatggagg	ctatctttct	ggcacatgga	1500
cccagtttta	aagagaagac	tgaagttgaa	ccatttgaaa	atattgaagt	ctataaccta	1560
atgtgtgatc	ttctacgc	tcaaccagca	ccaaacaatg	gaacccatgg	tagtttaa	1620
catcttctga	aggtgccttt	ttatgagcca	tcccatgcag	aggaggtgtc	aaagttttct	1680
gtttgtggct	ttgcta	attgccaca	gagtctcttg	actgtttctg	ccctcaccta	1740
caaaatagta	ctcagctgga	acaagtgaat	cagatgctaa	atctcacc	agaagaaata	1800
acagcaacag	tgaaagtaaa	tttgccat	gggaggccta	gggtactgca	gaagaacgtg	1860
gaccactgtc	tcctttacca	cagggaaat	gtcagtggt	ttggaaaagc	tatgaggatg	1920
cccatgtgga	gttcatacac	agtccccccag	ttgggagaca	catcgcctct	gcctcccact	1980

gtcccagact	gtctgcgggc	tgatgtcagg	gttcctcctt	ctgagagcca	aaaatgttcc	2040
ttctattttag	cagacaagaa	tatcaccac	ggcttcctct	atcctcctgc	cagcaataga	2100
acatcagata	gccaatatga	tgctttaatt	actagcaatt	tggtacctat	gtatgaagaa	2160
ttcagaaaaa	tgtgggacta	cttcacacgt	gttcttctta	taaaacatgc	cacagaaaga	2220
aatggagtaa	atgtgggttag	tggaaccaata	tttgattata	attatgatgg	ccattttgat	2280
gctccagatg	aaattaccaa	acatttagcc	aacactgatg	ttcccatccc	aacacactac	2340
tttgtggtgc	tgaccagttg	taaaaacaag	agccacacac	cggaaaactg	ccctgggtgg	2400
ctggatgtcc	taccctttat	catccctcac	cgacctacca	acgtggagag	ctgtcctgaa	2460
ggtaaaccag	aagctctttg	ggttgaagaa	agatttacag	ctcacattgc	cggggtccgt	2520
gatgtagaac	ttctcactgg	gcttgacttc	tatcaggata	aagtgcagcc	tgtctctgaa	2580
attttgcaac	taaagacata	tttaccaaca	tttgaaacca	ctatt		2625

SEQ. ID NO : 77 - ENPP1 核苷酸序列 :

atggaacggg	acggctgtgc	cggcggagga	tcaagaggcg	gagaaggcgg	cagagcccct	60
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	cgggtgcttcg	agcggacctt	cggcaactgc	360
agatgcgacg	ccgcctgtgt	ggaactgggc	aactgctgcc	tggactacca	ggaaacctgc	420
atcgagcccg	agcacatctg	gacctgcaac	aagttcagat	gcggcgagaa	gcggtgacc	480
agatccctgt	gtgcctgcag	cgacgactgc	aaggacaagg	gcgactgctg	catcaactac	540
agcagcgtgt	gccagggcga	gaagtcctgg	gtggaagaac	cctgcgagag	catcaacgag	600
ccccagtgcc	ctgccggcct	cgagacacct	cctaccctgc	tgttcagcct	ggacggcttt	660
cgggcccag	acctgcacac	atggggaggc	ctgctgcccg	tgatcagcaa	gctgaagaag	720
tgcggcacct	acaccaagaa	catgcggccc	gtgtacccca	ccaagacctt	cccccaaccac	780
tactccatcg	tgaccggcct	gtaccccag	agccacggca	tcacgcacaa	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	cggcatgggtg	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	tcctgcccga	gcggtgac	1500
ttcgccaaga	gcgacagaat	cgagcccctg	accttctacc	tggaccccca	gtggcagctg	1560
gccctgaatc	ccagcgagag	aaagtactgc	ggcagcggct	tccacggctc	cgacaacgtg	1620
ttcagcaaca	tgcaggccct	gttcgtgggc	tacggacccg	gctttaagca	cggcatcgag	1680
gccgacacct	tcgagaacat	cgagggtgtac	aatctgatgt	gcgacctgct	gaatctgacc	1740
cctgccccca	acaatggcac	ccacggcagc	ctgaaccatc	tgctgaagaa	ccccgtgtac	1800
acccctaagc	accccaaaga	ggtgcacccc	ctggtgcagt	gccccttcac	cagaaacccc	1860
agagacaacc	tgggctgtag	ctgcaacccc	agcatcctgc	ccatcgagga	cttcagacc	1920
cagttcaacc	tgaccgtggc	cgaggaaaag	atcatcaagc	acgagacact	gccctacggc	1980
agaccccg	tgctgcagaa	agagaacacc	atctgcctgc	tgagccagca	ccagttcatg	2040
agcggctact	cccaggacat	cctgatgccc	ctgtggacca	gctacaccgt	ggaccggaac	2100
gacagcttct	ccaccgagga	tttcagcaac	tgctgtacc	aggatttccg	gatccccctg	2160
agccccgtgc	acaagtgcag	cttctacaag	aacaacacca	agggtgtccta	cggcttctctg	2220
agccctcccc	agctgaacaa	gaacagctcc	ggcatctaca	gcgaggccct	gctgactacc	2280
aacatcgtgc	ccatgtacca	gagcttccaa	gtgatctggc	ggtacttcca	cgacaccctg	2340
ctgcggaagt	acgccgaaga	acggaacggc	gtgaacgtgg	tgtccggccc	agtgttcgac	2400
ttcgactacg	acggcagatg	tgacagcctg	gaaaatctgc	ggcagaaaag	aagagtgatc	2460
cggaaaccag	aaattctgat	ccctacccac	ttcttttatcg	tgctgacaag	ctgcaaggat	2520
accagccaga	ccccctgca	ctgcgagaac	ctggataccc	tggccttcac	cctgcctcac	2580
cggaccgaca	acagcgagag	ctgtgtgcac	ggcaagcacg	acagctcttg	ggtggaagaa	2640
ctgctgatgc	tgcaccgggc	cagaatcacc	gatgtggaac	acatcaccgg	cctgagcttt	2700
taccagcagc	ggaaagaacc	cgtgtccgat	atcctgaagc	tgaaaaccca	tctgccacc	2760

SEQ ID NO : 78 - 天青殺素-ENPP1-FC 核苷酸序列

ggtaccgccacca**atg**acaagactgacagtgctggctctgctggccggactggttggcctcttctaga
gct**gct**ccttctctgcgccaaagaagtgaagtcctgcaagggcagatgcttcgagcggaccttcggc
aactgtagatgtgacgccgcttgctggaactgggcaactgctgcctggactaccaagagacatgc
atcgagcccgagcacatctggacctgcaacaagttcagatgcggcgagaagcggctgaccagatct
ctgtgcgctgctctgacgactgcaaggacaaggcgactgctgcatcaactactcctctgtgtgc
cagggcgagaagtcctgggttgaagaaccctgagtgccatcaacgagcctcagtgtcctgccggc
ttcgagacacctcctactctgctgttctccctggatggcttcagagccgagtagctgcatacttg
ggaggcctgctgccagtgatctccaagctgaagaagtgcggcacctacaccaagaacatgaggcct
gtgtaccctaccaagacattccccaaccactactccatcgtgaccggcctgtatcctgagagccac
ggcatcatcgacaacaagatgtacgaccccaagatgaacgcctccttcagcctgaagtccaaagag
aagttcaaccccgagtgggtataagggcgagcctatctgggtcaccgctaagtaccagggactgaag
tctggcaccttcttttggcctgggtccgacgtggaaatcaacggcatcttccccgacatctataag
atgtacaacggctccgtgcctttcgaggaacgcattctggctgttctgcagtggctgcagctgcct
aaggatgagaggcctcacttctacaccctgtacctggaagaacctgactcctccggccactcttat
ggcctgtgtcctctgaagtgatcaaggccctgcagcagtgacggaatggtcggaatgctgatg
gacggcctgaaagagctgaacctgcacagatgcctgaacctgatcctgatctccgaccacggcatg
gaacaggggagctgcaagaagtacatctacctgaacaagtacctgggcgacgtgaagaacatcaaa
gtgatctacggcccagccgagactgaggccttctgatgtgcctgacaagtactactccttcaac
tacgaggggaatcgcccgaacctgtcctgcagagagcctaaccagcacttcaagccctacctgaag
cacttctgcctaagcggctgcacttcgccaagtctgacagaatcgagccctgaccttctatctg
gacctcagtggcagctggccctgaatcctagcgagagaaagtactgtggctccggccttcacggc
tccgacaacgtgttctctaataatgcaggccctgttcgtcggctacggccctggctttaaacacggc
atcgagggcgacaccttcgagaacatcgaggtgtacaatctgatgtgtgacctgctgaatctgacc
cctgctcctaacaacggcacccacggatctctgaacctatctgctgaagaatcccgtgtacaccct
aagcaccaccaagaggttcaccctctgggtccagtgctcctttcaccagaaatcctcgggacaacctg
ggctgctccttgcaacccttctatcctgcctatcgaggactttcagaccagttcaacctgaccgtg
gccgaggaaaagatcatcaagcacgagacactgccctacggcagacctagagtgtgcagaaagag
aacaccatctgcctgctgtcccagcaccagttcatgtccggctactcccaggacatcctgatgcct
ctgtggacctcctacaccgtggaccggaacgatagcttctccaccgaggacttcagcaactgcctg
taccaggatttcagaatccctctgagccccgtgcacaagtgcagcttctacaagaacaacaccaag
gtgtcctacggcttctgtctcctccacagctgaacaagaactccagcggcatctactctgaggcc
ctgctgaccaccaacatcgtgcccctgtaccagtccttccaagtgtctggcggtacttccacgac
accctgctgaggaagtacgccgaagaaagaaacggcgtgaacgtgggtgtctggccccgtgttcgac
ttcgactacgacggcagatgcgactctctggaaaacctgcggcagaaaagacgagtgtccggaat
caagagatcctgattcctacacacttctttatcgtgctgaccagctgcaaggatacctctcagacc
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gacggctcattcttctgtactctaagctgacagtgagacaagtcgggtggcagcaaggcaatgtg
ttttcctgctctgtgatgcacgaggccctccacaatcactacaccagaaagtcctgtctctgtcc
cctggcaaa**tgatag**ctcgag

符號 – **粗黑體** = 起始/終止密碼子；加底線 = 訊號肽的核苷酸序列

SEQ ID NO : 79 - 天青殺素-ENPP3-FC 核苷酸序列

atgaccagactgacgctgctggccctgctggccggcctgctggccagcagcagagccgccaagcagggcagct
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cggaag

選殖和表現 ENPP1 和 ENPP3 融合多肽

【0253】 如 US 2015/0359858 A1 中所述製備 ENPP1 或 ENPP1 多肽，該 US 2015/0359858 A1 係以全文引用的方式併入本文中。ENPP1 為一種侷限於細胞表面，具有不同膜內區之跨膜蛋白。為了表現 ENPP1 為一可溶性胞外蛋白，ENPP1 的跨膜區可與 ENPP2 的跨膜區或訊號肽序列，例如天青殺素交換，使得可溶性重組 ENPP1 堆積在桿狀病毒培養的胞外液中。任何其他已知蛋白的訊號序列可用於靶定供分泌的 ENPP1 胞外區以及，例如(但不限於)免疫球蛋白 κ 和 λ 輕鏈蛋白之訊號序列。再者，本揭露不應理解為限制文中所述的多肽，但亦包括含有任何具酵素活性的截斷 ENPP1 胞外區。

【0254】 ENPP1 係藉由刪去跨膜區而變為可溶。人類 ENPP1 (SEQ ID NO : 1) 係藉由以對應的人類 ENPP2 亞區 (NCBI 登錄號 NP 001124335，例如 12-30 殘基) 或天青殺素訊號序列 (SEQ ID NO : 42) 置換其跨膜區 (例如，77-98 殘基) 經修飾，用以表現一可溶的重組蛋白。

【0255】 將該修飾的 ENPP1 序列選殖至具有 TEV 蛋白酶裂解位之經修飾的 pFastbac FIT 載體中，接著 C-端 9-His 標籤，及選殖和於昆蟲細胞中表現，並將二種蛋白如先前所述於桿狀病毒系統中表現 (Albright, et al., 2012, *Blood* 120 : 4432-4440; Saunders, et al., 2011, *J. Biol. Chem.* 18 : 994-1004; Saunders, et al., 2008, *Mol. Cancer Ther.* 7 : 3352-3362)，使得可溶性重組蛋白堆積在胞外液。

【0256】 ENPP3 很難輸出到細胞表面。可溶性 ENPP3 多肽係藉由以天然的其他 ENPP 訊號序列或天青殺素或適合的訊號序列替代 ENPP3 的訊號序列所建構。數種 ENPP3 融合蛋白結構之實例係揭示於 WO 2017/087936 中。可溶性 ENPP3 構築體係藉由使用其他 ENPP 酵素的訊號輸出訊號序列來製備，例如(但不限於)ENPP7 及/或 ENPP5。可溶性 ENPP3 構築體係使用包括 ENPP1 和 ENPP2 之訊號序列組合(下文為「ENPP1-2-1」或「ENPP121」)所組成的訊號序列所製備。任何其他已知蛋白的訊號序列可用於靶定供分泌的 ENPP3 胞外區以及，例

如(但不限於)免疫球蛋白 κ 和 λ 輕鏈蛋白之訊號序列。再者，本揭露不應理解為限制文中所述的結構，但亦包括含有任何具酵素活性的截斷 ENPP3 胞外區。

【0257】 在特定的具體實例中，ENPP3 多肽為可溶性。在某些具體實例中，本揭露之多肽係包括缺乏 ENPP3 跨膜區的 ENPP3 多肽。在另外的具體實例中，本揭露之多肽係包括其中已移除 ENPP3 跨膜區並以另外多肽的跨膜區，例如，如非限制實例 ENPP2、ENPP5 或 ENPP7 或天青殺素訊號序列置換的 ENPP3 多肽。

【0258】 在某些具體實例中，本揭露之多肽係包括一 IgG Fc 結構域。在特定的具體實例中，本揭露之多肽係包括一白蛋白區。在其他的具體實例中，該白蛋白區係位於 ENPP 多肽的 C 端區。又在其他的具體實例中，該 IgG Fc 結構域係位於 ENPP3 多肽的 C 端區。又在其他的具體實例中，IgG Fc 結構域或白蛋白區的存在提升了 ENPP3 多肽的半衰期、溶解度，降低了 ENPP3 多肽的致免疫性以及增加 ENPP3 多肽的活性。

【0259】 在特定的具體實例中，本揭露之多肽係包括使 ENPP3 多肽前驅物得以分泌之訊號多肽，其係經歷蛋白水解處理，產生 ENPP3 多肽。在其他的具體實例中，該訊號肽係由下列組成之群中選出：ENPP2、ENPP5 和 ENPP7 之訊號肽。又在其他的具體實例中，該訊號肽係由 SEQ ID NOs：36-42 組成之群中選出。

【0260】 在特定的具體實例中，IgG Fc 結構域或白蛋白區係與藉由一連接子區與 ENPP3 多肽的 C 端相連接。在其他的具體實例中，該連接子係選自 SEQ ID NOs：43-75，其中 n 為範圍從 1-20 之整數。

製造和純化 ENPP1 和 ENPP3 融合多肽

【0261】 就製造活體外使用之可溶性重組 ENPP1 多肽，係將編碼 ENPP1 的多核苷酸(人類 NPP1(NCBI 登陸號 NP_006199))與 IgG 的 Fc 區(稱為「ENPP1-Fc」)融合並於穩定的 CHO 細胞株中表現。在某些具體實例中，係將編碼 NCBI 登錄號 NP_006199 之 96 至 925 殘基的 ENPP1 多核苷酸與 Fc 結構域融合。

【0262】 另一種選擇，ENPP1 多肽亦可使用適合的載體從 HEK293 細胞，桿狀病毒昆蟲細胞系統或 CHO 細胞或畢氏酵母菌(Yeast Pichia)表現系統加以表現。ENPP1 多肽可於黏附或懸浮細胞中製造。較佳地，ENPP1 多肽係於 CHO 中表現。就建立穩定細胞株，係將編碼 ENPP1 結構之核酸序列選殖至適合的載體中供大規模蛋白製造。

【0263】 ENPP3 係藉由在 CHO 或 HEK293 哺乳動細胞中建立穩定轉染所製造。將編碼 ENPP3 之 ENPP3 多核苷酸(人類 NPP3 (UniProtKB/Swiss-Prot : O14638.2)與 IgG 的 Fc 結構域融合(稱為「ENPP3-Fc」)並於穩定的 CHO 細胞中表現在某些具體實例中，係將 UniProtKB/Swiss-Prot : O14638.2 之 ENPP3 多核苷酸編碼殘基 49-875 與 Fc 結構域融合用以產生 ENPP3 多肽。ENPP3 多肽可於黏附或懸浮細胞中製造。就建立穩定細胞株，係將編碼本揭露之 NPP3 融合多肽的核酸選殖至適合的載體中供大規模蛋白製造。各種這些載體可從市面來源購得並可使用任何這些載體。依循 WO 2017/087936 中所建立的方法製造 ENPP3 多肽，其內容係以全文引用的方式併入。依循 Albright 等人 2015, Nat Commun. 6 : 10006 中所建立的方法製造 ENPP1 多肽，其內容係以全文引用的方式併入。

【0264】 含有所欲的 ENPP1 或 ENPP3 多肽結構之適合質體可使用已建立的技術，例如電穿孔或 lipofectamine，穩定轉染至表現質體中，且該細胞可在抗生素選擇下生長以便強化穩定轉染的細胞。然後建立單一穩定轉染細胞的選植株並篩選高表現所欲融合蛋白的選植株。就 ENPP1 或 ENPP3 多肽表現之單一細

胞選植株的篩選可以高通量方式於 96 孔盤中使用如先前所述的合成酵素基質 pNP-TMP 來進行(Saunders, et al, 2008, *Mol. Cancer Therap.* 7(10) : 3352-62; Albright, et al, 2015, *Nat Commun.* 6 : 10006)。

【0265】 經由篩選鑑別出高表現 ENPP3 或 ENPP1 多肽的選植株之後，可於先前就 ENPP1 所描述的震盪燒瓶或生物反應器中進行蛋白製造(Albright, et al, 2015, *Nat Commun.* 6 : 10006)。ENPP3 或 ENPP1 多肽的純化可使用本項技術中已知的標準純化技術組合來進行。這些技術已為本項技術所熟知且係選自例如管柱層析、超離心、過濾和沉澱之技術。管柱層析純化係使用親和力層析，例如蛋白-A 和蛋白-G 樹脂，金屬親和力樹脂例如鎳或銅，疏水性交換和逆相高壓層析(HPLC)使用 C8-C14 樹脂來進行。亦可運用離子交換，例如陰離子和陽離子交換層析，使用市售的樹脂，例如 Q-sepharose (陰離子交換)和 SP-sepharose (陽離子交換)，blue sepharose 樹脂和 blue-sephadex 樹脂，以及羥磷灰石樹脂。如本項技術中所知，亦可運用粒徑排阻層析使用市售的 S-75 和 S200 Superdex 樹脂。用於溶解蛋白並提供上述層析步驟選擇媒介之緩衝劑為從事蛋白化學技術和科學者已知的標準生物緩衝劑。

【0266】 某些用於製備的緩衝劑實例係包括本項技術熟知的檸檬酸鹽、磷酸鹽、乙酸鹽、三(羥甲基)胺基甲烷、食鹽水緩衝劑、甘胺酸-HCL 緩衝劑、二甲砷酸鹽緩衝劑和巴比特魯鈉(sodium barbital)緩衝劑。在單一純化步驟後，使用單一技術，或組合一系列技術，以及適當的緩衝系統，於考馬斯(Coomasie)染色的聚丙烯醯胺凝膠上並排純化 ENPP3 和粗起始物。然後可使用另外的技術及/或如上述之層析步驟另外純化 ENPP3 蛋白，達到實質上較高的純度，例如~99% 純度調整至適合的 pH，可從粗物質將所述的 ENPP1 或 ENPP3 多肽純化至大於 99%純度。

【0267】 純化後，將 ENPP1-Fc 或 ENPP3-F 透析至添加 Zn^{2+} 和 Mg^{2+} 的 PBS(PBSplus)，濃縮至介於 5 至 7 mg/ml 之間並以 200-500 μ l 的等份於-80°C 冷凍。在使用前再將各等份融化並藉由以 PBSplus 稀釋調整該特定的溶液活性至 31.25 au/ml(或約 0.7 mg/ml，依照製備物而定)。

給藥之劑量和模式

【0268】 在另外的具體實例中，hsNPP1 或 hsNPP3 係以一或多個分別含有約 1.0 mg/kg 至約 5.0 mg/kg NPP1 或約 1.0 mg/kg 至約 5.0 mg/kg NPP3 的劑量給藥。在另外的具體實例中，hsNPP1 或 hsNPP3 係以一或多個含有約 1.0 mg/kg 至約 10.0 mg/kg NPP1 或約 1.0 mg/kg 至約 10.0 mg/kg NPP3 的劑量給藥。

【0269】 hsNPP1 或 hsNPP3 給劑間隔的時間為至少 2 天且可為更長，例如至少 3 天，至少 1 週，2 週或 1 個月。在一具體實例中，係每週、每二周或每月給藥。

【0270】 重組的 hsNPP1 或 hsNPP3 可以任何適合的方式給藥，例如靜脈內、皮下或腹膜內。

【0271】 重組的 hsNPP1 或 hsNPP3 可與一或多種另外的治療劑組合給藥。示例的治療劑包括(但不限於)雙磷酸鹽類(Bisphosphonate)、他汀類(Statins)、纖維酸類(Fibrates)、菸鹼酸(Niacin)、阿斯匹靈(Aspirin)、氯吡格雷(Clopidogrel)和華法林(warfarin)。

【0272】 在某些具體實例中，重組的 hsNPP1 或 hsNPP3 和另外的治療劑係分開給藥及同時或先後給藥。在某些具體實例中，重組的 hsNPP1 或 hsNPP3 係在另外的治療劑給藥之前投予。在某些具體實例中，重組的 hsNPP1 或 hsNPP3 係在另外的治療劑給藥之後投予。在其他的具體實例中，重組的 hsNPP1 或 hsNPP3 係和另外的治療劑一起給藥。

核酸給藥和治療

用於活體內表現 ENPP1 和 ENPP3 之病毒載體

【0273】 編碼可用於本揭露內之多肽的核酸可用於治療文中所考量的疾病或病症的基因療法中。可將編碼該多肽的改良結構插入適當的基因治療載體中並投予病患，用以治療或防止感興趣的疾病或病症。

【0274】 載體，例如病毒載體，在先前技術中已用於將基因導入各種不同的目標細胞中。典型地，係將載體暴露於目標細胞，使足夠比例的細胞得以發生轉化，從表現所欲的多肽(例如受體)提供有用的治療或預防效用。轉染的核酸可永久地併入各目標細胞的基因體中，提供持久的效用，或另一種選擇，此治療可能必須週期性重複。在特定的具體實例中，(病毒)載體係在活體內以編碼本揭露多肽之基因物質轉染肝細胞。

【0275】 各種載體，病毒載體和質體載體已為本項技術所知(參見，例如美國專利第 5,252,479 號和 WO 93/07282)。特言之，許多的病毒已用作為基因轉移載體，其包括乳多泡病毒，例如 SV40，牛痘病毒，疱疹病毒包括 HSV 和 EBV，以及反轉錄病毒。先前技術中的許多基因治療法已應用失能的鼠科反轉錄病毒。數種新近獲證的專利係針對用於進行基因治療的方法和組成物(參見，例如美國專利第 6,168,916 號；第 6,135,976 號；第 5,965,541 號和第 6,129,705 號)。各前述之專利係以全文引用的方式併入本文中。因此，基因物質，例如包括一 NPP1 或 NPP3 序列的多核苷酸可導入哺乳動物中用以治療 VSMC 增生。

【0276】 特定經修飾的病毒常用作載體用以攜帶一編碼序列，因為在投予哺乳動物後，病毒感染細胞並表現該編碼的蛋白。根據本揭露可使用的經修飾病毒係衍生自下列病毒，其包括，例如小病毒、微小核糖核酸病毒、假性狂犬病毒、A、B 或 C 型肝炎病毒、乳突病毒、乳多泡病毒(例如多瘤和 SV40)或疱疹

病毒(例如 EB 病毒(Epstein-Barr Virus)、水痘-帶狀疱疹病毒、巨細胞病毒、帶狀疱疹病毒和單純疱疹病毒第 1 和 2 型)、RNA 病毒或反轉錄病毒，例如莫洛尼鼠白血病毒或慢病毒(亦即，衍生自人類免疫缺陷病毒、貓免疫缺陷病毒、馬傳染性貧血病毒等)。根據本揭露可使用的 DNA 病毒中有：腺相關病毒腺病毒、 α 病毒和慢病毒。

【0277】 病毒載體通常係藉由注射，最常見靜脈內(藉由 IV)直接投予體內，或直接投予特定的組織，在該處由個別細胞吸收。另一種選擇，病毒載體可藉由在體外將病毒載體與病患細胞的樣本接觸來投予，藉此讓病毒載體感染細胞，然後讓含有載體的細胞回到病患中。一旦病毒載體遞送了，該編碼序列表現並產生運作功能的蛋白。一般而言，藉由病毒載體的細胞感染和轉導係由一系列的下列連續事件所發生：病毒質體與目標細胞表面上的受體交互作用，藉由內吞作用內化，經由內吞/蛋白酶體隔室之胞內轉運，內小體脫離，核輸入，病毒體去殼及病毒 DNA 雙股轉換，其導致感興趣的重組編碼序列轉錄及表現(*Colella et al., Mol Ther Methods Clin Dev. 2017 Dec 1;8 : 87-104.*)。

根據本揭露之腺相關病毒載體

【0278】 AAV 係指屬於小病毒科之依賴病毒屬的病毒。AAV 基因體長度為大約 4700 個鹼基對且係由可能為正股或負股之直線型單股去氧核糖核酸(ssDNA)所組成。基因體係在 DNA 股的二端包括末端反向重複序列(ITR)，及二個開放閱讀框(ORF)：rep 和 cap。Rep 框係由四個編碼非結構複製(Rep)蛋白之重疊基因所構成，而該 Rep 蛋白為 AAV 生命週期所需。Cap 框係含有結構性 VP 殼體蛋白的重疊核苷酸序列：VP1、VP2 和 VP3，其係共同作用，形成二十面體對稱性殼體。

【0279】末端的 145 個核苷酸為自身互補並組織，而讓形成 T-形髮夾之能量上穩定的分子內二倍體得以形成。這些髮夾結構的功能為病毒 DNA 複製之起源，作為細胞 DNA 聚合酶複合物的引子。野生型 AAV 在哺乳動物細胞中感染後，分別從 P5 啟動子和 P19 啟動子表現 rep 基因(亦即 Rep78 和 Rep52)，且二種 Rep 蛋白在病毒基因體的複製上具有其功能。一 rep ORF 的剪接事件造成實際上四個 Rep 蛋白(亦即 Rep78、Rep68、Rep52 和 Rep40)表現。然而，其已顯示未剪接的 mRNA，編碼 Rep78 和 Rep52 蛋白，在哺乳動物細胞中足以用於 AAV 載體製造。在昆蟲細胞中 Rep78 和 Rep52 蛋白同樣足以供 AAV 載體製造。

【0280】AAV 為一輔助病毒依賴的病毒(helper-dependent virus)，亦即，其需要與一輔助病毒(例如腺病毒、疱疹病毒或牛痘病毒)共感染，以便於形成功能上完整的病毒體。在缺乏輔助病毒共感染下，AAV 建立了一潛伏狀態，其中病毒基因體係插入宿主細胞的染色體中或以游離基因組的形式存在，但感染的病毒體不具生產力。後續藉由輔助病毒感染「救援」該整合的基因體，使其得以複製並包裹至病毒殼體內，藉此重建感染的病毒體。當 AAV 可感染不同種類的細胞之同時，輔助病毒必須與宿主細胞為相同種類。因此，例如，人類 AAV 在經犬類腺病毒感染的犬類細胞中複製。

【0281】就製造含有異源性核酸序列的感染重組 AAV(rAAV)，可將適合的宿主細胞以含有異源性核酸序列，但缺乏 AAV 輔助功能基因 rep 和 cap 的 AAV 載體轉染。然後可於一分開的載體上提供 AAV-輔助功能基因。又，僅 AAV 製造所必需的輔助病毒基因(亦即附屬功能基因)可提供於一載體上，而非提供具複製能力的輔助病毒(例如，腺病毒、疱疹病毒或牛痘病毒)。

【0282】整體上，可於一或多個載體上提供 AAV 輔助功能基因(亦即，rep 和 cap)和附屬功能基因。然後輔助和附屬功能基因產物可於宿主細胞中表現，在宿主細胞中其將以異側作用在含有異源核酸序列的 rAAV 載體。然後含有異

源核酸序列的 rAAV 載體將被複製並包裹，如同野生型(wt) AAV 基因體一般，形成重組的病毒體。當以所產生的 rAAV 病毒體感染病患的細胞時，異源的核酸序列進入病患細胞中並於病患細胞中表現。

【0283】 因為病患細胞缺乏 rep 和 cap 基因以及附屬功能基因，因此 rAAV 無法進一步複製及包裹其基因體。再者，在無 rep 和 cap 基因的來源下，無法在病患細胞中形成 wtAAV。

【0284】 AAV 載體典型地係缺乏 rep 和 cap 框。當存在經編碼及表現 rep 和 cap 基因產物(亦即 AAV Rep 和 Cap 蛋白)之載體轉染的細胞中，且其中宿主細胞係經編碼和表現來自腺病毒開放閱讀框 E4 或 f6 之蛋白的載體轉染時，此等 AAV 載體可被複製並包裹至感染的病毒顆粒內。

【0285】 遞送感興趣蛋白至哺乳動物細胞係藉由首先產生包括編碼感興趣蛋白之 DNA 的 AAV 載體及然後將該載體投予哺乳動物來進行。因此，本揭露應理解為包括含有編碼感興趣多肽的 DNA 之 AAV 載體。一旦有了本揭露，產生包括編碼此/這些多肽的 DNA 之 AAV 載體對於熟習技術者將顯而易見。

【0286】 在一具體實例中，本揭露係關於包括編碼哺乳動物 ENPP1 或哺乳動物 ENPP3 序列之腺相關病毒(AAV)表現載體，並在一細胞中表現 ENPP1 或 ENPP3 前驅物的載體投予一哺乳動物後，該包括天青殺素訊號肽的前驅物則在其羧基端與 ENPP1 或 ENPP3 的胺基端融合。該 ENPP1 或 ENPP3 前驅物可包括一安定化區，例如 IgG Fc 區或人類白蛋白。在從細胞分泌前驅物後，訊號肽則裂解並於胞外提供具酵素活性的可溶性哺乳動物 ENPP1 或 ENPP3。

【0287】 AAV 表現載體可包括一含有轉錄調節區的表現匣，該轉錄調節區係操作上連接一包括轉錄調節區的核苷酸序列，又該轉錄調節區係操作上連接一編碼多肽的重組核酸序列，而該多肽係包括一天青殺素訊號肽序列和一外核苷酸焦磷酸酶/磷酸二酯酶(ENPP1)多肽序列。

【0288】 在某些具體實例中，表現匣係包括一啟動子和增強子，Kozak 序列 GCCACCATGG，編碼哺乳動物 NPP1 蛋白的核苷酸序列或編碼哺乳動物 NPP3 蛋白的核苷酸序列，其他適合的調節元件和多腺苷酸化訊號。

【0289】 在某些具體實例中，根據本揭露之 AAV 載體的 AAV 重組基因體係缺乏 rep 開放閱讀框及/或 cap 開放閱讀框。

【0290】 根據本揭露之 AAV 載體係包括來自任何血清型的殼體。一般而言，該 AAV 血清型係具有在胺基酸及核酸層級上明顯同源的基因體序列，提供相同的基因功能組，以及經由幾乎相同的機制複製和組合。特言之，本揭露之 AAV 可屬於 AAV 的血清型 1(AAV1)、AAV2、AAV3 (包括 3A 和 3B 型)、AAV4、AAV5、AAV6、AAV7、AAV8、AAV9、AAV10、AAVrh10、AAV11、禽類 AAV、牛 AAV、犬 AAV、馬 AAV、或羊 AAV。

【0291】 不同 AAV 血清型的基因體之序列實例可參見文獻或公開的資料庫，例如 GenBank。例如，GenBank 登錄號 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)和 AX753362.1 (AAV10)。

【0292】 在某些具體實例中，根據本揭露之腺相關病毒載體係包括由下列組成之群中選出的血清型所衍生之殼體：AAV2、AAV5、AAV7、AAV8、AAV9、AAV10 和 AAVrh10 血清型。在另外的具體實例中，該 AAV 的血清型為 AAV8。若病毒載體係包括編碼殼體蛋白的序列，則這些序列可經修飾以便於包括將 AAV 導向特定細胞類型的外生性序列，或用於增加將目標載體遞送至細胞的效率，或用於幫助純化或偵測 AAV，或降低宿主反應。

【0293】 在特定的具體實例中，本揭露之 rAAV 載體係包括數個必要的 DNA 元件。在特定的具體實例中，這些 DNA 元件係包括至少二條 AAV ITR 序列複製物，一啟動子/增強子元件，一轉錄終止訊號，任何必要的 5'或 3'末轉譯

區(側接編碼感興趣蛋白之 DNA 或其生物活性片段)。本揭露之 rAAV 載體亦可包括感興趣蛋白內含子的一部分。又，視需要，本揭露之 rAAV 載體係包括編碼突變的感興趣多肽之 DNA。

【0294】 在特定的具體實例中，該載體係包括一啟動子/調節序列，而該啟動子/調節序列包括能在許多不同細胞類型中驅動異源性基因高量表現之雜交啟動子。此等啟動子包括(但不限於)巨細胞病毒(CMV)媒介的早期啟動子/增強子序列，勞氏肉瘤病毒啟動子/增強子序列及諸如此類。在特定的具體實例中，本揭露之 rAAV 載體中的啟動子/調節序列為 CMV 立即早期啟動子/增強子。然而，用於驅動異源性基因表現的啟動子序列亦可為誘導型啟動子，例如，但不限於，類固醇誘導型啟動子，或可為組織特異性啟動子，例如，但不限於，肌肉組織特異性之骨骼 α -肌動蛋白啟動子，以及肌酸激酶啟動子/調節序列及諸如此類。

【0295】 在特定的具體實例中，本揭露之 rAAV 載體係包括一轉錄終止訊號。當任何轉錄終止訊號可包括在本揭露載體中的同時，在特定的具體實例中，該轉錄終止訊號為 SV40 轉錄終止訊號。

【0296】 在特定的具體實例中，本揭露之 rAAV 載體係包括編碼感興趣多肽或感興趣多肽之生物活性片段之分離的 DNA。本揭露應理解為包括任何已知或未知的哺乳動物之感興趣多肽序列。因此，本揭露應理解為包括來自人類以外的哺乳動物基因，該多肽係以實質上類似人類多肽的方式運作。較佳地，包括編碼感興趣多肽基因之核苷酸序列與編碼感興趣多肽之基因為約 50%同源的，更佳地約 70%同源的，甚佳地約 80%同源的，及最佳地約 90%同源的。

【0297】 再者，本揭露應理解為包括野生型蛋白序列之天然生成的變體或重組衍生的突變體，在本揭露的基因治療法中該變體或突變體賦予由此所編碼的多肽如同全長多肽的治療效用，或比全長多肽更具治療效用。

【0298】 本揭露亦應理解為包括編碼保留該多肽生物活性之變體的 DNA。此等變體包括已經或可使用重組 DNA 技術修飾的蛋白或多肽，使得該蛋白或多肽具有另外增進其用於文中所述方法中之適應性的性質，例如，但不限於，賦予蛋白在血漿中提升的安定性及增進蛋白的特異性活性之變體。類似物可能在保守性胺基酸序列差異上或不影響序列的修飾上或二者，不同於天然生成的蛋白或胜肽。例如，可改變保守性胺基酸，其雖然改變了蛋白或胜肽的一級序列，但通常不會改變其功能。

【0299】 本揭露不限於在實驗實例中作為例示的特定 rAAV 載體；而本揭露應理解為包括任何適合的 AAV 載體，其係包括，但不限於以 AAV-1、AAV-3、AAV-4 和 AAV-6 為基礎的載體及諸如此類。又本揭露係包括以一有效提供治療效用之量治療一具有疾病或病症之哺乳動物的方法。

【0300】 該方法係包括投予該哺乳動物一編碼感興趣多肽的 rAAV 載體。較佳地，該哺乳動物為人類。典型地，以單一注射投予哺乳動物之病毒載體基因體的數目範圍係從約 1×10^8 至約 5×10^{16} 。較佳地，以單一注射投予哺乳動物之病毒載體基因體的數目係從約 1×10^{10} 至約 1×10^{15} ；更佳地，以單一注射投予哺乳動物之病毒載體基因體的數目係從約 5×10^{10} 至約 5×10^{15} ；及最佳地，以單一注射投予哺乳動物之病毒載體基因體的數目係從約 5×10^{10} 至約 5×10^{14} 。

【0301】 當本揭露之方法係包括多位點同時注射，或包括在數小時的期間內(例如，從少於 1 小時至約 2 或 3 小時)注射不同位點之數個多位點注射時，所投予的病毒載體基因體之總數可與單一位點注射法中所述的數目相同或其分數比例或其倍數。

【0302】 就以單一位點注射投予本揭露之 rAAV 載體，在特定的具體實例中，包括該病毒的組成物係直接注射至該對象的器官中(例如，但不限於該對象的肝臟)。

【0303】 就投予哺乳動物，該 rAAV 載體可懸浮於醫藥上可接受的載劑中，例如 pH 約 7.8 之 HEPES 緩衝食鹽水。其他可使用的醫藥上可接受載劑包括，但不限於甘油、水、食鹽水、乙醇和其他醫藥上可接受鹽溶液，例如磷酸鹽和有機酸鹽類。這些和其他醫藥上可接受載劑之實例係描述於 Remington's Pharmaceutical Sciences (1991, Mack Publication Co., New Jersey)。本揭露之 rAAV 載體亦可以套組的形式提供，該套組係包括，例如於乾燥鹽類調配物中之載體凍乾製備物，用於懸浮載體/鹽類組成物之無菌水，以及懸浮該載體和將該載體投予哺乳動物之說明書。

【0304】 公開申請案 US 2017/0290926 –Smith 等人，詳細描述了產生、遞送和投予 AAV 載體之方法，該申請案內容之全文係以引用的方式併入本文中。

RNA 為基礎的活體內 ENPP1 和 ENPP3 多肽之表現

【0305】 本揭露係提供用於製造和遞送重組雙股 RNA 分子之組成物和方法(編碼文中所述之 ENPP1 或 ENPP3 多肽的 dsRNA。該雙股的 RNA 粒子(dsRP)可含有包封在殼體或外套蛋白中的 dsRNA 分子。該 dsRNA 分子可為病毒的基因體或衍生自一野生型病毒體之基因體的部分。該 RNA 分子可編碼一 RNA-依賴 RNA 聚合酶(RDRP)和形成至少一部份殼體或外套蛋白之多蛋白。該 RNA 分子亦可含有一 RNA 子序列，而該 RNA 子序列係編碼一藉由宿主細胞的胞內組份轉譯之 ENPP1 或 ENPP3 多肽。當 dsRP 轉染至宿主細胞時，該子序列可藉由宿主細胞的胞器轉譯，製造 ENPP1 或 ENPP3 多肽。

【0306】 在另外方面，本揭露係提供於宿主細胞中製造蛋白產物之方法。該方法係包括以具有一重組雙股 RNA 分子(dsRNA)和一殼體或外套蛋白之 dsRP 轉染一宿主細胞。該 RNA 分子可編碼一 RNA-依賴 RNA 聚合酶和一形成至少部分殼體或外套蛋白之多蛋白，且該 dsRP 能在宿主細胞中複製。該 RNA 分子具

有至少一編碼 ENPP1 或 ENPP3 多肽的 RNA 子序列，其係藉由宿主細胞的細胞組份轉譯。

【0307】 在另外方面本揭露係提供可藉由宿主細胞轉譯的 RNA 分子。該 RNA 分子可為任何編碼文中所述的 ENPP1 或 ENPP3 多肽之 RNA 分子。在一具體實例中，該 RNA 分子係編碼一 RNA-依賴 RNA 聚合酶和一形成至少部分 dsRP 之殼體或外套蛋白的多蛋白，及，視需要可具有至少一編碼另外蛋白產物之 RNA 子序列。

製造 dsRP

【0308】 本揭露之 dsRP 亦可藉由於一宿主細胞中呈現質體或其他編碼本揭露之 dsRP 或編碼 dsRP 基因的 DNA 分子來製造。然後將含有編碼所欲蛋白，例如 ENPP1 或 ENPP3 多肽之核苷酸序列的質體或 DNA 分子轉染至該宿主細胞中則該宿主細胞開始製造本揭露之 dsRP。dsRP 亦可在宿主細胞中藉由於宿主細胞中呈現一編碼 dsRP 基因的 RNA 分子來製造。該 RNA 分子可為(+)-股 RNA。

【0309】 一旦本揭露之 dsRP 已呈現於該宿主細胞(或編碼本揭露之 dsRP 基因的質體，或編碼該 dsRP 基因的 RNA 分子)，則將在宿主細胞內使用宿主細胞的細胞組份製造 dsRP。本揭露之 dsRP 因此在宿主細胞內自給自足並在宿主細胞內繁殖。該宿主細胞可為任何適合的宿主細胞，例如，舉例而言，真核細胞、哺乳動物細胞、真菌細胞、細菌細胞、昆蟲細胞或酵母菌細胞。宿主細胞可在呈現本揭露之重組 dsRNA 分子或編碼本揭露之 dsRP 的 DNA 分子並由宿主細胞吸收後，繁衍該重組的 dsRP。

製造 dsRNA 病毒或 dsRP 之方法

【0310】 本揭露亦提供製造本揭露之 dsRP 的方法。雙股或單股 RNA 或 DNA 分子可呈現於一宿主細胞。在宿主細胞中 dsRNA 分子的增幅係利用已存在許多類型宿主細胞(例如酵母菌)中之天然的製造和組合程序。本揭露之施行因此可藉由於一宿主細胞呈現本揭露之單股或雙股 RNA 或 DNA，該 RNA 或 DNA 係被宿主細胞吸收並使用宿主細胞的細胞組份用來製造重組的 dsRP 和蛋白或由 RNA 子序列所編碼的蛋白。本揭露亦可藉由提供宿主細胞一線形或環狀 DNA 分子(例如，質體或載體)來施行，而該線形或環狀 DNA 分子係含有一或多個編碼 RNA-依賴的 RNA 聚合酶的序列，形成至少部分 dsRP 之殼體或外套蛋白的多蛋白，及編碼感興趣蛋白，例如如文中所述的 ENPP1 或 ENPP3 多肽之子序列。

【0311】 呈現本揭露之 dsRNA 或 ssRNA 分子可以任何適合的方式來進行，例如，舉例而言，藉由直接於宿主細胞呈現一本揭露之 RNA 分子作為「裸露」或未經修飾的單股或雙股 RNA。該 RNA 分子可藉由任何適合的方法，例如藉由電穿孔，將宿主細胞暴露於磷酸鈣，或藉由產生與細胞膜融合並將病毒序列存放在其內的脂質體，轉染(或轉化)至酵母菌、細菌或哺乳動物細胞宿主細胞。其亦可藉由將殺手病毒之 dsRNA 或異源性 dsRNA 直接導入宿主細胞的特定胞器來進行。此步驟可使用一報導子系統最佳化，例如紅色螢光蛋白(RFP)，或藉由瞄準特定組成性基因在宿主細胞基因體內轉錄。此項可藉由使用具有明顯表型之標靶或藉由以定量反轉錄酶 PCR(RT-PCR)監測來進行。

【0312】 在某些具體實例中，係將編碼本揭露 RNA 分子之 DNA 分子(例如質體或其他載體)導入宿主細胞中。該 DNA 分子可含有編碼本揭露 dsRP 之 RNA 分子的序列。該 DNA 分子可編碼完整的 dsRP 基因體或其部分。該 DNA 分子可進一步編碼至少一製造另外(異源性)蛋白產物之 RNA 的子序列。該 DNA 序列亦可編碼 gag 蛋白或 gag-pol 蛋白，以及任何必須的或所欲的啟動子或其他

支持該分子表現和目的之序列。該 DNA 分子可為一線形 DNA、環狀 DNA、質體、酵母菌人工染色體，或可為方便特定應用之另外的形式。

【0313】 在一具體實例中，該 DNA 分子可進一步包括用於製造串聯體和髮夾結構的 T7 末端，因此得以在宿主細胞中繁殖病毒或 dsRP 序列。該 DNA 分子可轉染或轉化至宿主細胞內及然後使用宿主細胞胞器轉錄，並因此提供該宿主細胞具有至少一 RNA 之子序列的 dsRNA 分子。宿主細胞然後可製造該編碼的所欲 ENPP1 或 ENPP3 多肽。dsRNA 可使用宿主細胞代謝程序和機制，以如同野生型病毒的方式包裹。ENPP1 或 ENPP3 多肽同樣係使用宿主細胞代謝程序和細胞組份來製造。

【0314】 Brown 等人之專利 US 10266834 詳細描述了編碼多肽的 dsRNA 粒子之產生、遞送和投予方法，而該專利內容全文係以引用的方式併入本文中。

ENPP1 塗覆支架和 ENPP3 塗覆支架

【0315】 支架典型地為用於保持身體各種部位之內腔開放(例如，體內的開口)的狹長結構，使得含有這些內腔的身體部位可正常運作。支架通常係用於治療動脈粥樣硬化，一種其中動脈係部份且有時候完全被可能包括脂質、膽固醇、鈣和各種類型細胞，例如平滑肌細胞和血小板阻塞之血管系統的疾病。

【0316】 位於身體任何內腔中的支架並不一定總能防止部分或完全的再狹窄。特言之，在經皮穿腔血管成形術(PTA)後，支架並不一定總能防止動脈的再狹窄。在某些情況下，動脈或靜脈中導入或存在的支架本身可能製造創傷或組織損傷區域，例如在動脈內襯中稱為內皮的裂口，在支架置放後需要另外的手術。

【0317】 咸信此創傷或組織損傷可能觸發血管平滑肌細胞(其通常係藉由內皮與動脈腔隔開)遷移至動脈內腔，在其中增生而產生細胞團塊，其可能於數

日或數週內阻塞動脈。此再阻塞，有時候可在 PTA 後見到，為一再狹窄的實例。以治療劑，例如 ENPP1 藥劑或 ENPP3 藥劑塗覆支架預期防止及/或降低血管平滑肌細胞增生，其轉而降低再狹窄的發生或治療再狹窄。

【0318】 在某些具體實例中，病患由於存有之前植入的非析出型支架而需要手術及/或具有組織損傷。

【0319】 在某些具體實例中，病患由於存有之前植入的析出 ENPP1 藥劑或 ENPP3 藥劑以外之治療劑的析出型支架而需要手術及/或具有組織損傷。

【0320】 在某些具體實例中，係移除已造成組織損傷的先前支架並以 ENPP1 藥劑塗覆支架替代。

【0321】 在某些具體實例中，係移除已造成組織損傷的先前支架並以 ENPP3 藥劑塗覆支架替代。

【0322】 在某些具體實例中，並未移除已造成組織損失的先前支架且係於先前的支架旁植入 ENPP1 藥劑塗覆支架。

【0323】 在某些具體實例中，並未移除已造成組織損失的先前支架且係於先前的支架旁植入 ENPP3 藥劑塗覆支架。

【0324】 ENPP1 或 ENPP3 塗覆支架典型地為支桿或互連細絲所製的中空、圓柱形結構。支架通常係藉由將其以壓縮的狀態連接一導管，將其導引通過身體到達支架使用位置，植入體內其使用位置。血管支架常用於血管中打開血管並提供提升的血流。一旦支架置放於所欲的位置後，其可擴展大小，使其能藉由支撐內腔壁而保持內腔開放。血管支架可收縮用以降低其直徑，使得該支架可經引導通過病患的動脈或靜脈，到達部署位置。支架典型地係與氣球的外部結合，藉由擴大的氣球來擴展，或在移除束縛物，例如維持支架扁塌狀態的金屬絲或封套之後，自行擴展。

【0325】 血管支架通常係由金屬所製，用以提供支持阻塞動脈壁所需之強度。二種較佳的金屬為鎳和鈦的鎳鈦合金(Nitinol alloy)以及不鏽鋼。可用於編造支架之其他材料有陶瓷、聚合物和塑膠。聚合物可為無官能基團的聚合物。另一種選擇，聚合物可為具有官能基團但不與 ENPP1 藥劑或 ENPP3 藥劑反應的聚合物。聚合物可包括生物可降解聚合物。例如，聚合物可包括由下列組成之群中選出的聚合物：聚羧酸、聚酸酐、聚磷腈(polyphosphazenes)、聚烯烴草酸酯、生物可降解聚醯胺、聚原酸酯、聚磷酸酯、聚原碳酸，以及其混合物和共聚物。聚合物亦可包括生物穩定的聚合物，單獨或與生物可降解聚合物組合。例如，聚合物可包括由下列組成之群中選出的聚合物：聚氨酯、聚矽氧、聚丙烯酸酯、聚酯、聚環氧烷、聚醇、聚烯烴、聚氯乙烯、纖維素及其衍生物、氟化聚合物、生物穩定性聚醯胺及其混合物和共聚物。

【0326】 不同支架設計對藥物分布模式的效應已於實驗研究中詳查並亦以臨床試驗檢測(Hwang CW, Wu D, Edelman ER. 2001. *Physiological transport forces govern drug distribution for stent-based delivery. Circulation, 104 : 600-5; & Takebayashi H, Mintz GS, Carlier SG, et al. 2004. Nonuniform strut distribution correlates with more neointimal hyperplasia after Sirolimus-eluting stent implantation. Circulation, 110 : 3430-4*)。雖然至今已開發出大量的支架設計，但目前最常使用的僅多單元設計(multicellular design)；其可分類為「封閉單元」和「開放單元」構型(Rogers CDK. 2002. *Drug-eluting stents : role of stent design, delivery vehicle, and drug selection. Rev Cardiovasc Med, 3(Suppl 5) : S10-15.*)。封閉單元支架具有均勻的單元擴增和固定單元間距，當部署在一彎曲的血管段時，給予更均勻的藥物分布(Rogers 2002)。開放單元支架在彎曲血管段之內部和外部血管分布間的表面覆蓋上具有較大的變化，但在犧牲較不均勻的藥物分布下，給予彎曲表面較佳的舒適性(Rogers 2002)。目前大多數的支架係使用封閉單元設計。用於藥物

遞送之優化的支架設計，在部署後應具有大的支架表面積，小的單元間隔及最小的支桿形變，同時保持舒適性，徑向支撐和到達複雜冠狀動脈病灶之彈性。數種不同的幾何支架結構之實例係描述於 Paisal et al. (*Muhammad Sufyan Amir Paisal et al 2017 IOP Conf. Ser. : Mater. Sci. Eng. 165 012003*)。

【0327】 ENPP1 塗覆支架或 ENPP3 塗覆支架係藉由分別塗覆包含一有效量的 ENPP1 藥劑或 ENPP3 藥劑之塗層組成物來製備。該塗層組成物較佳地係包括治療上有效抑制斑塊再生長或抑制再狹窄或防止血管肌細胞增生之足量的 ENPP1 藥劑或 ENPP3 藥劑。

【0328】 在一具體實例中，以塗層組成物的總重量為基準，塗層組成物係包括約 1 重量%至約 50 重量% ENPP1 多肽，在另外的具體實例中，塗層組成物係包括約 5 重量%至約 30 重量% ENPP1 多肽。又在另外的具體實例中，塗層組成物係包括約 10 重量%至約 20 重量% ENPP1 多肽。

【0329】 在一具體實例中，以塗層組成物的總重量為基準，塗層組成物係包括約 1 重量%至約 50 重量% ENPP3 多肽。在另外的具體實例中，塗層組成物係包括約 5 重量%至約 30 重量% ENPP3 多肽。又在另外的具體實例中，塗層組成物係包括約 10 重量%至約 20 重量% ENPP3 多肽。

【0330】 在一具體實例中，塗層組成物係包括約 1 μ g/ml 至約 10 mg/ml 的 ENPP1 多肽。在另外的具體實例中，塗層組成物係包括約 100 μ g/ml 至 5mg/ml ENPP1 多肽。又在另外的具體實例中，塗層組成物係包括約 500 μ g/ml 至約 2 mg/ml ENPP1 多肽。

【0331】 在一相關的具體實例中，該塗層組成物的 ENPP1 多肽為 ENPP1-Fc。

【0332】 在一相關的具體實例中，該塗層組成物的 ENPP1 多肽為 ENPP1-白蛋白。

【0333】 在一具體實例中，該塗層組成物係包括約 1 $\mu\text{g/ml}$ 至約 10 mg/ml 的 ENPP3 多肽。在另外的具體實例中，塗層組成物係包括約 100 $\mu\text{g/ml}$ 至 5 mg/ml ENPP3 多肽。又在另外的具體實例中，塗層組成物係包括約 500 $\mu\text{g/ml}$ 至約 2 mg/ml ENPP3 多肽。

【0334】 在一相關的具體實例中，該塗層組成物的 ENPP3 多肽為 ENPP3-Fc。

【0335】 在一相關的具體實例中，該塗層組成物的 ENPP3 多肽為 ENPP3-白蛋白。

【0336】 在一具體實例中，該塗層組成物係包括約 1 $\text{ng}/\mu\text{l}$ 至約 1000 $\mu\text{g}/\mu\text{l}$ 的 ENPP1 mRNA。在另外的具體實例中，塗層組成物係包括約 100 $\text{ng}/\mu\text{l}$ 至 10 $\mu\text{g}/\mu\text{l}$ ENPP1 mRNA。又在另外的具體實例中，塗層組成物係包括約 50 $\text{ng}/\mu\text{l}$ 至約 5 $\mu\text{g}/\mu\text{l}$ ENPP1 mRNA。

【0337】 在一具體實例中，該塗層組成物係包括約 1 $\text{ng}/\mu\text{l}$ 至約 1000 $\mu\text{g}/\mu\text{l}$ 的 ENPP1-Fc mRNA。在另外的具體實例中，塗層組成物係包括約 100 $\text{ng}/\mu\text{l}$ 至 10 $\mu\text{g}/\mu\text{l}$ ENPP1 -Fc mRNA。又在另外的具體實例中，塗層組成物係包括約 50 $\text{ng}/\mu\text{l}$ 至約 5 $\mu\text{g}/\mu\text{l}$ ENPP1-Fc mRNA。

【0338】 在一具體實例中，該塗層組成物係包括約 1 $\text{ng}/\mu\text{l}$ 至約 1000 $\mu\text{g}/\mu\text{l}$ 的 ENPP1-白蛋白 mRNA。在另外的具體實例中，塗層組成物係包括約 100 $\text{ng}/\mu\text{l}$ 至 10 $\mu\text{g}/\mu\text{l}$ ENPP1-白蛋白 mRNA。又在另外的具體實例中，塗層組成物係包括約 50 $\text{ng}/\mu\text{l}$ 至約 5 $\mu\text{g}/\mu\text{l}$ ENPP1-白蛋白 mRNA。

【0339】 在一具體實例中，該塗層組成物係包括約 1 $\text{ng}/\mu\text{l}$ 至約 1000 $\mu\text{g}/\mu\text{l}$ 的 ENPP3 mRNA。在另外的具體實例中，塗層組成物係包括約 100 $\text{ng}/\mu\text{l}$ 至 5 $\mu\text{g}/\mu\text{l}$ ENPP3 mRNA。又在另外的具體實例中，塗層組成物係包括約 500 $\text{ng}/\mu\text{l}$ 至約 2 $\mu\text{g}/\mu\text{l}$ ENPP3 mRNA。

【0340】 在一具體實例中，該塗層組成物係包括約 1 ng/ μ l 至約 1000 μ g/ μ l 的 ENPP3-Fc mRNA。在另外的具體實例中，塗層組成物係包括約 100 ng/ μ l 至 5 μ g/ μ l ENPP3-Fc mRNA。又在另外的具體實例中，塗層組成物係包括約 500 ng/ μ l 至約 2 μ g/ μ l ENPP3-Fc mRNA。

【0341】 在一具體實例中，該塗層組成物係包括約 1 ng/ μ l 至約 1000 μ g/ μ l 的 ENPP3-白蛋白 mRNA。在另外的具體實例中，塗層組成物係包括約 100 ng/ μ l 至 5 μ g/ μ l ENPP3-白蛋白 mRNA。又在另外的具體實例中，塗層組成物係包括約 500 ng/ μ l 至約 2 μ g/ μ l ENPP3-白蛋白 mRNA。

【0342】 支架可塗覆上一物質，例如生物可降解或生物穩定的聚合物，用以提升支架的生物相容性，使其在病患中較不易造成過敏或其他免疫學反應。亦可加入塗層物質強化支架。某些已知的塗層物質包括有機酸，其衍生物和合成的生物可降解或生物穩定之聚合物。生物穩定的塗層物質在體內不會降解，而生物可降解塗層在體內可降解。

【0343】 塗層組成物係包括一有效量的載劑，其係在塗覆過程中幫助確保治療分子，例如 ENPP1 藥劑或 ENPP3 藥劑黏附在支架表面以及亦在支架置放位置促進治療劑釋放至體內。載劑可為液體載劑或固體載劑。塗層組成物可選擇性地在固體載劑中包括一種以上的固體化合物。塗層組成物可進一步包括液體載劑和固體體載劑二者。又在另一方面，此塗層組成物亦可在載劑中包括一種以上的非聚合或聚合化合物且可進一步在固體或液體載劑中包括聚合物質和非聚合物質二者。

【0344】 在另外的具體實例中，二或更多種生物可降解化合物(聚合物或非聚合物)可共同混合，得到一用於塗層組成物的液體載劑。生物可降解化合物，在其共同混合，例如形成均質的溶液、混合物或懸浮液前可為液體。另一種選擇，某些的生物可降解化合物，在與其他液體的生物可降解化合物混合之前可

為固體。固體的生物可降解化合物較佳地於混合液態生物可降解化合物時溶解，產生含有不同生物可降解化合物的液體載劑組成物。

【0345】 在另外的具體實例中，塗層組成物之生物可降解載劑組份為固體，其係在與生物活性組份及任何包括在塗層組成物中的其他組份混合時溶解。

【0346】 載劑可為聚合物載劑。某些載劑為合成的聚合物。作為儲池基質之合成聚合物的實例包括(但不限於)聚甲基丙烯酸正丁酯、聚乙烯／醋酸乙烯酯、聚(乳酸交酯-共- Σ -聚己內酯)共聚物、纖維蛋白(Fibrin)、纖維素、磷酸膽鹼。某些析出型支架係包括含有承載治療分子奈米共振腔之多孔 300 μm 陶瓷層。藥物釋放支架、支架結構和支架設計之實例可參見 *Drug-Eluting Stent : A Review and Update, Vasc Health Risk Manag. 2005 Dec; 1(4) :263-276* and *Modern Stents :Where Are We Going?, Rambam Maimonides Med J. 2020 Apr; 11(2) : e0017*。

【0347】 塗層組成物中的載劑可為生物可降解或生物穩定的。生物可降解聚合物常用於合成的生物可降解縫合線。這些聚合物包括聚羧酸。適合用於本發明的聚羧酸包括聚-L-乳酸、聚-DL-乳酸、聚甘醇酸，包括乳酸的均聚物和共聚物(包括由乳酸的所有立體異構物，例如 D-,L-乳酸和內消旋乳酸所製成的乳酸交酯)、聚內酯、聚己內酯、聚乙交酯、聚對二噁吡酮、聚 1,4-二氧吡-2-酮、聚 1,5-二氧吡-2-酮、聚 6,6-二甲基-1,4-二噁吡-2-酮、聚羥基戊酸酯、聚羥基丁酸酯、聚三亞甲基碳酸酯聚合物以及前述之混合物。

【0348】 適合用於本發明的聚內酯包括聚己內酯，例如聚(e-聚己內酯)，聚戊內酯例如聚(d-戊內酯)和聚丁內酯例如聚(丁內酯)。可使用的其他生物可降解聚合物有聚酸酐、聚磷腈、生物可降解聚醯胺例如合成的多肽如聚離胺酸和聚天門冬胺酸、聚烯烴草酸酯、聚原酸酯、聚磷酸酯和聚原碳酸酯。任何所列的聚合物之共聚物和混合物皆可使用。除了有或無括弧存在以外，聚合物名稱相同係代表相同的聚合物。

【0349】 適合用於本發明之生物穩定的聚合物包括，但不限於聚氨酯，聚矽氧(silicone)，例如聚烷基矽氧烷如二甲基矽氧烷和聚甲基丙烯酸丁酯，聚酯類例如聚(對苯二甲酸乙二酯)，聚環氧烷例如聚環氧乙烷或聚乙二醇、聚醇類例如聚乙醇和聚乙二醇，聚烯烴例如聚乙烯，聚丙烯，聚(乙烯-丙烯)橡膠和天然橡膠，聚氯乙烯，纖維素和修飾的纖維素衍生物例如嫟縈(rayon)，嫟縈-三乙酸酯、纖維素乙酸酯、纖維素乙酸丁酸酯、賽璐玢(cellophane)，纖維素硝酸酯，纖維素丙酸酯，纖維素醚例如羧甲基纖維素和烴烷基纖維素，氟化聚合物例如聚四氟乙烯(鐵氟龍(Teflon))和生物穩定的聚醯胺例如尼龍 66(Nylon 66)和聚己內醯胺。亦可使用固定的動物組織例如戊二醛固定的牛心包膜。聚酯和聚醯胺亦可為生物可降解或生物穩定的。酯和醯胺鍵易於水解，可歸類為生物可降解。

【0350】 在某些情況下，塗層組成物進一步可包括一有效量的非聚合物載劑。該非聚合物載劑可包括一或多種的脂肪酸、生物相容的油或蠟。非聚合生物可降解載劑之實例包括液體油酸、維生素 E、花生油和棉籽油，其為疏水性和生物相容之液體。在某些情況下，非聚合物或聚合物載劑在室溫和體溫下為液體。在某些情況下，非聚合物或聚合物載劑在室溫和體溫下為固體，或在室溫下為固體而在體溫下為液體。

【0351】 在另外的具體實例中，聚合物溶液可形成薄膜及然後將薄膜施用於支架。可使用任何形成薄膜的各種習知方法。例如，聚合物、ENPP1 藥劑或 ENPP3 藥劑和溶劑較佳的係混合成溶液及然後倒到一平滑表面，待溶液乾燥移除溶劑後使薄膜形成。然後可切割薄膜以符合所欲使用之支架。然後可藉由包裹將薄膜固定在支架的外表面。

【0352】 在另外的具體實例中，係藉由以包括治療劑，例如 ENPP1 藥劑或 ENPP3 藥劑之液體載劑噴灑支架，使支架之支桿上的塗層厚度均勻，製備塗覆支架。在另外的具體實例中，支架可浸塗或沒入包括載劑和治療劑的塗層溶

液中，使得溶液完全塗覆在支架的支桿上。另一種選擇，支架可例如以漆刷，塗刷上包括載劑和治療劑的塗層溶液。在各個這些塗層施用中，雖然在某些具體實例中僅塗覆任一或雙面的一部分，較佳地係塗覆支架的整個內和外表面。

【0353】 如上所論述，塗層組成物係包括生物活性組份和生物可降解載劑組份。較佳地，塗層組成物係包括 0.1%至 100%重量比的生物活性組份和 1%至 99%重量比的生物可降解載劑組份。更佳地，塗層組成物係包括 0.1%至 50%重量比的生物活性組份和 50%至 99.9%重量比的生物可降解載劑組份。塗層組成物可以許多的方法來製備，包括藉由將生物活性組份與載劑組份簡單混合形成一混合物，例如溶液或懸浮液。另一種選擇，生物活性組份和載劑組份可於適合的溶劑中混合，將塗層施用於支架並移除溶劑。較佳地塗層組成物係施用於擴展狀態的支架上。

【0354】 除了支架外，其他可依照文中所揭示的本發明態樣塗覆的醫療裝置之實例包括導管、心瓣膜、節律器導線、瓣環成形術環和其他醫療植入物。在其他特定的具體實例中，塗覆的血管成形術氣球和其他的塗覆醫療裝置可包括其中一種文中所述的塗層組成物。然而，支架為較佳的。塗層組成物可藉由許多的方法塗覆於支架上(或其他醫療裝置)，例如藉由於支架上噴灑塗層組成物，藉由將支架浸入塗層組成物中，或藉由以塗層組成物塗刷支架。較佳地，係塗覆於擴展形式的支架上(亦即，擴大徑長)，使得足量的塗層組成物可塗覆於整個擴展支架的表面。當支架係浸入塗層組成物中時，可移除支架表面上過量的塗層組成物，例如以漆刷來刷掉過量的塗層組成物。在各個這些塗層的施用中，較佳地係塗覆於支架的內和外表面。

【0355】 文中所述的塗層組成物，較佳地在支架導入體內後，係部分或實質上部分留在支架上歷時至少數天、數週及更佳地數月，藉此將治療劑，例如 ENPP1 藥劑或 ENPP3 藥劑緩慢釋放至血流中。

醫藥組成物和調配物

【0356】 本揭露係提供文中所述的方法內之包括本揭露多肽的醫藥組成物。此一醫藥組成物為適合投予一對象之形式，或該醫藥組成物可進一步包括一或多種醫藥上可接受載劑，一或多種另外的成份，或彼等之某些組合。各種醫藥組成物的組份可以生理上可接受鹽的形式存在，如本項技術中所熟知的，例如與生理上可接受陽離子或陰離子組合。

【0357】 在一具體實例中，可用於施行本揭露方法的醫藥組成物可經投予遞送介於 1 ng/kg/天至 100 mg/kg/天的劑量。在其他的具體實例中，可用於施行本揭露的醫藥組成物可經投予遞送介於 1 ng/kg/天至 500 mg/kg/天的劑量。

【0358】 本揭露之醫藥組成物中活性成份、醫藥上可接受載劑和任何另外成份的相對量將依照所治療對象的特質、體型和症狀而變，且進一步係依照組成物投予的路徑而定。舉例而言，組成物可包括介於約 0.1%至約 100% (w/w)活性成份。

【0359】 可用於本揭露方法中的醫藥組成物可經適當開發用於吸入、口服、直腸、陰道、非經腸、局部、經皮、肺部、鼻內、頰內、眼部、鞘內、靜脈內或另外的給藥路徑。其他考量的調配物包括計畫的奈米粒子、脂質體製備物、含有活性成份的釋放紅細胞以及免疫學為基礎的調配物。給藥路徑已為習知技術者所知且係依照任何許多的因子而定，包括所治療的疾病類型和嚴重度，所治療之動物或人類病患的類型和年齡及諸如此類。

【0360】 文中所述的醫藥組成物之調配物可藉由任何已知的方法或此後藥學技術所開發的方法來製備。一般而言，此等製備方法係包括將活性成份與載劑或一或多種其他必須成份結合的步驟，及若需要或所欲的，塑形或將產物包裝成所欲的單一或多劑量單位。

【0361】 如文中所用，「單位劑量」為包括一預計量活性成份之醫藥組成物的個別量。活性成份的量一般係等於投予一對象之活性成份的劑量或此一劑量的方便分量，例如，舉例而言，此劑量的一半或三分之一。單位劑型可為單一每日劑量或多個每日劑量的其中之一(例如，每天約 1 至 4 次或更多次)。當使用多個每日劑量時，該各給劑之單位劑型可相同或不同。

【0362】 給藥方案可能影響有效量之組成。例如，數個分開的劑量，以及可能每日或先後投予變動的劑量，或可連續輸注該劑量或可為大劑量注射。再者，當治療或預防情況顯示緊急需要時，則治療調配物的劑量可依比例增加或減少。在特定的具體實例中，投予本揭露化合物於一對象提升了該對象的血漿 PPI 至接近正常的程度，其中該哺乳動物中正常的 PPI 量為 1-3 μM 。「接近正常」係指 0 至 1.2 μM 或低於或高於正常量 0-40%，30 nM 至 0.9 μM 或低於或高於正常量 1-30%，0 至 0.6 μM 或低於或高於正常量 0-20%，或 0 至 0.3 μM 或低於或高於正常量 0-10%。

【0363】 將本揭露之組成物投予一病患，例如哺乳動物，例如人類，可使用已知的程序，以有效治療該病患之疾病或病症的劑量和時間來進行。達到治療效用所需的治療化合物之有效量可根據，例如所用的特定化合物之活性；給藥時間；化合物的排泄率；治療的持續時間；與該化合物組合使用的其他藥物、化合物或物質；疾病或病症的狀態，所治療病患之年齡、性別、狀況、整體健康和先前醫療史以及如醫療技術中熟知之因素而變。劑量療法可經調整，用以提供最適化治療反應。劑量係以治療化合物的生物活性為基礎來決定，其轉而係依照半衰期和血漿治療化合物之時間曲線下的面積而定。根據本揭露之多肽係以每 2 天，每 4 天或每周或每月之適合的時間間隔給藥，以便達到持續的血漿 PPI 量係接近正常(1-3 μM)量或高於(高於 30-50%)正常 PPI 量。本揭露多肽的治療劑量亦可以半衰期或該治療多肽的體內清除率為基準來決定。根據本揭露之

多肽係以每 2 天或每 4 天、每周或每月的適當時間間隔給藥，以便達到恆定量的 ENPP1 或 ENPP3 多肽之酵素活性。

【0364】 例如，每日可投予數個分劑量，或當治療情況顯示緊急需要時，該劑量可依比例降低。本揭露之治療化合物的有效劑量範圍的非限定實例係從約 0.01 至 50 mg/kg 體重/每天。在特定的具體實例中，本揭露之治療化合物的有效劑量範圍係從約 50 ng 至 500 ng/kg，較佳地 100 ng 至 300 ng/kg 體重。無需過度實驗，熟習技術者應能研究相關的因素並決定有關治療劑之有效劑量。

【0365】 化合物可以每天數次頻繁地投予一病患，或其可較不頻繁地給藥，例如一天一次，一週一次，每二週一次，一個月一次或甚至更低頻率，例如數個月一次或甚至一年一次或更低。請了解，在非限定實例中，依天給劑的化合物之量可以每天、每 2 天、每 3 天、每 4 天、每 5 天來投予。例如，就每隔一天給藥，可在星期一以 5 mg 的每日劑量開始，於星期三投予第一次隨後的 5 mg 每日劑量，於星期五投予第二次隨後的 5 mg 每日劑量等等。給藥頻率對於熟習技術者為顯而易見且係依照許多的因子而定，例如，但不限於，所治療疾病之類型和嚴重度，和病患的類型和年齡。本揭露醫藥組成物中活性成份的實際劑量可能不同，以便於在對病患無毒性之下得到該活性成份的量係有效達到對一特定病患、組成物和給藥模式之所欲的治療反應。

【0366】 醫師，例如具有本項技術之一般技術的醫生可容易決定和開立所需的醫藥組成物之有效量。例如，醫師或獸醫師可從低於達到所欲治療效用所需之醫藥組成物中所用的本揭露化合物之劑量開始，並逐漸增加劑量直到達成所欲的效用。

【0367】 在特定的具體實例中，本揭露之組成物係以範圍從每天 1 至 5 次或更多次的劑量投予病患。在其他的具體實例中，本揭露之組成物係以包括，但不限於每天一次，每二天，每三天至每週一次及每二週一次之劑量範圍投予

病患。各種組合的本揭露之組成物的給藥頻率，依照許多的因素，包括，但不限於年齡、所治療的疾病或病症、性別、整體健康和其他因子，係隨對象而不同。因此，本揭露不應理解為限制任何特定的劑量療法且投予任何病患的精確劑量和組成物將由主治醫師考量所有有關病患的其他因子來決定。

【0368】 在特定的具體實例中，本揭露係關於經包裝的醫藥組成物，其係包括盛裝單獨或與第二醫藥劑組合之治療上有效量之本揭露化合物的容器；及使用該化合物治療、防止或降低一或多個病患之疾病或病症徵候的說明書。

給藥路徑

【0369】 任何的本揭露組成物之給藥路徑係包括吸入、口服、鼻內、直腸、非經腸、舌下、經皮、經黏膜(例如，舌下、舌、(經)頰內、(經)尿道、陰道(例如經陰道和陰道周圍)、鼻(內)和直腸(內))、膀胱內、肺內、十二指腸內、胃內、鞘內、皮下、肌肉內、經皮、動脈內、靜脈內、支氣管內、吸入和局部給藥。

【0370】 適合的組成物和劑型包括，例如，錠劑、膠囊、囊片、丸劑、凝膠膠囊、口含片、分散液、懸浮液、溶液、糖漿、粒劑、微珠、經皮貼片、凝膠、散劑、丸團、乳漿劑、菱錠劑、乳霜劑、糊劑、藥膠片、乳液、紙錠、栓劑、鼻用液體噴霧或口服給藥、吸入用的乾粉或霧化調配物、膀胱內給藥的組成物和調配物及諸如此類。可用於本揭露的調配物和組成物不限於文中所述的特定調配物和組成物。

【0371】 醫藥組成物的「非經腸給藥」係包括任何特徵為肉體上破壞一對象的組織並經由該組織中的破口投予醫藥組成物之給藥路徑。非經腸給藥因此係包括，但不限於，藉由注射組成物來投予醫藥組成物，經由手術切口施予組成物，經由組織穿透非手術傷口施予組成物及諸如此類。特言之，非經腸給藥

預期係包括，但不限於，皮下、靜脈內、腹膜內、肌肉內、胸骨內注射和腎臟透析輸注技術。

實例

【0372】 本揭露進一步係以下列實例作為例示。該等實例僅作為說明之目的且不希望亦不應將其理解為以任何方式限制本揭露。

小鼠

【0373】 將蹣跚行走(*ttw/ttw*)小鼠和 WT 小鼠用於下列實驗。*ttw/ttw* 小鼠於 C57BL/6J 背景繁衍超過十世代，並經由異型合子交配生成 *ttw/ttw* 小鼠和野生型(WT)同窩對照(雄性和雌性)小鼠。

血漿收集

【0374】 以含有乙二胺四乙酸三鈉(EDTA)的注射器從 *ttw/ttw* 小鼠和 WT 小鼠(藉由心臟穿刺)收集全血並保持在冰上直到藉由離心(1000×g, 4°C, 20 min)進行血漿和紅血球分離。然後將血漿經由 300,000-kDa 質量截留過濾器過濾(2200×g, 4°C, 20 min)清空血小板並儲存於-20°C 直到進一步處理。

實例 1-ENPP1-Fc 投予 WT 和 *ttw/ttw* 小鼠的治療效用

【0375】 已知血管損傷誘發發炎反應和內皮活化，造成平滑肌細胞增生和血管內腔窄化(Exp Mol Med. 2018 Oct 29;50(10): 1-12)。於 WT 小鼠和 *ttw/ttw* 小鼠中進行頸動脈結紮製造一機械損傷的模型及然後用於研究 ENPP1-Fc 在受傷位置對平滑肌細胞增生之效用。因此，本實驗的主要目標為測定 ENPP1-Fc 對 WT 小鼠和同型合子 *ttw/ttw* 小鼠中肌內膜過度增生之治療效用。

【0376】 藉由異型合子交配生成 *ttw/ttw* 和野生型(WT)同窩對照(雄性和雌性)小鼠。讓仔鼠在 3-4 週大時斷奶及然後維持一般飼料飲食。在斷奶期間盲目計數仔鼠，無關基因型。依循 Okawa 等人所描述的方法，藉由尾部 DNA 之聚合

酶連鎖反應分析進行 ENPP1 基因型分型(Okawa A, Nakamura I, Goto S, Moriya H, Nakamura Y, Ikegawa S. Mutation in Npps in a mouse model of ossification of the posterior longitudinal ligament of the spine. Nature genetics. 1998;19(3) : 271-3)。

【0377】 左頸動脈結紮手術可在幼鼠，例如 6-8 週大的小鼠中進行。左頸動脈結紮手術係在 7 週大的 WT (n = 5)和 *ttw/ttw* 小鼠(n = 5)中進行。將小鼠藉由異氟烷(isoflurane)吸入以 1 l/min 氧氣至 3 體積%異氟烷之起始濃度，維持 0.6 l/min 氧氣至 1-1.5 體積%異氟烷的濃度麻醉(Forene® , Abbott GmbH & Co. KG, Wiesbaden)。使用卡洛芬(Carprofen)鎮痛(5 mg/kg 體重，經由皮下注射;Rimadyl® , Pfizer, Berlin, Germany)。經由一頸部的中央小切口暴露出左頸動脈並在大約距離頸動脈分叉處 2 mm 以 5-0 尼龍絲縫合線結紮。所有的動物從手術恢復良好並無顯現中風跡象。

【0378】 頸動脈結紮後 7 天，將 ENPP1-Fc 或媒劑投予一模型動物，例如 *ttw/ttw* 小鼠。在頸動脈結紮後 7 天，*ttw/ttw* 小鼠的內膜過度增生出現在血管中，但相較於結紮後 14 天的 *ttw/ttw* 小鼠，I/M 比率在第 7 天時為較低的(內膜面積和 I/M 比率 $p < 0.001$ ，分別為圖 6B 和 6C)。因此，結紮後 14 天，在對照小鼠中動脈阻塞(動脈內膜阻斷)為明顯的。

【0379】 為了測定若在頸動脈結紮後給藥，ENPP1-Fc 是否具有治療效用，係將 7 週大的 WT 和 *ttw/ttw* 小鼠進行頸動脈結紮並讓其復原。然後將小鼠以每隔一天由皮下注射 10 mg/kg 體重的媒劑(Tris 緩衝食鹽水 pH 7.4/對照組)或 ENPP1-Fc (實驗組)加以治療。在頸動脈結紮後 7 天開始 ENPP1-Fc 治療(10 mg/kg 體重每隔一天由皮下注射)並持續 7 天直到於結紮後 14 天收取頸動脈。將頸動脈以 4%多聚甲醛之 PBS 溶液固定供形態學分析。

【0380】 收集連續的切片(各 5 μm 的切片)。就結紮的頸動脈之形態學分析，係採集緊鄰結紮位置的切片。藉由使用每五個切距取一個切片，從接近結

紮位置大約 250 μm 的跨距，每隻動物總計分析 12 個切片(每 25 μm)。藉由使用彈性 van Gieson 染色(Roth, Karlsruhe, Germany)進行形態學分析(切片示意圖請參見圖 2)。使用 ImageJ 軟體測量外彈性層、內彈性層和腔緣的圓周。計算中膜面積、內膜面積和內膜/中膜比率(I/M 比率)。所有小鼠右邊未結紮的頸動脈不具有可測量的血管內膜，其顯示頸動脈結紮模擬血管分布之機械損傷，造成 VSMC 增生。

【0381】 使用學生試驗進行統計分析(工具為非成對二樣本檢定)。多組之比較係使用單因子變異數分析(one-way ANOVA)，接著 Bonferroni 事後檢定，以第 7 版 GraphPad Prism 軟體來進行。p < 0.05 的概率值係視為顯著的。

【0382】 在 *ttw/ttw* 小鼠中於頸動脈結紮損傷後，ENPP1 缺乏造成血管內膜病灶形成，且因此當相較於 WT 小鼠時，*ttw/ttw* 小鼠具有較高量的 VSMC 增生。在 *ttw/ttw*-小鼠和 WT 小鼠中距離結紮處 100 或 200 μm 尾端的代表性染色切片顯示，頸動脈結紮造成內膜過度增生，使得內腔窄化，其中越接近結紮處(100 μm)窄化越嚴重而較遠離的(200 μm)阻塞較不嚴重(參見 3 和 5D)。

【0383】 在 *ttw/ttw* 小鼠中內膜過度增生的程度增加，因為在距離結紮處 200 μm 尾端的內腔幾乎完全阻塞。結紮的總頸動脈之連續切片的定量分析顯示，相較於 WT 小鼠，*ttw/ttw* 小鼠在結紮誘發的血管重塑 14 天之後，具有明顯增加的血管內膜增生(參見圖 5A-C)，但中膜面積並未增厚。相應地，相較於 WT 小鼠，*ttw/ttw* 小鼠的 I/M 比率明顯增加。預期 *ttw/ttw* 小鼠在投予 ENPP1-Fc 後，因為小鼠本身缺乏 ENPP1 蛋白，VSMC 增生應會下降。相當令人驚訝地，在 ENPP1-Fc 投予後，WT 小鼠中的 VSMC 增生亦下降，儘管事實為 WT 小鼠並無 ENPP1 蛋白缺乏。此實驗因此係顯示將 ENPP1 蛋白量提升至高於正常生理量在因機械傷害所造成的血管分布中係具有降低 VSMC 增生的治療效用之確切證據。

【0384】 此等結果驗證了在 ENPP1 缺乏(*ttw/ttw*)和無 ENPP1-缺乏(WT)小鼠的血管損傷小鼠模型中，皮下投予重組的 ENPP1-Fc 融合蛋白治療了內膜過度增生。此項令人驚訝的發現係顯示，ENPP1 在因手術組織損傷、心肌梗塞、中風、和甚至非手術組織損傷而遭受 VSMC 增生的病患中具有治療內膜過度增生之治療潛力。

實例 2-ENPP1-Fc 投予 WT 和 *ttw/ttw* 小鼠之預防效用

【0385】 本實驗的主要目標為測定 ENPP1-Fc 對 WT 小鼠和同型合子 *ttw/ttw* 小鼠中內膜過度增生的預防效用。使用 ENPP1-Fc 之預防性治療的流程係如圖 1 所示。

【0386】 在此預防性方法中，在頸動脈結紮前將二種小鼠(WT & *ttw/ttw* 小鼠)治療 7 天，且在手術後或頸動脈結紮後持續治療 14 天。依照實例 I 中所概述的方法於 7 週大的 WT 和 *ttw/ttw* 小鼠中進行左頸動脈結紮手術。然後依照實驗 I 的相同方法於頸動脈結紮後 14 天使用 CO₂ 吸入讓小鼠安樂死。

【0387】 為了測定 ENPP1 對內膜過度增生之預防性效用，係在頸動脈結紮前將二種小鼠(WT & *ttw/ttw* 小鼠)以媒劑(對照組)或 ENPP1-Fc(實驗組)治療 7 天，並於手術後持續治療 14 天。

【0388】 手術後 14 天，相較於以媒劑治療的小鼠，以 ENPP1-Fc 治療的 WT-和 *ttw/ttw*-小鼠二者顯示中膜面積(圖 4A，分別為 $p<0.05$ 和 $p<0.01$)，內膜面積(圖 4B，二者 $p<0.001$)和 I/M 比率(圖 4C，分別為 $p<0.01$ 和 $p<0.001$)大大降低。以 ENPP1-Fc 治療的 *ttw/ttw*-小鼠之內膜和中膜面積以及 I/M 比率與以 ENPP1-Fc 治療的 WT-小鼠($p>0.05$)程度近似，然而相較於以媒劑治療的 WT-小鼠，以媒劑治療的 *ttw/ttw*-小鼠發生顯著增加的內膜面積和 I/M 比率(分別為 $p<0.01$ 和 $p<0.05$)。

【0389】 就進一步的 WT-和 *ttw/ttw*-小鼠之頸動脈細胞凋亡研究，係讓以媒劑單獨治療的一亞組保持結紮 21 天並使用原位細胞死亡偵測套組，依照製造商的說明進行 TUNEL 染色(TMR red, Roche Diagnostics GmbH, Penzberg, Germany)。就負對照，係進行無 TUNEL 酵素染色；就正對照，係於室溫藉由 I 級 DNA 酶 I(DNase I grade I)降解樣本 DNA 歷時 10 分鐘。

【0390】 相較於以媒劑治療的 WT 小鼠，以 ENPP1-Fc 治療的 WT 小鼠顯示內膜過度增生大大降低。同樣的，相較於以媒劑治療的 *ttw/ttw* 小鼠，以 ENPP1-Fc 治療的 *ttw/ttw* 小鼠內膜過度增生大大降低。結紮 14 天小鼠的組織學彈性 van Gieson 染色顯示內膜過度增生在 ENPP1-Fc 治療的 WT-和 *ttw/ttw*-小鼠中比以媒劑治療的小鼠少很多，以 ENPP1-Fc 治療的 *ttw/ttw*-小鼠接近經 ENPP1-Fc 治療的 WT 小鼠所見到的程度(參見圖 4 G)。

【0391】 相較於以媒劑治療的小鼠，結紮 21 天並以 ENPP1-Fc 預防性治療 28 天的 WT-和 *ttw/ttw*-小鼠亦顯示中膜面積(圖 4 D，二者 $p < 0.01$)，內膜面積(圖 4 E，分別為 $p < 0.001$ 和 $p < 0.01$)和 I/M 比率(圖 4 F，分別為 $p < 0.001$ 和 $p < 0.05$)大大降低。ENPP1-Fc 治療的 WT-和 *ttw/ttw*-小鼠的血管內膜過度增生量接近相同，然而相較於結紮 14 天並治療 21 天的 WT-和 *ttw/ttw*-小鼠，內膜增生並未停止而是進一步惡化(I/M 比率：分別為 $p < 0.01$ 和 $p < 0.05$)。

【0392】 有利地，結紮 21 天媒劑治療的之 *ttw/ttw*-小鼠的頸動脈比媒劑治療的 WT-小鼠具有較小的內膜面積(圖 4 E)。結紮 21 天媒劑治療的 *ttw/ttw*-小鼠的頸動脈組織學染色在內膜面積顯露伴隨彈性纖維降解而來的組織退化(圖 7A)，導致較小的內膜面積。相較於 WT-小鼠，在結紮 21 天的 *ttw/ttw*-小鼠之內膜面積中，TUNEL 染色顯示陽性染色增加(圖 7B)，其係顯示在以媒劑治療的 *ttw/ttw*-小鼠之結紮動脈中細胞凋亡增加。

【0393】 媒劑治療的 WT 小鼠中所得到的血管內膜和中模面積以及結紮總頸動脈之 I/M 比率的定量分析結果顯示與無治療的 WT 小鼠相類似。同樣的，在媒劑治療的 *ttw/ttw* 小鼠中得到的血管內膜和中模面積以及結紮總頸動脈之 I/M 比率顯示與無治療的 *ttw/ttw* 小鼠相類似。

【0394】 相較於媒劑治療的 WT 小鼠，接受皮下 ENPP1-Fc 之 WT 小鼠的內膜面積顯著降低，而介於外層和內層之間的中膜面積仍不變。相較於媒劑治療的 WT 小鼠，在 ENPP1-Fc 治療的 WT 小鼠中 I/M 比例顯示統計上顯著的降低(參見圖 4)，其顯示在頸動脈結紮前的 ENPP1-Fc 預防性治療藉由降低 VSMC 增生量而具有預防性效用。

【0395】 再者，相較於治療性治療，預防性治療頸動脈結紮的 *ttw/ttw*-小鼠導致內膜面積和 I/M 比率下降更多(參見圖 8B 和 C，二者 $p < 0.001$)。因此可結論出，在 ENPP1 缺乏的情況下，在頸動脈損傷發生前開始以 ENPP1-Fc 治療為更有效，亦即越早越好。換言之，頸動脈結紮的 WT-小鼠在預防性和治療性治療組中在內膜和 I/M 比例並無顯現差異(圖 8B 和 C)。此項顯示，在野生型小鼠中於頸動脈損傷之前和之後開始以 ENPP1-Fc 治療對於停止內膜增生同樣有效。

實例 3-ENPP3-Fc 投予 WT 和 *ttw/ttw* 小鼠之治療效用

【0396】 本實驗的主要目標為測定在 WT 小鼠和同型結合 *ttw/ttw* 小鼠中 ENPP3-Fc 對內膜過度增生之治療效用。使用他處所述之先前建立的方法製備 ENPP3-Fc。依照實例 1 中所述的方法，於 6 週大 WT 和 *ttw/ttw* 小鼠中進行左頸動脈結紮手術。

【0397】 就測定在頸動脈結紮後投予 ENPP3-Fc 是否可能具有治療效用，係於 6 週大的 WT 和 *ttw/ttw* 小鼠中進行頸動脈結紮並讓其復原。然後將二種小

鼠以每隔一天由皮下注射 10 mg/kg 體重的媒劑(Tris 緩衝食鹽水 pH 7.4/對照組)或 ENPP3-Fc(實驗組)治療。ENPP3-Fc 治療(每隔一天由皮下注射 10 mg/kg 體重)係於頸動脈結紮後 7 天開始並持續 7 天直到在結紮後 14 天收取頸動脈。將頸動脈以 4%多聚甲醛之 PBS 溶液固定供形態學分析。

【0398】 收集連續的切片(各 5 μ m 的切片)並依照實例 1 中所述的方法分析。如實例 I 所述進行統計分析。如實例 I 中所見，在 *ttw/ttw* 小鼠中於頸動脈結紮損傷後，ENPP1 缺乏造成血管內膜病灶形成且因此在與 WT 小鼠比較時，*ttw/ttw* 小鼠具有較高量的 VSMC 增生。

【0399】 在 *ttw/ttw* 小鼠中內膜過度增生的程度增加，因為在距離結紮處 200 μ m 尾端的內腔幾乎阻塞。結紮的總頸動脈之連續切片的定量分析顯示，相較於 WT 小鼠，*ttw/ttw* 小鼠在結紮誘發的血管重塑 14 天之後，具有明顯增加的血管內膜增生。

【0400】 預期在投予 ENPP3-Fc 後 *ttw/ttw* 小鼠中的 VSMC 增生將下降，因為這些突變小鼠缺乏 ENPP1 蛋白。預期在 ENPP3-Fc 投予後，WT 小鼠中的 VSMC 增生將下降。此等結果將證明 ENPP3-Fc 蛋白藉由降低因機械性損傷所造成的血管分布之 VSMC 增生而具有治療效用。

【0401】 預期此等結果驗證了在 ENPP1 缺乏(*ttw/ttw*)和無 ENPP1-缺乏(WT)小鼠的血管損傷小鼠模型中，皮下投予重組的 ENPP3-Fc 融合蛋白可治療內膜過度增生。因此，ENPP3-Fc 可在因手術組織損傷、心肌梗塞、中風、和甚至非手術組織損傷而遭受 VSMC 增生的病患中作為治療劑。

實例 4—ENPP3-Fc 投予 WT 和 *ttw/ttw* 小鼠之預防性效用

【0402】 本實驗的主要目標為測定 ENPP3-Fc 對 WT 小鼠和同型合子 *ttw/ttw* 小鼠之內膜過度增生的預防效用。使用 ENPP3-Fc 之預防性治療的流程係如圖 1 所示。

【0403】 在此預防性方法中，係在頸動脈結紮前將二種小鼠(WT & *ttw/ttw* 小鼠)治療 7 天，且在手術後或頸動脈結紮後持續治療 14 天。依照實例 I 中所概述的方法於 6 週大的 WT 和 *ttw/ttw* 小鼠中進行左頸動脈結紮手術。然後依照如實驗 I 的相同方法於頸動脈結紮後 14 天使用 CO₂ 吸入讓小鼠安樂死。

【0404】 為了測定 ENPP3 對內膜過度增生之預防性效用，係在頸動脈結紮前將二種小鼠(WT & *ttw/ttw* 小鼠)以媒劑(對照組)或 ENPP3-Fc(實驗組)治療 7 天，並於手術後持續治療 14 天。相較於以媒劑治療的 WT 小鼠，以 ENPP3-Fc 治療的 WT 小鼠預期顯示內膜過度增生大大降低。同樣的，相較於以媒劑治療的 *ttw/ttw* 小鼠，以 ENPP3-Fc 治療的 *ttw/ttw* 小鼠預期顯示內膜過度增生大大降低。

【0405】 媒劑治療的 WT 小鼠中所得到的結紮總頸動脈之血管內膜和中模面積以及 I/M 比率的定量分析結果預期與無治療的 WT 小鼠相類似。同樣的，在媒劑治療的 *ttw/ttw* 小鼠中得到的結紮總頸動脈之血管內膜和中模面積以及 I/M 比率顯示與無治療的 *ttw/ttw* 小鼠相類似。

【0406】 相較於媒劑治療的 WT 小鼠，接受皮下 ENPP3-Fc 之 WT 小鼠的內膜面積預期顯著降低，而介於外層和內層之間的中膜面積預期仍不變。相較於媒劑治療的 WT 小鼠，在 ENPP3-Fc 治療的 WT 小鼠中 I/M 比例預期顯示統計上顯著的降低，其表示在頸動脈結紮前的 ENPP3-Fc 預防性治療藉由降低 VSMC 增生量而具有預防性效用。因此，除了頸動脈結紮 *ttw/ttw* 小鼠之外，預期 ENPP3-Fc 給藥在頸動脈結紮 WT 小鼠中防止和有效地治療肌內膜增生和狹窄。

此實驗預期驗證了即使在 WT 小鼠中於頸動脈結紮之前和之後投予 ENPP3 防止內膜過度增生。

實例 5-用於治療動脈粥樣硬化血管之 ENPP1 釋放塗覆支架

【0407】 動脈粥樣硬化為最常見的動脈血管發炎疾病，其可能導致威脅生命的心肌梗塞或缺血性中風。本實驗的主要目標為測定 ENPP1 或 ENPP1-Fc 析出型支架抑制血管內膜形成和發炎的能力，藉此降低會增加心臟手術後出血性併發症風險之血栓及/或血管阻塞。

【0408】 無受限於任一理論，預期在支架移植後，引發支架移植位置的 ENPP1 或 ENPP1-Fc 過度表現應能造成下列一或多項：(i)降低血小板活化，(ii)降低再狹窄和發炎反應，及(iii)降低 VSMC 增生。此治療係基於將 ENPP1 mRNA (或 ENPP1-Fc mRNA 或 ENPP1-白蛋白 mRNA)遞送至內膜細胞，然後其在支架移植位置於 mRNA 轉譯後轉而表現 ENPP1 蛋白。

製造 ENPP1 mRNA

【0409】 將含有 ENPP1 DNA 模板的 pcDNA 3.3 質體(Eurofins Genomics GmbH, Ebersberg, Germany)使用 HotStar HiFidelity 聚合酶套組(Qiagen, Hilden, Germany)根據製造商的說明書增幅。將 PCR 產物(PCR 循環儀：Eppendorf, Wesseling, Germany)以 Qiaquick PCR 純化套組(Qiagen)純化。以 MEGAscript1 T7 套組(Ambion, Glasgow, Scotland)根據製造商的說明書產生活體外轉錄的 mRNA。

【0410】 就修飾 mRNA，係將 3'-0-Mem7 G(5')ppp(5')G RNA Cap 結構類似物(New England Biolabs, Frankfurt, Germany)以及分別取代 UTP 和 CTP 的假尿嘧啶核苷-5'-三磷酸鹽和 5-甲基胞嘧啶核苷-5'-三磷酸鹽(TriLink Biotech, San

Diego, CA, USA)加到反應中。就 RNA 酶抑制，係將 1 μ l 的 RNA 酶抑制劑(Thermo Scientific, Waltham)加到每個反應中。然後以 RNeasy 套組(Qiagen)純化活體外轉錄的 mRNA。將純化的 mRNA 使用 Antarctic Phosphatase 套組(New England Biolabs)去磷酸化並再次以 RNeasy 套組(Qiagen)純化。使用 eGFP DNA 重複相同的程序產生強化的綠色螢光蛋白(eGFP) mRNA(Avci-Adali M, Behring A, Keller T, Krajewski S, Schlensak C, Wendel HP (2014), *Optimized conditions for successful transfection of human endothelial cells with in vitro synthesized and modified mRNA for induction of protein expression. J Biol Eng* 8 : 8)。

【0411】 藉由轉染的 HEK293 細胞在 ATP 水解後由測量游離的磷酸鹽驗證所產生的 ENPP1 mRNA 功能。將 ENPP1 mRNA 轉染的 HEK293 細胞以 20 μ M ATP (möLab, Langenfeld, Germany)或 PBS 作為對照於 37°C 在震盪平台上 (Polymax 1040, Heidolph, Schwabach, Germany)培養 10 min。在 ENPP1 存在下，ATP 基質隨時間降解，伴隨酵索性產物 AMP 堆積。使用不同濃度的 ATP 基質，在 ATP 存在下衍生 ENPP1 之起初比率速度，並將此數據擬合一曲線用以衍生酵素速率常數。

支架塗層

【0412】 為了開發能在活體內局部遞送 ENPP1mRNA 和轉染內皮細胞之具生物活性的支架塗層，首先將產生的 ENPP1 mRNA 塗覆在 thermanox 塑膠片上。由此使用 thermanox 塑膠片模擬支架塗層(Nunc, Thermo scientific, USA)。首先，於一 12-孔盤上，每孔植入 100.000 個 HEK293 細胞。

【0413】 24 小時後，將 2 μ l Lipofectamin 以及 10 μ g ENPP1 mRNA 與 50 μ l Opti-MEM 混合並於室溫培養 20 min。同時將 10 μ l 來自聚乳酸-甘醇酸共聚物

(PLGA)(Evoniks, Darmstadt)儲存液(20 mg/ml))以 990 μ l 乙酸乙酯稀釋(最終濃度 200 μ g/ml)，然後將 200 μ l 的 PLGA 溶液與轉染複合物混合。

【0414】 將 thermanox 膠片於室溫以逐步法塗覆上該溶液。使用 eGFP mRNA 和無菌水作為對照。供應新的培養基給 HEK293 細胞之後將乾燥的膠片面朝下覆蓋在細胞上。將細胞與膠片於 37°C 和 5% CO₂ 培養 24 hrs、48 hrs 和 72 hrs 及然後使用 FACScan 細胞儀分析。

【0415】 使用流式細胞儀計算 HEK293 細胞的 ENPP1 表現。以抗-ENPP1-螢光異氰酸鹽(FITC)抗體將塗覆 ENPP1 的 thermonox 膠片暴露細胞和對照細胞染色。以 ENPP1mRNA/PLGA 覆蓋的 thermanox 膠片培養後，HEK293 細胞之流式細胞儀分析預期顯現 ENPP1 mRNA 從 PLGA 塗層釋出，由此預期在暴露於膠片 24 小時、48 小時和 72 小時後，可偵測到增加的 ENPP1 表現。

【0416】 相較於對照的 HEK293 細胞(其係暴露於單獨塗覆上 Lipofectamine 的 thermonox 膠片)，預期 0.5-1 μ g 的 ENPP1 mRNA 係足以在暴露於塗覆 ENPP1 mRNA 之 thermonox 膠片的 HEK 細胞中，即使在 24 小時的暴露後，引發 ENPP1 蛋白表現增加。

【0417】 不受限於任一理論，如從實例 1 和 2 的結果可看出的，文中建議在支架移植位置表現的 ENPP1 預期防止了內膜增生並降低血小板阻塞，藉此降低心臟手術後的血栓併發症風險。

實例 6-製備和移植 ENPP1 析出型塗覆支架用於治療動脈粥樣硬化血管

【0418】 製備 ENPP1 藥劑塗覆支架及然後植入冠狀動脈。在本實例中，使用仔豬動物模型進行 ENPP1-塗覆支架移植，用以測定 ENPP1 塗覆支架抑制血管內膜形成、再狹窄和發炎的功效。

製備 ENPP1 塗覆支架

【0419】 任何支架皆能塗覆 ENPP1 藥劑。最常見的市售支架來源之實例包括亞培(Abbot)、波士頓科技(Boston Scientific)、美敦力(Medtronic)、Alvimedica、樂普醫療科技(Lepu Medical Technology)、Cordis、Balton 或百多力(Biotronik)。

【0420】 例如，普通的支架，例如單純的金屬支架可藉由在支架內部置入一包括 ENPP1 mRNA 的聚合物薄膜，或藉由在支架表面上噴灑上包括 ENPP1 mRNA 或 ENPP1 多肽之聚合性或非聚合性溶液，轉變成 ENPP1 塗覆的析出型支架。

【0421】 一些 ENPP1 聚合物膜之實例係如下所示，ENPP1 聚合物薄膜可置入支架內部製造出 ENPP1 塗覆的析出型支架。視需要，非聚合物載劑，例如維生素 E、維生素 E 乙酸鹽、維生素 E 琥珀酸鹽、油酸、花生油和棉籽油可加入溶液中，提升 ENPP1 藥劑在聚合物薄膜中的安定性。

(a) ENPP1 藥劑塗層組成物(A)-將 10 mg PCL(聚己內酯)聚合物和 100 µg ENPP1 mRNA(或 ENPP1-Fc mRNA 或 ENPP1-白蛋白 mRNA)於室溫溶於無菌再蒸餾水。將溶液倒在一玻璃板上並讓溶劑蒸發 12-24 小時。幾乎完全移除溶劑後，從玻璃板將承載 ENPP1 的 PCL 薄膜移出並切成 1.5 cm x 1.5 cm 大小。然後將包括 ENPP1 mRNA(或 ENPP1-Fc mRNA 或 ENPP1-白蛋白 mRNA)的聚合物薄膜嵌入不鏽鋼支架。可重複相同的方法，藉由使用 50 µg 的載體 DNA，製備塗覆上表現 ENPP1 多肽(ENPP1 或 ENPP1-Fc 或 ENPP1-白蛋白)之載體的支架。

(b) ENPP1 藥劑塗層組成物(B)-將 10 mg EVA(乙烯-乙酸乙烯酯)聚合物和 100 µg ENPP1 mRNA(或 ENPP1-Fc mRNA 或 ENPP1-白蛋白 mRNA)於室溫溶於無菌再蒸餾水。將溶液倒在一玻璃板上並讓溶劑蒸發 12-24 小時。幾乎完全移除溶劑後，從玻璃板將承載 ENPP1-mRNA(或 ENPP1-Fc mRNA 或 ENPP1-白蛋

白 mRNA)的 EVA 薄膜移出並切成 1.5 cm x 1.5 cm 大小。然後將包括 ENPP1 mRNA(或 ENPP1-Fc mRNA 或 ENPP1-白蛋白 mRNA)的聚合物薄膜嵌入不鏽鋼支架。可重複相同的方法，藉由使用 50 μ g 的載體 DNA，製備塗覆上表現 ENPP1 多肽(ENPP1 或 ENPP1-Fc 或 ENPP1-白蛋白)之載體的支架。

【0422】 一些包括 ENPP1 之噴霧溶液的實例係如下所示。噴霧溶液可施用於支架上製造出 ENPP1 塗覆的析出型支架。視需要，非聚合物載劑，例如維生素 E、維生素 E 乙酸鹽、維生素 E 琥珀酸鹽、油酸、花生油和棉籽油可加入噴霧溶液中，提升 ENPP1 藥劑的安定性。

(c) ENPP1 藥劑塗層組成物(C)-將 10 mg PCL(聚己內酯)聚合物和 100 μ g ENPP1 mRNA 於室溫溶於無菌再蒸餾水。將 100 μ l 包括 ENPP1 mRNA (或 ENPP1-Fc mRNA 或 ENPP1-白蛋白 mRNA)的聚合 PCL 溶液使用半自動霧化器裝置噴灑在支架上(6 mmx20 mm)。霧化器噴灑系統係提供以一控制的速率旋轉和穿越支架長度之工具。該裝置的穿越組份係含有一玻璃霧化器系統，以每分鐘 3 ml 的速率，將霧化的聚己內酯溶液施用於支架。一旦塗覆上，藉由供應 60°C 熱風大約 5 秒，聚合物塗層「回流」。回流聚合物的過程提供對支架表面較佳的黏附。可重複相同的方法，藉由使用 50 μ g 的載體 DNA，製備塗覆表現 ENPP1 多肽(ENPP1 或 ENPP1-Fc 或 ENPP1-白蛋白)之載體的支架。

(d) ENPP1 藥劑塗層組成物(D)-將 1%的未固化二部份矽橡膠溶液溶於三氯乙烯及然後如上(C)中所述，使用霧化器噴灑系統噴灑在支架上。將塗覆支架於室溫乾燥 15 分鐘，讓三氯乙烯蒸發。將包括聚矽氧的塗層支架於真空烘箱中加熱四小時以便於交聯聚矽氧塗層。將塗覆支架從烘箱中移出並使其冷卻 1 小時。將 100 μ g ENPP1 mRNA 於室溫溶於無菌再蒸餾水。將體積 100 μ l 之包括 ENPP1 的噴霧溶液以逐滴的方式施用於各支架的聚矽氧塗層上。讓交聯的聚矽氧吸附溶液，其中溶劑隨後於室溫下蒸發，留下陷在聚矽氧內的

ENPP1 mRNA(或 ENPP1-Fc mRNA 或 ENPP1-白蛋白 mRNA)。可重複相同的方法，藉由使用 50 μ g 的載體 DNA，製備塗覆上表現 ENPP1 多肽(ENPP1 或 ENPP1-Fc 或 ENPP1-白蛋白)之載體的支架。隨後於室溫下蒸發溶劑，留下陷在聚矽氧內的 ENPP1 編碼載體。

- (e) ENPP1 藥劑塗層組成物(E)-將 10 mg PCL(聚己內酯)聚合物和 ENPP1 多肽(任一 ENPP1 或 ENPP1-Fc 或 ENPP1-白蛋白)於室溫溶於無菌再蒸餾水，達到 10 mg/ml 之 ENPP1 多肽濃度。將 100 μ l 的包含 ENPP1 多肽的聚合物 PCL 溶液(10 mg/ml)如(C)中所述噴灑在支架上。
- (f) ENPP1 藥劑塗層組成物(F)-如(d)中所論述製備包括聚矽氧之塗覆支架。將塗覆支架從烘箱中移出並使其冷卻 1 小時。將 ENPP1 多肽(ENPP1 或 ENPP1-Fc 或 ENPP1-白蛋白)於室溫溶於無菌再蒸餾水，達到 10 mg/ml 之 ENPP1 多肽濃度。將體積 100 μ l 之包括 ENPP1 的噴霧溶液(10 mg/ml)以逐滴方式施用於各支架的聚矽氧塗層。讓交聯的聚矽氧吸附溶液，隨後於室溫蒸發溶劑，留下陷在聚矽氧內的 ENPP1 mRNA。

動物模型

【0423】 從市售來源購買 30 隻重量 25-35 kg 之 4-至-5-個月大的仔豬。從市售來源，例如亞培(Abbot)、波士頓科技(Boston Scientific)、美敦力(Medtronic)、Alvimedica、樂普醫療科技(Lepu Medical Technology)、Cordis、Balton 或百多力(Biotronik)，購得 30 支不鏽鋼支架。將購得的 30 支支架依循上述用於塗覆之方法，塗上 ENPP1 mRNA。使用 30 支購自亞培(Abbott)公司的單純金屬支架(BMS)作為對照組。然後使用環氧乙烷將 ENPP1 塗覆支架殺菌，壓縮並裝置在氣球血管成形術導管上。然後使用標準的氣球血管成型技術部署於一動脈中的位置。

【0424】 將支架隨機分配並置入 30 隻豬的左前降支動脈、迴旋支動脈或右冠狀動脈(每條動脈一支支架)，每隻豬一支塗覆支架。然後每天保持給予豬隻 75 mg 氯吡格雷(clopidogrel)和 100 mg 阿斯匹靈(aspirin)並分別於 7 天和 14 天後犧牲動物。

【0425】 支架移植後 7 或 14 天，使用靜脈注射戊巴比妥(pentobarbital)安死液(100 mg/kg)讓動物安樂死，並收取裝入支架的冠狀動脈。從距離支架的近端、中段和遠端將動脈切成 3 至 5 mm 片段，固定在 4%甲醛歷經 48 h，並嵌入石蠟中。依照實例 1 中所述的方法，將切片進行組織學和形態學測量，測定內膜、中膜面積和 I/M 比率。相較於來自具有非析出型不鏽鋼單純網狀支架之豬隻的動脈切片，得自接受 ENPP1 塗覆支架的豬隻之動脈切片的內膜面積預期顯著下降。相較於具有非析出型不鏽鋼支架之豬隻，在具有 ENPP1 塗覆支架的豬隻的動脈切片中 I/M 比率預期顯現統計上顯著的下降。因此，藉由使用 ENPP1 塗層支架原位投予 ENPP1 藥劑預期防止並有效治療損傷位置中的血管內膜增生及/或再狹窄。

實例 7-製備及植入 ENPP3 析出型塗覆支架用於治療動脈粥樣血管硬化

【0426】 製備 ENPP3 藥劑塗層支架及然後植入冠狀動。在本實例中，係使用仔豬動物模型進行 ENPP3 塗層支架移植，用以測定 ENPP3 塗層支架抑制血管內膜形成、再狹窄和發炎的功效。

製備 ENPP3 塗覆支架

【0427】 任何支架皆能塗覆上 ENPP3 藥劑。最常見的市售支架來源之實例包括亞培(Abbot)、波士頓科技(Boston Scientific)、美敦力(Medtronic)、

Alvimedica、樂普醫療科技(Lepu Medical Technology)、Cordis、Balton 或百多力(Biotronik)。

【0428】 例如，普通的支架，例如單純的金屬支架可藉由在支架內部置入一包括 ENPP3 mRNA 的聚合物薄膜，或藉由在支架表面上噴灑上包括 ENPP3 mRNA 或 ENPP3 多肽之聚合性或非聚合性溶液，轉變成 ENPP3 塗覆支架。

【0429】 一些 ENPP3 聚合物薄膜之實例係如下所示，ENPP3 聚合物薄膜可置入支架內部製造出 ENPP3 塗覆的析出型支架。視需要，非聚合性載劑，例如維生素 E、維生素 E 乙酸鹽、維生素 E 琥珀酸鹽、油酸、花生油和棉籽油可加入溶液中，提升 ENPP3 藥劑在聚合物薄膜中的安定性。

(a) ENPP3 藥劑塗層組成物(A)-將 10 mg PCL (聚己內酯)聚合物和 100 µg ENPP3 mRNA(或 ENPP3-Fc mRNA 或 ENPP3-白蛋白 mRNA)於室溫溶於無菌再蒸餾水。將溶液倒在一玻璃板上並讓溶劑蒸發 12-24 小時。幾乎完全移除溶劑後，從玻璃板將承載 ENPP3 的 PCL 薄膜移出並切成 1.5 cm x 1.5 cm 大小。然後將包括 ENPP3 mRNA(或 ENPP3-Fc mRNA 或 ENPP3-白蛋白 mRNA)的聚合物薄膜嵌入不鏽鋼支架。可重複相同的方法，藉由使用 50 µg 的載體 DNA，製備塗覆表現 ENPP3 多肽(ENPP3 或 ENPP3-Fc 或 ENPP3-白蛋白)之載體的支架。

(b) ENPP3 藥劑塗層組成物(B)-將 10 mg EVA (乙烯-乙酸乙烯酯)聚合物和 100 µg ENPP3 mRNA(或 ENPP3-Fc mRNA 或 ENPP3-白蛋白 mRNA)於室溫溶於無菌再蒸餾水。將溶液倒在一玻璃板上並讓溶劑蒸發 12-24 小時。幾乎完全移除溶劑後，從玻璃板將承載 ENPP3-mRNA(或 ENPP3-Fc mRNA 或 ENPP3-白蛋白 mRNA)的 EVA 薄膜移出並切成 1.5 cm x 1.5 cm 大小。然後將包括 ENPP3 mRNA(或 ENPP3-Fc mRNA 或 ENPP3-白蛋白 mRNA)的聚合物薄膜嵌入不鏽

鋼支架。可重複相同的方法，藉由使用 50 μg 的載體 DNA，製備塗覆表現 ENPP3 多肽(ENPP3 或 ENPP3-Fc 或 ENPP3-白蛋白)之載體的支架。

【0430】 一些包括 ENPP3 之噴霧溶液的實例係如下所示，該噴霧溶液可施用於支架上製造出 ENPP3 塗覆的析出型支架。視需要，非聚合物載劑，例如維生素 E、維生素 E 乙酸鹽、維生素 E 琥珀酸鹽、油酸、花生油和棉籽油可加入噴霧溶液中，提升 ENPP3 藥劑的安定性。

(c) ENPP3 藥劑塗層組成物(C)-將 10 mg PCL(聚己內酯)聚合物和 100 μg ENPP3 mRNA(或 ENPP3-Fc mRNA 或 ENPP3-白蛋白 mRNA)於室溫溶於無菌再蒸餾水。如上實例 5 中所述，將 100 μl 包括 ENPP3 mRNA(或 ENPP3-Fc mRNA 或 ENPP3-白蛋白 mRNA)的聚合物 PCL 溶液使用半自動霧化器裝置噴灑在支架上(6 mmx20 mm)。可重複相同的方法，藉由使用 50 μg 的載體 DNA，製備塗覆表現 ENPP3 多肽(ENPP3 或 ENPP3-Fc 或 ENPP3-白蛋白)之載體的支架。

(d) ENPP3 藥劑塗層組成物(D)-將 1%的未固化二部份矽橡膠溶液溶於三氯乙烯及然後如上實例 5 中所述，使用霧化器噴灑系統噴灑在支架上。將塗覆支架從烘箱中移出並使其冷卻 1 小時。將 100 μg ENPP3 mRNA(或 ENPP3-Fc mRNA 或 ENPP3-白蛋白 mRNA)於室溫溶於無菌再蒸餾水。將體積 100 μl 之包括 ENPP3 mRNA(或 ENPP3-Fc mRNA 或 ENPP3-白蛋白 mRNA)的噴霧溶液以逐滴的方式施用於各支架的聚矽氧塗層上。讓交聯的聚矽氧吸附溶液，其中隨後於室溫下蒸發溶劑，留下陷在聚矽氧內的 ENPP3 mRNA(或 ENPP3-Fc mRNA 或 ENPP3-白蛋白 mRNA)。可重複相同的方法，藉由使用 50 μg 的載體 DNA，製備塗覆表現 ENPP3 多肽(ENPP3 或 ENPP3-Fc 或 ENPP3-白蛋白)之載體的支架。隨後於室溫下蒸發溶劑，留下陷在聚矽氧內的 ENPP3 編碼載體。

- (e) ENPP3 藥劑塗層組成物(E)-10 mg PCL (聚己內酯)聚合物和 ENPP3 多肽(任一 ENPP3 或 ENPP3-Fc 或 ENPP3-白蛋白)於室溫溶於無菌再蒸餾水，達到 10 mg/ml 之 ENPP3 多肽濃度。如上實例 5 中所述將 100 μ l 包含 ENPP3 多肽的聚合物 PCL 溶液(10 mg/ml)噴灑在支架上。
- (f) ENPP3 藥劑塗層組成物(F)-如實例 5 中所述製備包括聚矽氧之塗覆支架。將塗覆支架從烘箱中移出並使其冷卻 1 小時。將 ENPP3 多肽(ENPP3 或 ENPP3-Fc 或 ENPP3-白蛋白)於室溫溶於無菌再蒸餾水，達到 10 mg/ml 之 ENPP3 多肽濃度。將體積 100 μ l 之包括 ENPP3 的噴霧溶液(10 mg/ml)以逐滴方式施用於各支架的聚矽氧塗層。讓交聯的聚矽氧吸附溶液，其中隨後於室溫蒸發溶劑，留下陷在聚矽氧內的 ENPP1 mRNA。

動物模型

【0431】 如實例 5 中所述，從市售來源購買 30 隻重量 25–35 kg 之 4-至-5-個月大的仔豬。從市售來源購得 30 支不鏽鋼支架。將購得的 30 支支架依循上述用於塗覆之方法塗覆上 ENPP3 mRNA。使用 30 支購自亞培(Abbott)公司的單純金屬支架(BMS)作為對照組。然後使用環氧乙烷將 ENPP3 塗層支架殺菌，壓縮並裝置在氣球血管成形術導管上。然後使用標準的氣球血管成型技術部署於一動脈中的位置。

【0432】 將支架隨機分配並置入 30 隻豬的左前降支動脈、迴旋支動脈或右冠狀動脈(每條動脈一支支架)，每隻豬一支塗層支架。然後每天保持給予豬隻 75 mg 氯吡格雷和 100 mg 阿斯匹靈並分別於 7 天和 14 天後犧牲動物。支架移植後 7 或 14 天，使用靜脈注射戊巴比妥安死液(100 mg/kg)讓動物安樂死，並收取裝入支架的冠狀動脈。從支架的近端、中段和遠端將動脈切成 3 至 5 mm 片段，固定在 4%甲醛歷經 48 h，並嵌入石蠟中。

【0433】 依照實例 1 中所述的方法，將切片進行組織學和形態學測量，測定內膜、中膜面積和 I/M 比率。相較於來自具有非析出型不鏽鋼單純網狀支架之豬隻的動脈切片，得自接受 ENPP3 塗覆支架的豬隻之動脈切片的內膜面積預期顯著下降。相較於具有非析出型不鏽鋼支架之豬隻，在具有 ENPP3 塗覆支架之豬隻的動脈切片中 I/M 比率預期顯現統計上顯著的下降。因此，藉由使用 ENPP3 塗層支架原位投予 ENPP3 藥劑預期防止並有效治療損傷位置中的血管內膜增生及/或再狹窄。

以引用的方式併入

【0434】 文中所引述的各個和每個美國專利和外國專利之揭示文及申請中的專利申請案和公開案係特別地以全文引用的方式併入本文中，序列表和圖式之內容亦如是。

同等物

【0435】 熟習本項技術者應了解或僅僅使用例行的實驗能探悉許多文中所述之特定具體實例的同等物。此等同等物希望涵蓋在下列的申請專利範圍中。在許多附屬項或實例中所揭示的任何具體實例之組合擬議係在本揭露的範圍內。

其他具體實例

【0436】 由前述說明書，顯見地可對文中所述的揭示文做變化和修改以便使其適應各種用途和狀況，包括在具有不同啟動子或增強子之不同的病毒載體或本項技術中已知的不同細胞類型中，使用不同的訊號序列表現 ENPP1 或 ENPP3 的功能變體或其組合用以治療特徵為存有病理性鈣化或骨化的任何疾病，係在根據本揭露之範圍內。根據本揭露之其他具體實例係在下列申請專利範圍內。

【0437】 在文中一變數之任何定義中所敘述的元件列表係包括該變數作為任何單一元件或所列元件之組合(或次組合)的定義。文中具體實例之敘述包括作為任何單一具體實例或與任何其他具體實例或其部分組合之具體實例。

【0438】 說明書中所提及的所有的出版物和專利申請案係說明熟習本揭露相關技術者的技術程度。所有的出版物和專利申請案係以全文引用的方式併入本文中，其程度係如同各個別的出版物或專利申請案係特意和個別地以引用地方式併入。

【0439】 其他具體實例係在下列申請專利範圍內。

【符號說明】

10 動脈

12 內皮

14 平滑肌細胞層

16 小裂口

18 團塊

20 動脈腔

21 未塗覆支架

22 塗覆支架

24 塗層

60 處置

65 ENPP1藥劑

110144-序列表

序列表

<110> 美商伊諾臻醫藥公司(Inozyme Pharma, Inc.)
明斯特大學(Westfaelische Wilhelms-Universitaet Muenster)
魯奇, 法蘭克(Rutsch, Frank)
湯普森, 大衛(Thompson, David)
尼奇克, 伊凡(Nitschke, Yvonne)
泰克爾陶布, 羅伯特(Terkeltaub, Robert)

<120> 用於抑制血管平滑肌細胞增生之組成物與方法

<130> 4427-10102

<140> 尚未分配

<141> 2021-05-26

<150> US 63/030,870

<151> 2020-05-27

<160> 72

<170> PatentIn version 3.5

<210> 1

<211> 925

<212> PRT

<213> 人工序列

<220>

<223> ENPP1胺基酸序列 - 野生型

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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

110144-序列表
90

85

95

Leu	Lys	Pro	Ser	Cys	Ala	Lys	Glu	Val	Lys	Ser	Cys	Lys	Gly	Arg	Cys	
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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	
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	290					295					300					

110144-序列表

Pro 305	Ile	Trp	Val	Thr	Ala 310	Lys	Tyr	Gln	Gly	Leu 315	Lys	Ser	Gly	Thr	Phe 320
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Tyr	Lys	Met	Tyr 340	Asn	Gly	Ser	Val	Pro 345	Phe	Glu	Glu	Arg	Ile 350	Leu	Ala
Val	Leu	Gln 355	Trp	Leu	Gln	Leu	Pro 360	Lys	Asp	Glu	Arg	Pro 365	His	Phe	Tyr
Thr 370	Leu	Tyr	Leu	Glu	Glu	Pro 375	Asp	Ser	Ser	Gly	His 380	Ser	Tyr	Gly	Pro
Val 385	Ser	Ser	Glu	Val	Ile 390	Lys	Ala	Leu	Gln	Arg 395	Val	Asp	Gly	Met	Val 400
Gly	Met	Leu	Met	Asp 405	Gly	Leu	Lys	Glu	Leu 410	Asn	Leu	His	Arg	Cys 415	Leu
Asn	Leu	Ile	Leu	Ile	Ser	Asp	His	Gly 425	Met	Glu	Gln	Gly	Ser 430	Cys	Lys
Lys	Tyr	Ile 435	Tyr	Leu	Asn	Lys	Tyr 440	Leu	Gly	Asp	Val	Lys 445	Asn	Ile	Lys
Val 450	Ile	Tyr	Gly	Pro	Ala	Ala 455	Arg	Leu	Arg	Pro	Ser 460	Asp	Val	Pro	Asp
Lys 465	Tyr	Tyr	Ser	Phe	Asn 470	Tyr	Glu	Gly	Ile	Ala 475	Arg	Asn	Leu	Ser	Cys 480
Arg	Glu	Pro	Asn	Gln 485	His	Phe	Lys	Pro	Tyr 490	Leu	Lys	His	Phe	Leu 495	Pro
Lys	Arg	Leu	His 500	Phe	Ala	Lys	Ser	Asp 505	Arg	Ile	Glu	Pro	Leu 510	Thr	Phe
Tyr	Leu	Asp 515	Pro	Gln	Trp	Gln	Leu 520	Ala	Leu	Asn	Pro	Ser 525	Glu	Arg	Lys

110144-序列表

Tyr	Cys	Gly	Ser	Gly	Phe	His	Gly	Ser	Asp	Asn	Val	Phe	Ser	Asn	Met
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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		

110144-序列表

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

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<223> 天青殺素(天青殺素(Azurocidin))-ENPP1-FC

110144-序列表

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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

110144-序列表

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	

110144-序列表

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	

110144-序列表

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			

110144-序列表

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

110144-序列表

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
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Lys Ser Leu Ser Leu Ser Pro Gly Lys
1070 1075

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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

110144-序列表

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		

110144-序列表

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					

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Asn 545	Leu	Gly	Cys	Ser	Cys 550	Asn	Pro	Ser	Ile	Leu 555	Pro	Ile	Glu	Asp	Phe 560
Gln	Thr	Gln	Phe	Asn 565	Leu	Thr	Val	Ala	Glu 570	Glu	Lys	Ile	Ile	Lys 575	His
Glu	Thr	Leu	Pro 580	Tyr	Gly	Arg	Pro	Arg 585	Val	Leu	Gln	Lys	Glu 590	Asn	Thr
Ile	Cys	Leu 595	Leu	Ser	Gln	His	Gln 600	Phe	Met	Ser	Gly	Tyr 605	Ser	Gln	Asp
Ile 610	Leu	Met	Pro	Leu	Trp	Thr 615	Ser	Tyr	Thr	Val	Asp 620	Arg	Asn	Asp	Ser
Phe 625	Ser	Thr	Glu	Asp	Phe 630	Ser	Asn	Cys	Leu	Tyr 635	Gln	Asp	Phe	Arg	Ile 640
Pro	Leu	Ser	Pro	Val 645	His	Lys	Cys	Ser	Phe 650	Tyr	Lys	Asn	Asn	Thr 655	Lys
Val	Ser	Tyr	Gly 660	Phe	Leu	Ser	Pro	Pro 665	Gln	Leu	Asn	Lys	Asn 670	Ser	Ser
Gly	Ile	Tyr 675	Ser	Glu	Ala	Leu	Leu 680	Thr	Thr	Asn	Ile	Val 685	Pro	Met	Tyr
Gln 690	Ser	Phe	Gln	Val	Ile	Trp 695	Arg	Tyr	Phe	His	Asp 700	Thr	Leu	Leu	Arg
Lys 705	Tyr	Ala	Glu	Glu	Arg 710	Asn	Gly	Val	Asn	Val 715	Val	Ser	Gly	Pro	Val 720
Phe	Asp	Phe	Asp	Tyr 725	Asp	Gly	Arg	Cys	Asp 730	Ser	Leu	Glu	Asn	Leu 735	Arg
Gln	Lys	Arg	Arg 740	Val	Ile	Arg	Asn	Gln 745	Glu	Ile	Leu	Ile	Pro 750	Thr	His
Phe	Phe	Ile 755	Val	Leu	Thr	Ser	Cys 760	Lys	Asp	Thr	Ser	Gln 765	Thr	Pro	Leu

110144-序列表

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	

110144-序列表

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				

110144-序列表

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			

110144-序列表

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

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<211> 1594
<212> PRT
<213> 人工序列

<220>
<223> 天青殺素(Azurocidin)-ENPP1

<220>
<221> 訊號
<222> (19)..(20)
<223> 訊號序列的裂解點

<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

110144-序列表

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

110144-序列表
290 295 300

Gly 305	Pro	Val	Ser	Ser	Glu 310	Val	Ile	Lys	Ala	Leu 315	Gln	Arg	Val	Asp	Gly 320
Met	Val	Gly	Met	Leu 325	Met	Asp	Gly	Leu	Lys 330	Glu	Leu	Asn	Leu	His 335	Arg
Cys	Leu	Asn	Leu 340	Ile	Leu	Ile	Ser	Asp 345	His	Gly	Met	Glu	Gln	Gly	Ser
Cys	Lys	Lys 355	Tyr	Ile	Tyr	Leu	Asn 360	Lys	Tyr	Leu	Gly	Asp 365	Val	Lys	Asn
Ile	Lys 370	Val	Ile	Tyr	Gly	Pro 375	Ala	Ala	Arg	Leu	Arg 380	Pro	Ser	Asp	Val
Pro 385	Asp	Lys	Tyr	Tyr	Ser	Phe	Asn	Tyr	Glu	Gly 395	Ile	Ala	Arg	Asn	Leu 400
Ser	Cys	Arg	Glu	Pro 405	Asn	Gln	His	Phe	Lys 410	Pro	Tyr	Leu	Lys	His 415	Phe
Leu	Pro	Lys	Arg 420	Leu	His	Phe	Ala	Lys 425	Ser	Asp	Arg	Ile	Glu	Pro	Leu
Thr	Phe	Tyr 435	Leu	Asp	Pro	Gln	Trp 440	Gln	Leu	Ala	Leu	Asn 445	Pro	Ser	Glu
Arg	Lys 450	Tyr	Cys	Gly	Ser	Gly 455	Phe	His	Gly	Ser	Asp 460	Asn	Val	Phe	Ser
Asn 465	Met	Gln	Ala	Leu	Phe 470	Val	Gly	Tyr	Gly	Pro 475	Gly	Phe	Lys	His	Gly 480
Ile	Glu	Ala	Asp	Thr 485	Phe	Glu	Asn	Ile	Glu 490	Val	Tyr	Asn	Leu	Met 495	Cys
Asp	Leu	Leu	Asn 500	Leu	Thr	Pro	Ala	Pro 505	Asn	Asn	Gly	Thr	His 510	Gly	Ser

110144-序列表

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	

110144-序列表

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	

110144-序列表

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

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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			

110144-序列表

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> 人工序列

<220>
<223> ENPP2胺基酸序列 - 野生型

<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

110144-序列表

Val 145	Asp	Asp	Asp	Cys	Glu 150	Glu	Ile	Lys	Ala	Ala 155	Glu	Cys	Pro	Ala	Gly 160
Phe	Val	Arg	Pro	Pro 165	Leu	Ile	Ile	Phe	Ser 170	Val	Asp	Gly	Phe	Arg 175	Ala
Ser	Tyr	Met	Lys 180	Lys	Gly	Ser	Lys	Val 185	Met	Pro	Asn	Ile	Glu 190	Lys	Leu
Arg	Ser	Cys 195	Gly	Thr	His	Ser	Pro 200	Tyr	Met	Arg	Pro	Val 205	Tyr	Pro	Thr
Lys	Thr 210	Phe	Pro	Asn	Leu	Tyr 215	Thr	Leu	Ala	Thr	Gly 220	Leu	Tyr	Pro	Glu
Ser 225	His	Gly	Ile	Val	Gly 230	Asn	Ser	Met	Tyr	Asp 235	Pro	Val	Phe	Asp	Ala 240
Thr	Phe	His	Leu	Arg 245	Gly	Arg	Glu	Lys	Phe 250	Asn	His	Arg	Trp 255	Trp	Gly
Gly	Gln	Pro	Leu 260	Trp	Ile	Thr	Ala	Thr 265	Lys	Gln	Gly	Val	Lys 270	Ala	Gly
Thr	Phe	Phe 275	Trp	Ser	Val	Val	Ile 280	Pro	His	Glu	Arg	Arg 285	Ile	Leu	Thr
Ile 290	Leu	Gln	Trp	Leu	Thr	Leu 295	Pro	Asp	His	Glu	Arg 300	Pro	Ser	Val	Tyr
Ala 305	Phe	Tyr	Ser	Glu	Gln 310	Pro	Asp	Phe	Ser	Gly 315	His	Lys	Tyr	Gly	Pro 320
Phe	Gly	Pro	Glu	Met 325	Thr	Asn	Pro	Leu	Arg 330	Glu	Ile	Asp	Lys	Ile 335	Val
Gly	Gln	Leu	Met 340	Asp	Gly	Leu	Lys	Gln 345	Leu	Lys	Leu	His	Arg 350	Cys	Val
Asn	Val	Ile 355	Phe	Val	Gly	Asp	His 360	Gly	Met	Glu	Asp	Val 365	Thr	Cys	Asp

110144-序列表

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		

110144-序列表

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

110144-序列表

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> 人工序列

<220>
<223> ENPP3的胞外區

<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

110144-序列表

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	

110144-序列表

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			

110144-序列表

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		

110144-序列表

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

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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 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

110144-序列表

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	

110144-序列表

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					

110144-序列表

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

110144-序列表

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

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Met Thr Arg Leu Thr Val Leu Ala Leu Leu Ala Gly Leu Leu Ala Ser
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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

110144-序列表

210 215 220

Pro 225	Met	Asn	Leu	Thr	Ala 230	Met	Tyr	Gln	Gly	Leu 235	Lys	Ala	Ala	Thr	Tyr 240
Phe	Trp	Pro	Gly	Ser 245	Glu	Val	Ala	Ile	Asn 250	Gly	Ser	Phe	Pro	Ser 255	Ile
Tyr	Met	Pro	Tyr 260	Asn	Gly	Ser	Val	Pro 265	Phe	Glu	Glu	Arg	Ile 270	Ser	Thr
Leu	Leu	Lys 275	Trp	Leu	Asp	Leu	Pro 280	Lys	Ala	Glu	Arg	Pro 285	Arg	Phe	Tyr
Thr 290	Met	Tyr	Phe	Glu	Glu	Pro 295	Asp	Ser	Ser	Gly	His 300	Ala	Gly	Gly	Pro
Val 305	Ser	Ala	Arg	Val	Ile 310	Lys	Ala	Leu	Gln	Val 315	Val	Asp	His	Ala	Phe 320
Gly	Met	Leu	Met	Glu 325	Gly	Leu	Lys	Gln	Arg 330	Asn	Leu	His	Asn 335	Cys	Val
Asn	Ile	Ile	Leu 340	Leu	Ala	Asp	His	Gly 345	Met	Asp	Gln	Thr	Tyr 350	Cys	Asn
Lys	Met	Glu 355	Tyr	Met	Thr	Asp	Tyr 360	Phe	Pro	Arg	Ile	Asn 365	Phe	Phe	Tyr
Met 370	Tyr	Glu	Gly	Pro	Ala	Pro 375	Arg	Ile	Arg	Ala	His 380	Asn	Ile	Pro	His
Asp 385	Phe	Phe	Ser	Phe	Asn 390	Ser	Glu	Glu	Ile	Val 395	Arg	Asn	Leu	Ser	Cys 400
Arg	Lys	Pro	Asp	Gln 405	His	Phe	Lys	Pro	Tyr 410	Leu	Thr	Pro	Asp	Leu 415	Pro
Lys	Arg	Leu	His 420	Tyr	Ala	Lys	Asn	Val 425	Arg	Ile	Asp	Lys	Val 430	His	Leu

110144-序列表

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		

110144-序列表

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		

110144-序列表

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

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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

110144-序列表

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			

110144-序列表

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

110144-序列表

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

110144-序列表

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

110144-序列表

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			

110144-序列表

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

110144-序列表

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> 人工序列

<220>
<223> 天青殺素(Azurocidin)-ENPP3

<220>
<221> 訊號
<222> (19)..(20)
<223> 訊號序列的裂解點

<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

110144-序列表

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			

110144-序列表

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	

110144-序列表

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

110144-序列表
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> 人工序列

<220>
<223> ENPP4胺基酸序列 - 野生型

<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

110144-序列表

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	

110144-序列表

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> 人工序列

<220>
<223> ENPP51胺基酸序列

<220>
<221> 訊號
<222> (24)..(25)
<223> 訊號序列的裂解點

<220>
<221> 訊號
<222> (24)..(25)
<223> 訊號肽序列的裂解點

<400> 12

110144-序列表

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					

110144-序列表

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	

110144-序列表

435 440 445

Asn	Pro	Ser	Glu	Arg	Lys	Tyr	Cys	Gly	Ser	Gly	Phe	His	Gly	Ser	Asp
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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	

110144-序列表

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
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<223> 表示白蛋白序列

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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

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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		

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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		

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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

110144-序列表																	
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					

110144-序列表

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			

110144-序列表

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			

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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
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Cys Lys Asp Ala Leu Ala Arg Ser Trp Ser His Pro Gln Phe Glu
1460 1465 1470

Lys

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<223> 訊號肽序列的裂解點

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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

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			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					

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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			

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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	

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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	

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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		
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Ser	Leu	Ser	Pro	Gly	Lys											
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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						

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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

110144-序列表

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

110144-序列表

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

110144-序列表

Trp	Ala	Val	Ala	Arg	Leu	Ser	Gln	Thr	Phe	Pro	Asn	Ala	Asp	Phe
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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			

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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
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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
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Glu Thr Cys Ile Glu Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg
65 70 75 80

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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					

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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	

110144-序列表

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

110144-序列表

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	

110144-序列表

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> 人工序列

<220>
<223> ENPP71-Fc氨基酸序列

<220>
<221> 訊號
<222> (22)..(23)
<223> 訊號肽序列的裂解點

<220>
<221> MISC_FEATURE
<222> (856)..(1082)
<223> 表示 Fc 序列

<400> 18

Met Arg Gly Pro Ala Val Leu Leu Thr Val Ala Leu Ala Thr Leu Leu

110144-序列表																	
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						

110144-序列表

Pro 225	Glu	Trp	Tyr	Lys	Gly 230	Glu	Pro	Ile	Trp	Val 235	Thr	Ala	Lys	Tyr	Gln 240
Gly	Leu	Lys	Ser	Gly 245	Thr	Phe	Phe	Trp	Pro 250	Gly	Ser	Asp	Val	Glu	Ile 255
Asn	Gly	Ile	Phe	Pro 260	Asp	Ile	Tyr	Lys 265	Met	Tyr	Asn	Gly	Ser	Val	Pro 270
Phe	Glu	Glu	Arg	Ile	Leu	Ala	Val 280	Leu	Gln	Trp	Leu	Gln	Leu	Pro	Lys 285
Asp	Glu 290	Arg	Pro	His	Phe	Tyr 295	Thr	Leu	Tyr	Leu	Glu 300	Glu	Pro	Asp	Ser
Ser 305	Gly	His	Ser	Tyr	Gly 310	Pro	Val	Ser	Ser	Glu 315	Val	Ile	Lys	Ala	Leu 320
Gln	Arg	Val	Asp	Gly 325	Met	Val	Gly	Met	Leu 330	Met	Asp	Gly	Leu	Lys	Glu 335
Leu	Asn	Leu	His 340	Arg	Cys	Leu	Asn	Leu 345	Ile	Leu	Ile	Ser	Asp	His	Gly 350
Met	Glu	Gln	Gly	Ser	Cys	Lys	Lys 360	Tyr	Ile	Tyr	Leu	Asn 365	Lys	Tyr	Leu 370
Gly	Asp 370	Val	Lys	Asn	Ile	Lys 375	Val	Ile	Tyr	Gly	Pro 380	Ala	Ala	Arg	Leu 385
Arg 385	Pro	Ser	Asp	Val	Pro 390	Asp	Lys	Tyr	Tyr	Ser 395	Phe	Asn	Tyr	Glu	Gly 400
Ile	Ala	Arg	Asn	Leu 405	Ser	Cys	Arg	Glu	Pro 410	Asn	Gln	His	Phe	Lys	Pro 415
Tyr	Leu	Lys	His 420	Phe	Leu	Pro	Lys	Arg 425	Leu	His	Phe	Ala	Lys 430	Ser	Asp 435
Arg	Ile	Glu 435	Pro	Leu	Thr	Phe	Tyr 440	Leu	Asp	Pro	Gln	Trp 445	Gln	Leu	Ala 450

110144-序列表

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		

110144-序列表

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

110144-序列表

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

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110144-序列表

<220>
<223> ENPP71 (缺乏NPP1 N-端 GLK)胺基酸序列

<220>
<221> 訊號
<222> (22)..(23)
<223> 訊號肽序列的裂解點

<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

110144-序列表

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	

110144-序列表

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	

110144-序列表

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			

110144-序列表

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> 人工序列

<220>
<223> ENPP71 (缺乏NPP1 N-端 GLK) - Fc胺基酸序列

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<221> 訊號
<222> (22)..(23)
<223> 訊號肽序列的裂解點

<220>
<221> MISC_FEATURE
<222> (854)..(1079)
<223> 表示 Fc 序列

<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

110144-序列表

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	

110144-序列表

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

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Arg 545	Asp	Asn	Leu	Gly	Cys 550	Ser	Cys	Asn	Pro	Ser 555	Ile	Leu	Pro	Ile	Glu 560
Asp	Phe	Gln	Thr	Gln 565	Phe	Asn	Leu	Thr	Val 570	Ala	Glu	Glu	Lys	Ile 575	Ile
Lys	His	Glu	Thr 580	Leu	Pro	Tyr	Gly	Arg 585	Pro	Arg	Val	Leu	Gln 590	Lys	Glu
Asn	Thr	Ile 595	Cys	Leu	Leu	Ser	Gln 600	His	Gln	Phe	Met	Ser 605	Gly	Tyr	Ser
Gln 610	Asp	Ile	Leu	Met	Pro	Leu 615	Trp	Thr	Ser	Tyr	Thr 620	Val	Asp	Arg	Asn
Asp 625	Ser	Phe	Ser	Thr	Glu 630	Asp	Phe	Ser	Asn	Cys 635	Leu	Tyr	Gln	Asp	Phe 640
Arg	Ile	Pro	Leu	Ser 645	Pro	Val	His	Lys	Cys 650	Ser	Phe	Tyr	Lys	Asn 655	Asn
Thr	Lys	Val	Ser 660	Tyr	Gly	Phe	Leu	Ser 665	Pro	Pro	Gln	Leu	Asn 670	Lys	Asn
Ser	Ser	Gly 675	Ile	Tyr	Ser	Glu	Ala 680	Leu	Leu	Thr	Thr 685	Asn	Ile	Val	Pro
Met 690	Tyr	Gln	Ser	Phe	Gln	Val 695	Ile	Trp	Arg	Tyr	Phe 700	His	Asp	Thr	Leu
Leu 705	Arg	Lys	Tyr	Ala	Glu 710	Glu	Arg	Asn	Gly	Val 715	Asn	Val	Val	Ser	Gly 720
Pro	Val	Phe	Asp	Phe 725	Asp	Tyr	Asp	Gly	Arg 730	Cys	Asp	Ser	Leu	Glu 735	Asn
Leu	Arg	Gln	Lys 740	Arg	Arg	Val	Ile	Arg 745	Asn	Gln	Glu	Ile	Leu 750	Ile	Pro
Thr	His	Phe 755	Phe	Ile	Val	Leu	Thr 760	Ser	Cys	Lys	Asp	Thr 765	Ser	Gln	Thr

110144-序列表

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			

110144-序列表

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
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Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
1070 1075

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<223> 訊號肽序列的裂解點

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

110144-序列表

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

110144-序列表

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					

110144-序列表

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

110144-序列表

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	

110144-序列表

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

110144-序列表

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			

110144-序列表

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

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- <211> 1072
- <212> PRT
- <213> 人工序列
- <220>
- <223> ENPP7-NPP3-Fc序列

110144-序列表

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<223> 訊號肽序列的裂解點

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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

110144-序列表

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			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	

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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	
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Arg	Met	Pro	Met	Trp	Ser	Ser	Tyr	Thr	Val	Pro	Gln	Leu	Gly	Asp	Thr	

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

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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				

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His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
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Ser Pro Gly Lys
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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

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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

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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					

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Pro 545	Arg	Asp	Asn	Leu	Gly 550	Cys	Ser	Cys	Asn	Pro 555	Ser	Ile	Leu	Pro	Ile 560
Glu	Asp	Phe	Gln	Thr 565	Gln	Phe	Asn	Leu	Thr 570	Val	Ala	Glu	Glu	Lys 575	Ile
Ile	Lys	His	Glu 580	Thr	Leu	Pro	Tyr	Gly 585	Arg	Pro	Arg	Val	Leu	Gln	Lys
Glu	Asn	Thr 595	Ile	Cys	Leu	Leu	Ser 600	Gln	His	Gln	Phe	Met 605	Ser	Gly	Tyr
Ser 610	Gln	Asp	Ile	Leu	Met	Pro 615	Leu	Trp	Thr	Ser	Tyr 620	Thr	Val	Asp	Arg
Asn 625	Asp	Ser	Phe	Ser	Thr 630	Glu	Asp	Phe	Ser	Asn 635	Cys	Leu	Tyr	Gln	Asp 640
Phe	Arg	Ile	Pro	Leu 645	Ser	Pro	Val	His	Lys 650	Cys	Ser	Phe	Tyr	Lys 655	Asn
Asn	Thr	Lys	Val 660	Ser	Tyr	Gly	Phe	Leu 665	Ser	Pro	Pro	Gln	Leu 670	Asn	Lys
Asn	Ser	Ser 675	Gly	Ile	Tyr	Ser	Glu 680	Ala	Leu	Leu	Thr	Thr 685	Asn	Ile	Val
Pro 690	Met	Tyr	Gln	Ser	Phe	Gln 695	Val	Ile	Trp	Arg	Tyr 700	Phe	His	Asp	Thr
Leu 705	Leu	Arg	Lys	Tyr	Ala 710	Glu	Glu	Arg	Asn	Gly 715	Val	Asn	Val	Val	Ser 720
Gly	Pro	Val	Phe	Asp 725	Phe	Asp	Tyr	Asp	Gly 730	Arg	Cys	Asp	Ser	Leu 735	Glu
Asn	Leu	Arg	Gln 740	Lys	Arg	Arg	Val	Ile 745	Arg	Asn	Gln	Glu	Ile	Leu	Ile 750
Pro	Thr	His 755	Phe	Phe	Ile	Val	Leu 760	Thr	Ser	Cys	Lys	Asp 765	Thr	Ser	Gln

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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

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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						

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Phe	Val	Glu	Asp	Gln	Glu	Val	Cys	Lys	Asn	Tyr	Ala	Glu	Ala	Lys
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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
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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

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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			

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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	

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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

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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

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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

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Arg	Arg	His	Pro	Asp	Tyr	Ser	Val	Ser	Leu	Leu	Leu	Arg	Leu	Ala
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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			

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

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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	

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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				

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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		

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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		

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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		

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1175						1180						1185			
Glu	Asn	Gln	Ala	Thr	Ile	Ser	Ser	Lys	Leu	Gln	Thr	Cys	Cys	Asp	
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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	
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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				
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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
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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
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Asp Ala Leu Ala
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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

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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				

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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
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110144-序列表

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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

110144-序列表

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	

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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

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

110144-序列表

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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Gly Arg Ala Pro Arg Glu Gly Pro Ala Gly Asn Gly Arg Asp Arg Gly
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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

110144-序列表
50 55 60

Arg 65	Ala	Arg	Thr	Ala	Lys 70	Asp	Pro	Asn	Thr	Tyr 75	Lys	Ile	Ile	Ser	Leu 80
Phe	Thr	Phe	Ala	Val 85	Gly	Val	Asn	Ile	Cys 90	Leu	Gly	Phe	Thr	Ala	Gly 95
Leu	Lys	Pro	Ser 100	Cys	Ala	Lys	Glu	Val 105	Lys	Ser	Cys	Lys	Gly	Arg	Cys 110
Phe	Glu	Arg 115	Thr	Phe	Gly	Asn	Cys 120	Arg	Cys	Asp	Ala	Ala	Cys	Val	Glu 125
Leu	Gly 130	Asn	Cys	Cys	Leu	Asp 135	Tyr	Gln	Glu	Thr	Cys 140	Ile	Glu	Pro	Glu 145
His 145	Ile	Trp	Thr	Cys	Asn 150	Lys	Phe	Arg	Cys	Gly 155	Glu	Lys	Arg	Leu	Thr 160
Arg	Ser	Leu	Cys	Ala 165	Cys	Ser	Asp	Asp	Cys 170	Lys	Asp	Lys	Gly	Asp	Cys 175
Cys	Ile	Asn 180	Tyr	Ser	Ser	Val	Cys	Gln 185	Gly	Glu	Lys	Ser	Trp	Val	Glu 190
Glu	Pro	Cys 195	Glu	Ser	Ile	Asn	Glu	Pro	Gln	Cys	Pro	Ala	Gly	Phe	Glu 200
Thr 210	Pro	Pro	Thr	Leu	Leu	Phe 215	Ser	Leu	Asp	Gly	Phe	Arg	Ala	Glu	Tyr 220
Leu 225	His	Thr	Trp	Gly	Gly 230	Leu	Leu	Pro	Val	Ile 235	Ser	Lys	Leu	Lys	Lys 240
Cys	Gly	Thr	Tyr	Thr 245	Lys	Asn	Met	Arg	Pro	Val	Tyr	Pro	Thr	Lys	Thr 250
Phe	Pro	Asn 260	His	Tyr	Ser	Ile	Val	Thr 265	Gly	Leu	Tyr	Pro	Glu	Ser	His 270

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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	

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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	

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Ser	Pro	Val	His	Lys 725	Cys	Ser	Phe	Tyr	Lys 730	Asn	Asn	Thr	Lys	Val 735	Ser
Tyr	Gly	Phe	Leu 740	Ser	Pro	Pro	Gln	Leu 745	Asn	Lys	Asn	Ser	Ser	Gly	Ile
Tyr	Ser	Glu 755	Ala	Leu	Leu	Thr	Thr 760	Asn	Ile	Val	Pro	Met 765	Tyr	Gln	Ser
Phe	Gln 770	Val	Ile	Trp	Arg	Tyr 775	Phe	His	Asp	Thr	Leu 780	Leu	Arg	Lys	Tyr
Ala 785	Glu	Glu	Arg	Asn	Gly 790	Val	Asn	Val	Val	Ser 795	Gly	Pro	Val	Phe	Asp 800
Phe	Asp	Tyr	Asp	Gly 805	Arg	Cys	Asp	Ser	Leu 810	Glu	Asn	Leu	Arg	Gln 815	Lys
Arg	Arg	Val	Ile 820	Arg	Asn	Gln	Glu	Ile 825	Leu	Ile	Pro	Thr	His 830	Phe	Phe
Ile	Val	Leu 835	Thr	Ser	Cys	Lys	Asp 840	Thr	Ser	Gln	Thr	Pro 845	Leu	His	Cys
Glu	Asn 850	Leu	Asp	Thr	Leu	Ala 855	Phe	Ile	Leu	Pro	His 860	Arg	Thr	Asp	Asn
Ser 865	Glu	Ser	Cys	Val	His 870	Gly	Lys	His	Asp	Ser 875	Ser	Trp	Val	Glu	Glu 880
Leu	Leu	Met	Leu	His 885	Arg	Ala	Arg	Ile	Thr 890	Asp	Val	Glu	His	Ile 895	Thr
Gly	Leu	Ser	Phe 900	Tyr	Gln	Gln	Arg	Lys 905	Glu	Pro	Val	Ser	Asp 910	Ile	Leu
Lys	Leu	Lys 915	Thr	His	Leu	Pro	Thr 920	Phe	Ser	Gln	Glu	Asp 925	Leu	Ile	Asn
Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly

110144-序列表

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					

110144-序列表

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
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<211> 1550
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<221> 訊號
<222> (92)..(93)
<223> 訊號肽序列的裂解點

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<222> (933)..(1550)
<223> 表示白蛋白序列

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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

110144-序列表

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	

110144-序列表

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

110144-序列表

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					

110144-序列表

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

110144-序列表

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

110144-序列表

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			

110144-序列表

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
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- <213> 人工序列
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- <223> ENPP121-NPP3-Fc序列
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- <222> (95)..(96)
- <223> 訊號肽序列的裂解點
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- <221> MISC_FEATURE

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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

110144-序列表

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		

110144-序列表

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	

110144-序列表

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					

110144-序列表

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

110144-序列表

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

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<223> 訊號肽序列的裂解點

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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

110144-序列表

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

110144-序列表

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		

110144-序列表

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

110144-序列表

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				

110144-序列表

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

110144-序列表

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			

110144-序列表

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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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

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<211> 623

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<213> 人工序列

<220>

<223> 白蛋白序列

<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

110144-序列表

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

110144-序列表

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

110144-序列表

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

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<400> 34

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

110144-序列表

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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110144-序列表

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<400> 35
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

110144-序列表

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	

110144-序列表

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

<210> 36
<211> 16
<212> PRT

110144-序列表

<213> 人工序列

<220>

<223> ENPP2 訊號肽

<400> 36

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

<210> 37

<211> 20

<212> PRT

<213> 人工序列

<220>

<223> 訊號序列 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
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<210> 38

<211> 22

<212> PRT

<213> 人工序列

<220>

<223> 訊號序列 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> 人工序列

<220>

<223> 訊號序列 ENPP1-2-1

110144-序列表

<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> 人工序列

<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> 人工序列

<220>
<223> 訊號序列 ENPP5

<400> 41

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

110144-序列表									
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Leu	Ser	Thr	Thr	Phe	Ser				
			20						
<210>		42							
<211>		19							
<212>		PRT							
<213>		人工序列							
<220>									
<223>		訊號序列 - 天青殺素(Azurocidin)							
<400>		42							
Met	Thr	Arg	Leu	Thr	Val	Leu	Ala	Leu	Leu
1				5				10	15
Ser	Arg	Ala							
<210>		43							
<211>		15							
<212>		PRT							
<213>		人工序列							
<220>									
<223>		連接子							
<220>									
<221>		MISC FEATURE							
<223>		任一或所有的1-15胺基酸可存在或不存在之本列表特色部分							
<400>		43							
Arg	Arg	Arg	Arg	Arg	Arg	Arg	Arg	Arg	Arg
1				5				10	15
<210>		44							
<211>		16							
<212>		PRT							
<213>		人工序列							
<220>									
<223>		連接子							
<400>		44							

110144-序列表

Asp Ser Ser Ser Glu Glu Lys Phe Leu Arg Arg Ile Gly Arg Phe Gly
1 5 10 15

<210> 45
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 45

Glu Glu Glu Glu Glu Glu Glu Pro Arg Gly Asp Thr
1 5 10

<210> 46
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> 連接子
<400> 46

Ala Pro Trp His Leu Ser Ser Gln Tyr Ser Arg Thr
1 5 10

<210> 47
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 47

Ser Thr Leu Pro Ile Pro His Glu Phe Ser Arg Glu
1 5 10

<210> 48
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 48

110144-序列表

Val Thr Lys His Leu Asn Gln Ile Ser Gln Ser Tyr
1 5 10

<210> 49
<211> 15
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<220>
<221> MISC FEATURE
<223> 任一或所有的2-15胺基酸可存在或不存在之本列表特徵部分

<400> 49

Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu
1 5 10 15

<210> 50
<211> 6
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 50

Gly Gly Ser Gly Gly Ser
1 5

<210> 51
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 51

Arg Ser Gly Ser Gly Gly Ser
1 5

<210> 52
<211> 15
<212> PRT

110144-序列表

<213> 人工序列

<220>

<223> 連接子

<220>

<221> MISC_FEATURE

<223> 任一或所有的2-15胺基酸可存在或不存在之本列表特徵部分

<400> 52

Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp
1 5 10 15

<210> 53

<211> 16

<212> PRT

<213> 人工序列

<220>

<223> 連接子

<400> 53

Leu Val Ile Met Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5 10 15

<210> 54

<211> 15

<212> PRT

<213> 人工序列

<220>

<223> 連接子

<400> 54

Val Ile Met Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5 10 15

<210> 55

<211> 14

<212> PRT

<213> 人工序列

<220>

<223> 連接子

<400> 55

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

110144-序列表
10

1 5

<210> 56
<211> 13
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 56

Met Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5 10

<210> 57
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 57

Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5 10

<210> 58
<211> 11
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 58

Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5 10

<210> 59
<211> 10
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 59

110144-序列表

Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5 10

<210> 60
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 60

Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5

<210> 61
<211> 8
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 61

Gly Leu Gly Leu Gly Leu Arg Lys
1 5

<210> 62
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 62

Leu Gly Leu Gly Leu Arg Lys
1 5

<210> 63
<211> 6
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 63

110144-序列表

Gly Leu Gly Leu Arg Lys
1 5

<210> 64
<211> 5
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 64

Leu Gly Leu Arg Lys
1 5

<210> 65
<211> 4
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<400> 65

Gly Leu Arg Lys
1

<210> 66
<211> 15
<212> PRT
<213> 人工序列

<220>
<223> 連接子

<220>
<221> MISC_FEATURE
<223> 任一或所有的1-15胺基酸可存在或不存在之本列表特色部分

<400> 66

Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys
1 5 10 15

<210> 67
<211> 15
<212> PRT

110144-序列表

<213> 人工序列

<220>

<223> 連接子

<220>

<221> MISC_FEATURE

<223> 任一或所有的2-15胺基酸可存在或不存在之本列表特色部分

<400> 67

Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp
1 5 10 15

<210> 68

<211> 50

<212> PRT

<213> 人工序列

<220>

<223> 連接子

<220>

<221> MISC_FEATURE

<223> 位置6開始在5(GGGGS)基團中胺基酸6-50可存在或不存在

<400> 68

Gly Gly Gly Gly Ser Gly Gly Gly Gly Gly Ser Gly Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Gly Ser Gly Gly Gly Gly Gly Ser Gly Gly
20 25 30

Gly Gly Ser Gly Gly Gly Gly Gly Ser Gly Gly Gly Gly Gly Ser Gly Gly Gly
35 40 45

Gly Ser
50

<210> 69

<211> 2625

<212> DNA

<213> 人工序列

<220>

<223> ENPP3核苷酸序列

110144-序列表

<400> 69	
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tataaaatag cttgcattgt tcttcttgct ttgctggatga tcatgtcact tggattaggc	120
ctggggcttg gactcaggaa actggaaaag caaggcagct gcaggaagaa gtgctttgat	180
gcatcattta gaggactgga gaactgccgg tgtgatgtgg catgtaaaga ccgaggtgat	240
tgctgctggg attttgaaga cacctgtgtg gaatcaactc gaatatggat gtgcaataaa	300
tttcgtttgt gagagaccag attagaggcc agcctttgct cttgttcaga tgactgtttg	360
cagaggaaag attgctgtgc tgactataag agtgtttgcc aaggagaaac ctcatggctg	420
gaagaaaact gtgacacagc ccagcagtct cagtgcccgag aagggtttga cctgccacca	480
gttatcttgt tttctatgga tggatttaga gctgaatatt tatacacatg ggatacttta	540
atgccaaata tcaataaact gaaaacatgt ggaattcatt caaaatacat gagagctatg	600
tatcctacca aaaccttccc aaatcattac accattgtca cgggctttga tccagagtca	660
catggcatca ttgacaataa tatgtatgat gtaaattctca acaagaattt ttcactttct	720
tcaaaggaac aaaataatcc agcctgggtg catgggcaac caatgtggct gacagcaatg	780
tatcaagggt taaaagccgc tacctacttt tggcccggat cagaagtggc tataaatggc	840
tcctttcctt ccataacat gccttacaac ggaagtgtcc catttgaaga gaggatttct	900
acactgttaa aatggctgga cctgccc aaa 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 tgattatfff ccagaataa acttcttcta catgtacgaa	1200
gggcctgccc cccgcatccg agctcataat atacctcatg acttttttag ttttaattct	1260
gaggaaattg ttagaaacct cagttgccga aaacctgac agcatttcaa gccctatttg	1320
actcctgatt tgccaaagcg actgcactat gccaaagac tcagaatcga caaagttcat	1380
ctctttgtgg atcaacagtg gctggctgtt aggagtaaat caaatacaaa ttgtggagga	1440
ggcaacctat gttataacaa tgagtttagg agcatggagg ctatctttct ggcacatgga	1500
cccagtttta aagagaagac tgaagttgaa ccatttgaaa atattgaagt ctataacct	1560
atgtgtgatc ttctacgcat tcaaccagca ccaacaatg gaacctatgg tagtttaaac	1620

110144-序列表

catcttctga aggtgccttt ttatgagcca tcccatgcag aggaggtgtc aaagttttct	1680
gtttgtggct ttgctaatec attgcccaca gagtctcttg actgtttctg ccttcaccta	1740
caaaatagta ctcagctgga acaagtgaat cagatgctaa atctcaccca agaagaaata	1800
acagcaacag tgaaagtaaa ttgtccattt gggaggccta gggfactgca gaagaacgtg	1860
gaccactgtc tcttttacca cagggaatat gtcagtggat ttggaaaagc tatgaggatg	1920
cccatgtgga gttcatacac agtccccag ttgggagaca catcgctctt gcctcccact	1980
gtcccagact gtctgcgggc tgatgtcagg gtctctctt ctgagagcca aaaatgttcc	2040
ttctatttag cagacaagaa tatcacccac ggcttctctt atcttcttgc cagcaataga	2100
acatcagata gccaatatga tgctttaatt actagcaatt tggctacctat gtatgaagaa	2160
ttcagaaaaa tgtgggacta ctccacagt gtcttcttta taaaacatgc cacagaaaga	2220
aatggagtaa atgtggttag tggaccaata ttgattata attatgatgg ccattttgat	2280
gtccagatg aaattacca acatttagcc aacactgatg ttcccatccc aacacactac	2340
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ctggatgtcc taccctttat catccctcac cgacctacca acgtggagag ctgtcttgaa	2460
ggtaaaccag aagctctttg ggttgaagaa agatttacag ctacattgc ccgggtccgt	2520
gatgtagaac ttctactgg gcttgacttc tatcaggata aagtgcagcc tgtctctgaa	2580
attttgcaac taaagacata tttaacca tttgaaacca ctatt	2625

<210> 70
<211> 2775
<212> DNA
<213> 人工序列

<220>	
<223> ENPP1核苷酸序列	
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agagaaggac ctgccggcaa cggcagagac agaggcagat ctcatgccgc cgaagccct	120
ggcgatcctc aggcctgtgc ttctctgtctg gccccatgg atgtgggcga ggaacctctg	180
gaaaaggccg ccagagccag aaccgccaag gacccaaca cctacaaggt gctgagcctg	240
gtgctgtccg tgtgcgtgct gaccaccatc ctgggctgca tcttcggcct gaagcccagc	300
tgcgccaaag aagtgaagtc ctgcaagggc cggctgttcg agcggacctt cggcaactgc	360

110144-序列表

agatgcgacg ccgcctgtgt ggaactgggc aactgctgcc tggactacca ggaaacctgc	420
atcgagcccc 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 ctgctgcccc tgatcagcaa gctgaagaag	720
tgcggcacct acaccaagaa catgcggccc gtgtacccca ccaagacctt ccccaaccac	780
tactccatcg tgaccggcct gtaccccgag agccacggca tcatcgacaa caagatgtac	840
gacccaaga tgaacgccag cttcagcctg aagtccaaag agaagttcaa ccccgagtgg	900
tataagggcg agcccatctg ggtcacccgc aagtaccagg gcctgaaaag cggcacattc	960
ttttggcccc gcagcgacgt ggaaatcaac ggcatcttcc ccgacatcta taagatgtac	1020
aacggcagcg tgcccttcga ggaacggatc ctggctgtgc tgcagtggct gcagctgccc	1080
aaggatgagc ggccccactt ctacacctg tacttggaag 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
gacgtgcccc acaagtacta cagcttcaac tacgagggaa tcgcccgga cctgagctgc	1440
agagagccca accagcacct caagccctac ctgaagcact tccctgccc aa gcggtgcac	1500
ttcgccaaga gcgacagaat cgagccctg accttctacc tggaccccca gtggcagctg	1560
gacctgaatc ccagcgagag aaagtactgc ggcagcggct tccacggctc cgacaacgtg	1620
ttcagcaaca tgcaggccct gtctgtgggc tacggaccgg gctttaagca cggcatcgag	1680
gccgacacct tcgagaacat cgagggtgtac aatctgatgt gcgacctgct gaatctgacc	1740
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accctaagc accccaaaga ggtgcacccc ctgggtgcagt gccccttcac cagaaacccc	1860
agagacaacc tgggctgtag ctgcaacccc agcatcctgc ccatcgagga ctccagacc	1920
cagttcaacc tgacctggc cgaggaaaag atcatcaagc acgagacact gccctacggc	1980
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110144-序列表

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cggaaccagg	aaattctgat	ccctaccac	ttctttatcg	tgttgacaag	ctgcaaggat	2520
accagccaga	ccccctgca	ctgcgagAAC	ctggataccc	tggccttcat	cctgcctcac	2580
cggaccgaca	acagcgagag	ctgtgtgcac	ggcaagcacg	acagctcttg	ggtggaagaa	2640
ctgctgatgc	tgcaccgggc	cagaatcacc	gatgtggaac	acatcaccgg	cctgagcttt	2700
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ttcagccagg	aagat					2775

- <210> 71
- <211> 3255
- <212> DNA
- <213> 人工序列
- <220>
- <223> 天青殺素(Azurocidin)-ENPP1-FC核苷酸序列

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tctagagctg ctcccttctg cgccaaagaa gtgaagtcct gcaagggcag atgcttcgag	120
cggaccttcg gcaactgtag atgtgacgcc gcttgcgtgg aactgggcaa ctgctgcctg	180
gactaccaag agacatgcat cgagcccgag cacatctgga cctgcaacaa gttcagatgc	240
ggcgagaagc ggctgaccag atctctgtgc gccctgctctg acgactgcaa ggacaagggc	300
gactgctgca tcaactactc ctctgtgtgc cagggcgaga agtcctgggt tgaagaaccc	360
tgcgagtcca tcaacgagcc tcagtgtcct gccggcttcg agacacctcc tactctgctg	420
ttctccctgg atggcttcag agccgagtac ctgcatactt ggggaggcct gctgccagtg	480
atctccaagc tgaagaagtg cggcacctac accaagaaca tgaggcctgt gtaccctacc	540

110144-序列表

aagacattcc ccaaccacta ctccatcgtg accggcctgt atcctgagag ccacggcatic	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
cgagtggacg gaatggtcgg aatgctgatg gacggcctga aagagctgaa cctgcacaga	1020
tgctgaacc tgatcctgat ctccgaccac ggcatggaac aggggagctg caagaagtac	1080
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110144-序列表

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<212> DNA
<213> 人工序列

<220>
<223> 天青殺素(Azurocidin)-ENPP3-FC核苷酸序列
<400> 72

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agatgcgacg	tggcctgcaa	ggacagaggc	gactgtctgt	gggacttcga	ggacacctgc	180
gtggagagca	ccagaatctg	gatgtgcaac	aagttcagat	gcggcgagac	cagactggag	240
gccagcctgt	gcagctgcag	cgacgactgc	ctgcagagaa	aggactgctg	cgccgactac	300

110144-序列表

aagagcgtgt gccagggcga gaccagctgg ctggaggaga actgcgacac cgcccagcag	360
agccagtgcc ccgagggcct cgacctgccc cccgtgatcc tgttcagcat ggacggcttc	420
agagccgagt acctgtacac ctgggacacc ctgatgcccc acatcaacaa gctgaagacc	480
tgcggcatcc acagcaagta catgagagcc atgtaccccc ccaagacctt ccccaaccac	540
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gacgtgaacc tgaacaagaa cttcagcctg agcagcaagg agcagaacaa ccccgccctg	660
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gccggcggcc ccgtgagcgc cagagtgatc aaggccctgc aggtggtgga ccacgccttc	960
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110144-序列表

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cacggcttcc tgtaccccc cgccagcaac agaaccagcg acagccagta cgacgccttg	2040
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gagagattca ccgcccacat cgccagagtg agagacgtgg agctgctgac cggcctggac	2460
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ctgggaggcc ccagcgtgtt cctgttcccc cccaagccca aggacaccct gatgatcagc	2640
agaacccccg aggtgacctg cgtggtggtg gacgtgagcc acgaggacc cagagtgaa	2700
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cagtacaaca gcacctacag agtggtgagc gtgctgaccg tgctgcacca ggactggctg	2820
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accatcagca aggccaagg ccagcccaga gagccccagg tgtacacct gccccccagc	2940
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ccccccgtgc tggacagcga cggcagcttc ttctgtaca gcaagctgac cgtggacaag	3120
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cactacacc agaagagcct gagcctgagc cccggcaag	3219

【發明申請專利範圍】

【請求項1】 一種於一具有組織損傷的對象中降低及/或防止血管平滑肌細胞增生惡化的方法，該方法係包括：向該對象投予一有效降低及/或防止該對象損傷位置的血管平滑肌細胞增生惡化之 ENPP1 藥劑量，其中該對象並無 ENPP1 缺乏，藉此降低及/或防止血管平滑肌細胞增生惡化。

【請求項2】 如請求項 1 之方法，其中該組織損傷係包括動脈之損傷。

【請求項3】 如請求項 1 或 2 之方法，其中該組織損傷係包括動脈中置入支架。

【請求項4】 如請求項 1-3 中任一項之方法，其中該對象係處於發生再狹窄(restenosis)的風險中。

【請求項5】 如請求項 1-3 中任一項之方法，其中該對象係患有再狹窄。

【請求項6】 如請求項 5 之方法，其中該對象係患有動脈再狹窄。

【請求項7】 一種於一具有需要手術之病症的對象中在手術位置降低及/或防止血管平滑肌細胞增生惡化的方法，該方法係包括：向該對象投予一有效在該對象的手術位置降低及/或防止血管平滑肌細胞增生惡化之 ENPP1 藥劑量，其中該對象並無 ENPP1 缺乏，藉此降低及/或防止該對象手術位置之血管平滑肌細胞增生惡化。

【請求項8】 如請求項 7 之方法，其中該藥劑係在手術之前，手術期間或手術後投予該對象。

【請求項9】 如請求項 7 或 8 之方法，進一步係包括進行該手術。

【請求項10】 如請求項 7-9 中任一項之方法，其中該手術係包括動脈繞道手術。

【請求項11】 如請求項 7-10 中任一項之方法，其中該手術係包括置入動脈支架。

【請求項12】 如請求項 7-11 中任一項之方法，其中該手術係包括血管成形術。

【請求項13】 一種於患有心肌梗塞或中風之對象中改善心肌梗塞或中風的方法，該方法係包括：向該對象投予一有效改善心肌梗塞或中風之 ENPP1 藥劑量，藉此改善該心肌梗塞或中風。

【請求項14】 一種於患有心肌梗塞或中風之對象中降低及/或防止血管平滑肌細胞增生惡化之方法，該方法係包括：向該對象投予一有效降低及/或防止與該對象心肌梗塞或中風有關的血管系統之血管平滑肌細胞增生惡化的 ENPP1 藥劑量，藉此降低及/或防止與該對象心肌梗塞或中風有關的血管系統之血管平滑肌細胞增生惡化。

【請求項15】 如請求項 13 或 14 之方法，其中該對象無 ENPP1 缺乏。

【請求項16】 如請求項 1-15 中任一項之方法，其中該 ENPP1 藥劑係包括一 ENPP1 多肽。

【請求項17】 如請求項 1-15 中任一項之方法，其中該 ENPP1 藥劑為一編碼 ENPP1 多肽的核酸。

【請求項18】 如請求項 1-15 中任一項之方法，其中該 ENPP1 藥劑係包括一病毒載體，而該病毒載體係包括一編碼 ENPP1 多肽之核酸。

【請求項19】 如請求項 16-18 中任一項之方法，其中該 ENPP1 多肽係包括 ENPP1 的胞外區。

【請求項20】 如請求項 16-18 中任一項之方法，其中該 ENPP1 多肽係包括的催化區。

【請求項21】 如請求項 16-18 中任一項之方法，其中該 ENPP1 多肽係包括 SEQ ID NO：1 的胺基酸 99 至 925。

【請求項22】 如請求項 16-18 中任一項之方法，其中該 ENPP1 多肽係包括一異源蛋白。

【請求項23】 如請求項 22 之方法，其中該異源蛋白係增加 ENPP1 多肽在哺乳動物中的循環半衰期。

【請求項24】 如請求項 22 或 23 之方法，其中該異源蛋白為一免疫球蛋白分子之 Fc 區。

【請求項25】 如請求項 24 之方法，其中該免疫球蛋白分子為一 IgG1 分子。

【請求項26】 如請求項 22 或 23 之方法，其中該異源蛋白為一白蛋白分子。

【請求項27】 如請求項 22-26 中任一項之方法，其中該異源蛋白連接該 ENPP1 多肽之羧基端。

【請求項28】 如請求項 22-27 中任一項之方法，其中 ENPP1 藥劑係包括一連接子。

【請求項29】 如請求項 28 之方法，其中該連接子係隔開該 ENPP1 多肽和該異源蛋白。

【請求項30】 如請求項 28 或 29 之方法，其中該連接子係包括下列胺基酸序列： $(GGGS)_n$ ，其中 n 為 1 至 10 之整數。

【請求項31】 根據請求項 1-30 中任一項之方法，其中該 ENPP1 藥劑係由皮下投予該對象。

【請求項32】 根據請求項 1-30 中任一項之方法，其中該 ENPP1 藥劑由靜脈內投予該對象。

【請求項33】 一種於一具有組織損傷的對象中降低及/或防止血管平滑肌細胞增生惡化的方法，該方法係包括：向該對象投予一有效降低及/或防止該對象損傷位置的血管平滑肌細胞增生惡化之 ENPP3 藥劑量，藉此降低及/或防止血管平滑肌細胞增生惡化。

【請求項34】 如請求項 33 之方法，其中該組織損傷係包括動脈之損傷。

【請求項35】 如請求項 33 或 34 之方法，其中該組織損傷係包括動脈中置入支架。

【請求項36】 如請求項 33-35 中任一項之方法，其中該對象係處於發生再狹窄的風險中。

【請求項37】 如請求項 33-36 中任一項之方法，其中該對象係患有再狹窄。

【請求項38】 如請求項 37 之方法，其中該對象係患有動脈再狹窄。

【請求項39】 一種於一具有需要手術之病症的對象中在手術位置降低及/或防止血管平滑肌細胞增生惡化的方法，該方法係包括：向該對象投予一有效降低及/或防止該對象手術位置的血管平滑肌細胞增生惡化之 ENPP3 藥劑量，藉此降低及/或防止該手術位置之血管平滑肌細胞增生惡化。

【請求項40】 如請求項 39 之方法，其中該藥劑係在手術之前，手術期間或手術後投予該對象。

【請求項41】 如請求項 39 或 40 之方法，進一步係包括進行該手術。

【請求項42】 如請求項 39-41 中任一項之方法，其中該手術係包括動脈繞道手術。

【請求項43】 如請求項 39-42 中任一項之方法，其中該手術係包括置入動脈支架。

【請求項44】 如請求項 39-43 中任一項之方法，其中該手術係包括血管成形術。

【請求項45】 一種於患有心肌梗塞或中風之對象中改善心肌梗塞或中風的方法，該方法係包括：向該對象投予一有效改善心肌梗塞或中風之 ENPP3 藥劑量，藉此改善該心肌梗塞或中風。

【請求項46】 一種於患有心肌梗塞或中風之對象中降低及/或防止血管平滑肌細胞增生惡化之方法，該方法係包括：向該對象投予一有效降低及/或防止與該對象心肌梗塞或中風有關的血管系統之血管平滑肌細胞增生惡化的 ENPP3 藥劑量，藉此降低及/或防止與該對象心肌梗塞或中風有關的血管系統之血管平滑肌細胞增生惡化。

【請求項47】 如請求項 33-46 中任一項之方法，其中該對象無 ENPP1 缺乏。

【請求項48】 如請求項 33-47 中任一項之方法，其中該 ENPP3 藥劑係包括一 ENPP3 多肽。

【請求項49】 如請求項 33-47 中任一項之方法，其中該 ENPP3 藥劑為一編碼 ENPP3 多肽的核酸。

【請求項50】 如請求項 33-47 中任一項之方法，其中該 ENPP3 藥劑係包括一病毒載體，而該病毒載體係包括一編碼 ENPP3 多肽之核酸。

【請求項51】 如請求項 33-50 中任一項之方法，其中該 ENPP3 多肽係包括 ENPP3 的胞外區。

【請求項52】 如請求項 33-51 中任一項之方法，其中該 ENPP3 多肽係包括的催化區。

【請求項53】 如請求項 33-51 中任一項之方法，其中該 ENPP3 多肽係包括 SEQ ID NO：7 的胺基酸 49-875。

【請求項54】 如請求項 33-53 中任一項之方法，其中該 ENPP3 多肽係包括一異源蛋白。

【請求項55】 如請求項 54 之方法，其中該異源蛋白係增加 ENPP3 多肽在哺乳動物中的循環半衰期。

【請求項56】 如請求項 54 或 55 之方法，其中該異源蛋白為一免疫球蛋白分子之 Fc 區。

【請求項57】 如請求項 56 之方法，其中該免疫球蛋白分子為一 IgG1 分子。

【請求項58】 如請求項 54 或 55 之方法，其中該異源蛋白為一白蛋白分子。

【請求項59】 如請求項 54-58 中任一項之方法，其中該異源蛋白連接該 ENPP3 多肽羧基端。

【請求項60】 如請求項 33-59 中任一項之方法，其中 ENPP3 藥劑係包括一連接子。

【請求項61】 如請求項 60 之方法，其中該連接子係隔開該 ENPP3 多肽和該異源蛋白。

【請求項62】 如請求項 60 或 61 之方法，其中該連接子係包括下列胺基酸序列： $(GGGS)_n$ ，其中 n 為 1 至 10 之整數。

【請求項63】 根據請求項 33-62 中任一項之方法，其中該 ENPP3 藥劑係由皮下投予該對象。

【請求項64】 根據請求項 33-62 中任一項之方法，其中該 ENPP3 藥劑由靜脈內投予該對象。

【請求項65】 一種塗覆支架，其係包括：
一血管支架；及

一該支架上的塗層，該塗層係包括一 ENPP1 藥劑；及

一用於該 ENPP1 藥劑之載劑，

其中該塗層係經配置用於以每天 1-10 $\mu\text{g/ml}$ 之速率從支架釋放該 ENPP1 藥劑。

【請求項66】 如請求項 65 之塗覆支架，以塗層的總重量為基準，其中該 ENPP1 藥劑之量係介於 1 重量百分比(wt %)至 50wt %。

【請求項67】 如請求項 66 之塗覆支架，其中該 ENPP1 藥劑係由下列組成之群中選出：ENPP1、ENPP1-Fc、ENPP1-白蛋白及 ENPP1 mRNA。

【請求項68】 如請求項 65 之塗覆支架，其中該載劑不會與該 ENPP1 藥劑反應。

【請求項69】 如請求項 65 之塗覆支架，其中該載劑係包括物理上與該 ENPP1 藥劑結合的聚合物載劑。

【請求項70】 如請求項 65 之塗覆支架，其中該載劑係包括化學上與該 ENPP1 藥劑結合的聚合物載劑。

【請求項71】 如請求項 65 之塗覆支架，其中該載劑係包括一生物可降解的聚合物載劑。

【請求項72】 如請求項 65 之塗覆支架，其中該載劑係包括一非聚合物載劑。

【請求項73】 如請求項 72 之塗覆支架，其中該非聚合物載劑係由下列組成之群中選出：維生素 E、維生素 E 乙酸鹽、維生素 E 琥珀酸鹽、油酸、花生油和棉籽油。

【請求項74】 如請求項 65 之塗覆支架，其中該載劑在體溫下為液體。

【請求項75】 如請求項 65 之塗覆支架，其中該載劑在體溫下為固體。

【請求項76】 一種於一具有組織損傷的對象中降低及/或防制血管平滑肌細胞增生惡化之方法，該方法係包括：將一塗覆 ENPP1 藥劑的動脈支架植入接

近該對象組織損傷的動脈中，其中該植入的支架係配置為以一有效降低及/或防止該對象損傷位置之血管平滑肌細胞增生惡化的量釋放該 ENPP1 藥劑，其中該對象並無 ENPP1 缺乏，藉此在該對象之損傷位置降低及/或防止血管平滑肌細胞增生惡化。

【請求項77】 如請求項 76 之方法，其中該組織損傷係包括動脈中置入支架。

【請求項78】 如請求項 76 或 77 之方法，其中該組織損傷係由於先前置放非析出型動脈支架或由於先前置放釋出該 ENPP1 以外之治療劑的析出型動脈支架於該動脈中。

【請求項79】 如請求項 76-78 中任一項之方法，其中該對象係處於發生再狹窄的風險中。

【請求項80】 一種用於一具有需要手術之病症的對象中在手術位置降低及/或防止血管平滑肌細胞增生惡化的方法，該方法係包括：將一塗覆 ENPP1 藥劑的動脈支架植入接近該對象手術位置的動脈中，其中該植入的支架係配置為以有效降低及/或防止血管平滑肌細胞增生惡化的量釋放該 ENPP1 藥劑，其中該對象無 ENPP1 缺乏，藉此在該手術位置降低及/或防止血管平滑肌細胞增生惡化。

【請求項81】 如請求項 80 之方法，其中該藥劑係在手術之前、手術期間及/或手術後投予該對象。

【請求項82】 如請求項 80 或 81 之方法，進一步係包括進行該手術。

【請求項83】 如請求項 80-82 中任一項之方法，其中該手術係包括動脈繞道手術。

【請求項84】 如請求項 80 之方法，其中需要手術的病症係由於之前在該動脈中置放非析出型動脈支架。

【請求項85】 如請求項 80 之方法，其中需要手術的病症係由於之前在該動脈中置放析出型動脈支架，而該析出型動脈支架係釋出該 ENPP1 藥劑以外的治療劑。

【請求項86】 如請求項 80-85 中任一項之方法，其中該手術係包括血管成形術。

【請求項87】 一種於患有心肌梗塞或中風之對象中改善心肌梗塞或中風之方法，該方法係包括：將一塗覆 ENPP1 藥劑的動脈支架植入該對象的動脈中，其中該植入的支架係配置為以有效改善心肌梗塞或中風的量釋放該 ENPP1 藥劑，藉此改善該心肌梗塞或中風。

【請求項88】 一種於患有心肌梗塞或中風之對象中降低及/或防止血管平滑肌細胞增生惡化的方法，該方法係包括：將一塗覆 ENPP1 藥劑的動脈支架植入該對象的動脈中，其中該植入的支架係配置為以有效降低及/或防止與心肌梗塞或中風有關的血管系統之血管平滑肌細胞增生惡化的量釋放該 ENPP1 藥劑，藉此降低及/或防止與該對象之心肌梗塞或中風有關的血管系統之血管平滑肌細胞增生惡化。

【請求項89】 如請求項 87 或 88 之方法，其中該對象無 ENPP1 缺乏。

【請求項90】 如請求項 77-89 中任一項之方法，其中該 ENPP1 藥劑係包括一 ENPP1 多肽。

【請求項91】 如請求項 77-89 中任一項之方法，其中該 ENPP1 藥劑為一編碼 ENPP1 多肽的核酸。

【請求項92】 如請求項 77-89 中任一項之方法，其中該 ENPP1 藥劑係包括一病毒載體，而該病毒載體係包括一編碼 ENPP1 多肽之核酸。

【請求項93】 如請求項 90-92 中任一項之方法，其中該 ENPP1 多肽係包括 ENPP1 的胞外區。

【請求項94】 如請求項 90-92 中任一項之方法，其中該 ENPP1 多肽係包括 ENPP1 的催化區。

【請求項95】 如請求項 90-92 中任一項之方法，其中該 ENPP1 多肽係包括 SEQ ID NO：1 的胺基酸 99 至 925。

【請求項96】 如請求項 90-92 中任一項之方法，其中該 ENPP1 多肽係包括一異源蛋白。

【請求項97】 如請求項 96 之方法，其中該異源蛋白係增加 ENPP1 多肽在哺乳動物中的循環半衰期。

【請求項98】 如請求項 96 或 97 之方法，其中該異源蛋白為一免疫球蛋白分子之 Fc 區。

【請求項99】 如請求項 98 之方法，其中該免疫球蛋白分子為一 IgG1 分子。

【請求項100】 如請求項 96 或 97 之方法，其中該異源蛋白為一白蛋白分子。

【請求項101】 如請求項 96-100 中任一項之方法，其中該異源蛋白連接 ENPP1 多肽之羧基端。

【請求項102】 如請求項 96-101 中任一項之方法，其中該 ENPP1 藥劑係包括一連接子。

【請求項103】 如請求項之方法，其中該連接子隔開了 ENPP1 多肽和異源蛋白。

【請求項104】 如請求項 102 或 103 之方法，其中該連接子係包括下列胺基酸序列：(GGGGS) n ，其中 n 為 1 至 10 之整數。

【請求項105】 一種於一具有組織損傷的對象中降低及/或防止血管平滑肌細胞增生惡化之方法，該方法係包括：將一塗覆 ENPP3 藥劑的動脈支架植入接

近該對象組織損傷位置的動脈中，其中該植入的支架係配置為以有效降低及/或防止該對象損傷位置之血管平滑肌細胞增生惡化的量釋放該 ENPP3 藥劑，藉此在該對象的損傷位置降低及/或防止血管平滑肌細胞增生惡化。

【請求項106】 如請求項 105 之方法，其中該組織損傷係包括動脈損傷。

【請求項107】 如請求項 105 或 106 之方法，其中該組織損傷係包括動脈內置入支架。

【請求項108】 如請求項 105-107 中任一項之方法，其中該對象係處於發生再狹窄的風險中。

【請求項109】 一種於一具有需要手術之病症的對象中在手術位置降低及/或防止血管平滑肌細胞增生惡化的方法，該方法包括：將一塗覆 ENPP3 藥劑的動脈支架植入接近該對象手術位置的動脈中，其中該植入的支架係配置為以有效降低及/或防止血管平滑肌細胞增生惡化的量釋放該 ENPP3 藥劑，藉此降低及/或防止在該手術位置的血管平滑肌細胞增生惡化。

【請求項110】 如請求項 109 之方法，其中該藥劑係在手術之前，手術期間及/或手術後投予該對象。

【請求項111】 如請求項 109 或 110 之方法，進一步係包括進行該手術。

【請求項112】 如請求項 109-111 中任一項之方法，其中該手術係包括動脈繞道手術。

【請求項113】 如請求項 109 之方法，其中該需要手術的病症係由於先前在該動脈中置入非析出型動脈支架。

【請求項114】 如請求項 109 之方法，其中該需要手術的病症係由於之前在該動脈中置入析出型動脈支架，而該析出型動脈支架係釋出該 ENPP3 藥劑以外的治療劑。

【請求項115】 如請求項 109-114 中任一項之方法，其中該手術係包括血管成形術。

【請求項116】 一種於一患有心肌梗塞或中風之對象中改善心肌梗塞或中風之方法，該方法係包括：將一塗覆 ENPP3 藥劑的動脈支架植入該對象的動脈中，其中該植入的支架係配置為以有效改善心肌梗塞或中風的量析出該 ENPP3 藥劑，藉此改善該心肌梗塞或中風。

【請求項117】 一種於一患有心肌梗塞或中風之對象中降低及/或防止血管平滑肌細胞增生惡化的方法，該方法係包括：將一塗覆 ENPP3 藥劑的動脈支架植入該對象的動脈中，其中該植入的支架係配置為以有效降低及/或防止與心肌梗塞或中風有關的血管系統之血管平滑肌細胞增生惡化的量釋放該 ENPP3 藥劑，藉此降低及/或防止與該對象之心肌梗塞或中風有關的血管系統之血管平滑肌細胞增生惡化。

【請求項118】 如請求項 105-117 中任一項之方法，其中該對象無 ENPP1 缺乏。

【請求項119】 如請求項 105-118 中任一項之方法，其中該 ENPP3 藥劑係包括一 ENPP3 多肽。

【請求項120】 如請求項 105-119 中任一項之方法，其中該 ENPP3 藥劑為一編碼 ENPP3 多肽的核酸。

【請求項121】 如請求項 105-120 中任一項之方法，其中該 ENPP3 藥劑係包括一病毒載體，而該病毒載體係包括一編碼 ENPP3 多肽之核酸。

【請求項122】 如請求項 105-121 中任一項之方法，其中該 ENPP3 多肽係包括一異源蛋白。

【請求項123】 如請求項 105-121 中任一項之方法，其中該 ENPP3 多肽係包括 ENPP3 的胞外區。

【請求項124】 如請求項 105-123 中任一項之方法，其中該 ENPP3 多肽係包括 ENPP3 的催化區。

【請求項125】 如請求項 105-124 中任一項之方法，其中該 ENPP3 多肽係包括 SEQ ID NO：7 的胺基酸 49-875。

【請求項126】 如請求項 119-125 中任一項之方法，其中該 ENPP3 多肽係包括一異源蛋白。

【請求項127】 如請求項 126 之方法，其中該異源蛋白係增加 ENPP3 多肽在哺乳動物中的循環半衰期。

【請求項128】 如請求項 126 或 127 之方法，其中該異源蛋白為一免疫球蛋白分子之 Fc 區。

【請求項129】 如請求項 128 之方法，其中該免疫球蛋白分子為一 IgG1 分子。

【請求項130】 如請求項 126 或 127 之方法，其中該異源蛋白為一白蛋白分子。

【請求項131】 如請求項 124-130 中任一項之方法，其中該異源蛋白連接 ENPP3 多肽之羧基端。

【請求項132】 如請求項 105-131 中任一項之方法，其中該 ENPP3 係包括一連接子。

【請求項133】 如請求項 132 之方法，其中該連接子隔開了 ENPP3 多肽和異源蛋白。

【請求項134】 如請求項 132 或 133 之方法，其中該連接子係包括下列胺基酸序列： $(GGGGS)_n$ ，其中 n 為 1 至 10 之整數。

【請求項135】 一種塗覆支架，其係包括：
一血管支架；及

一該支架上的塗層，該塗層係包括一 ENPP3 藥劑；及

一用於該 ENPP3 藥劑之載劑，

其中該塗層係經配置用於以每天 1-10 $\mu\text{g/ml}$ 之速率從支架釋放該 ENPP3 藥劑。

【請求項136】 如請求項 135 之塗覆支架，以塗層的總重量為基準，其中該 ENPP3 藥劑之量係介於 1wt %至 50wt %。

【請求項137】 如請求項 136 之塗覆支架，其中該 ENPP3 藥劑係由下列組成之群中選出：ENPP3、ENPP3-Fc、ENPP3-白蛋白及 ENPP3 mRNA。

【請求項138】 如請求項 135 之塗覆支架，其中該載劑不會與該 ENPP3 藥劑反應。

【請求項139】 如請求項 135 之塗覆支架，其中該載劑係包括物理上與 ENPP3 藥劑結合的聚合物載劑。

【請求項140】 如請求項 135 之塗覆支架，其中該載劑係包括化學上與 ENPP3 藥劑結合的聚合物載劑。

【請求項141】 如請求項 135 之塗覆支架，其中該載劑係包括生物可降解聚合物載劑。

【請求項142】 如請求項 135 之塗覆支架，其中該載劑係包括一非聚合物載劑。

【請求項143】 如請求項 142 之塗覆支架，其中該非聚合物載劑係由下列組成之群中選出：維生素 E、維生素 E 乙酸鹽、維生素 E 琥珀酸鹽、油酸、花生油和棉籽油。

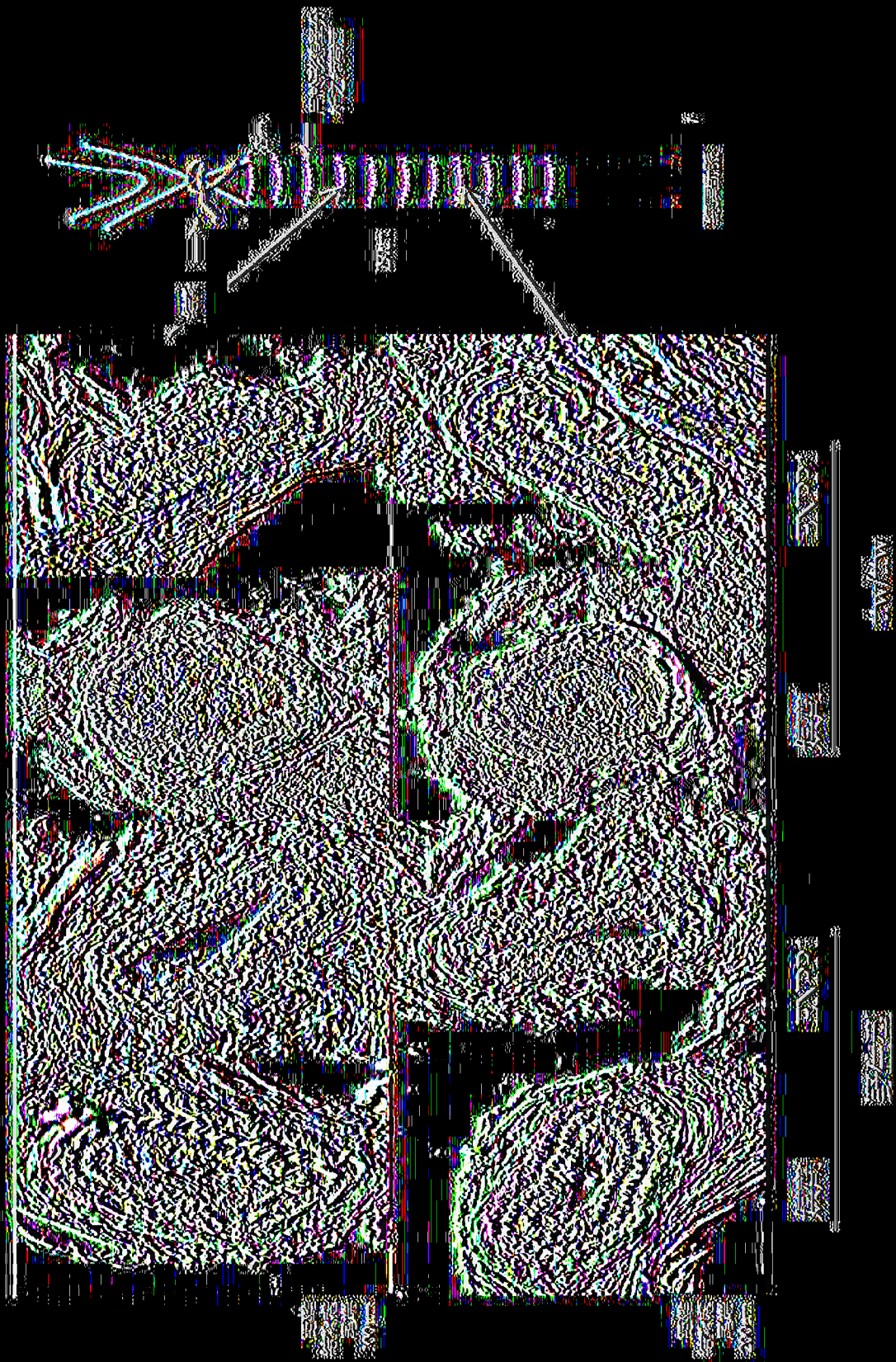
【請求項144】 如請求項 135 之塗覆支架，其中該載劑在體溫下為液體。

【請求項145】 如請求項 135 之塗覆支架，其中該載劑在體溫下為固體。

【請求項146】 如請求項 1-44 和 76-104 中任一項之方法，其中該 ENPP1 藥劑係包括保留酵素活性之 ENPP1 變體。

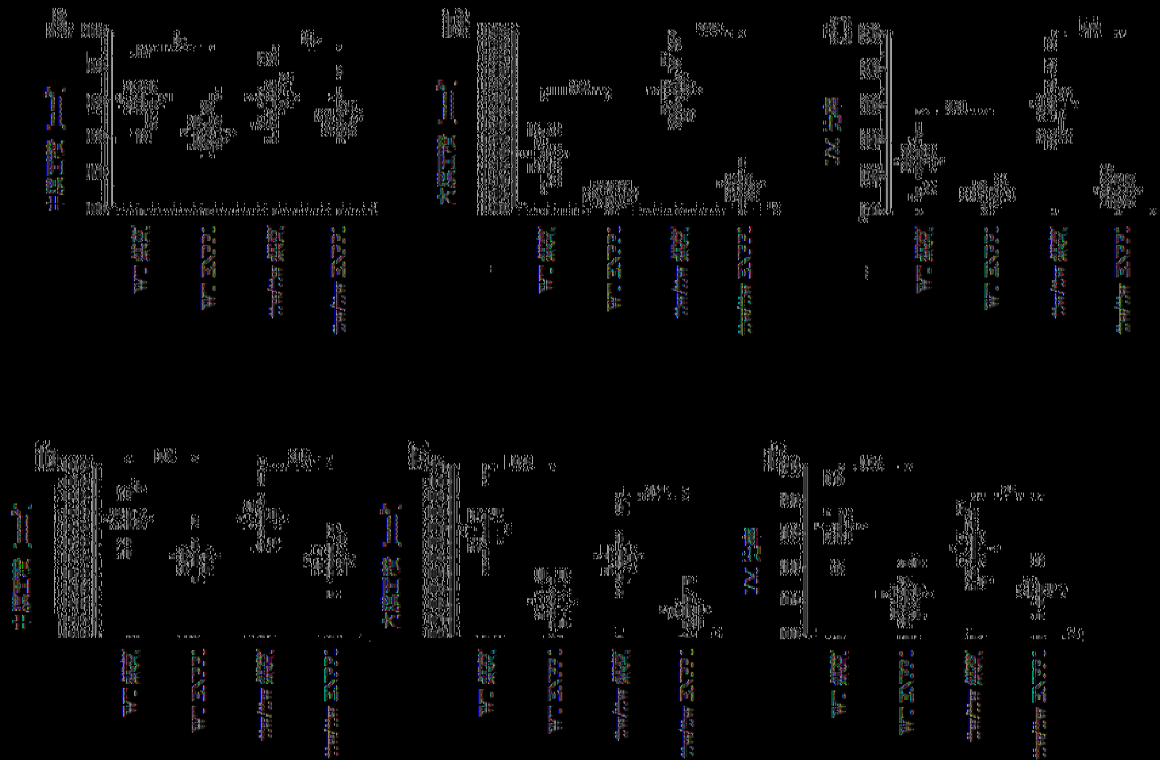
【請求項147】 如請求項 45-64 和 105-134 中任一項之方法，其中該 ENPP3 藥劑係包括保留酵素活性之 ENPP3 變體。

肉膜面養生'膜面膜

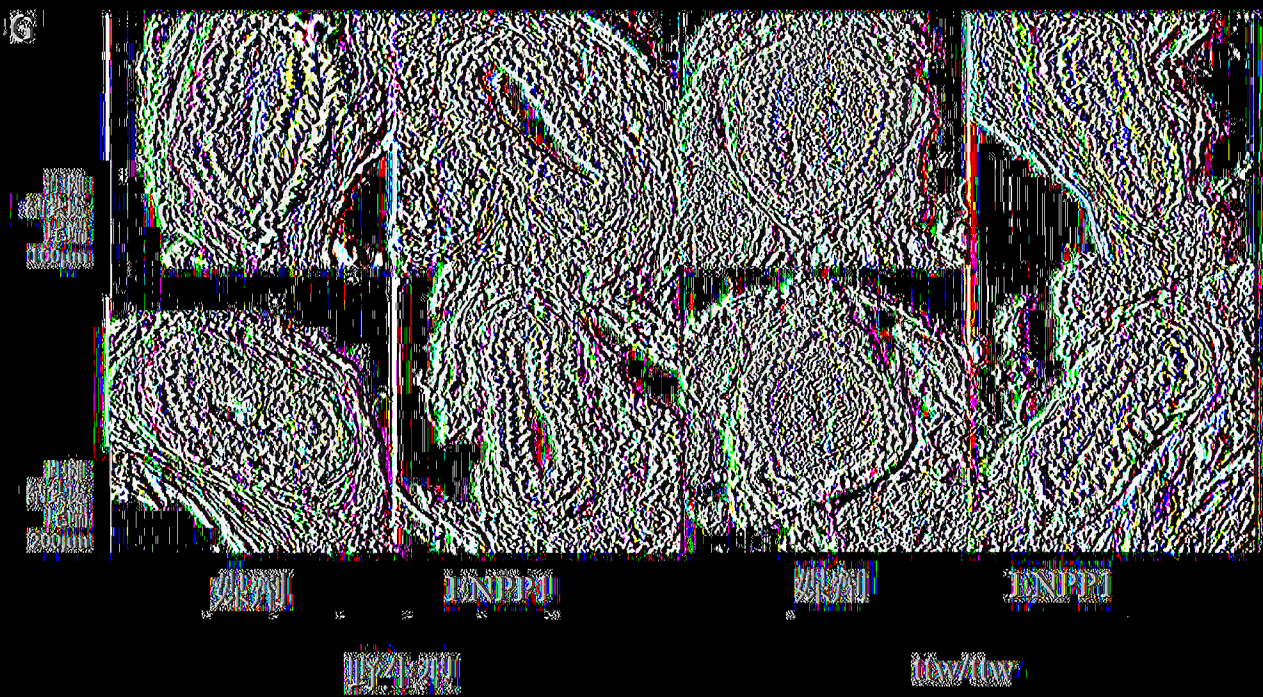
 $|\langle [M]_3 \rangle|$

預防性(防止性)治療

ENPP1-Fc 治療係在搏動脈結暴前 7 天開始，並在搏動脈結暴後 14 天(A-C)
或 21 天(D-E)採集變態性的左搏動脈切片

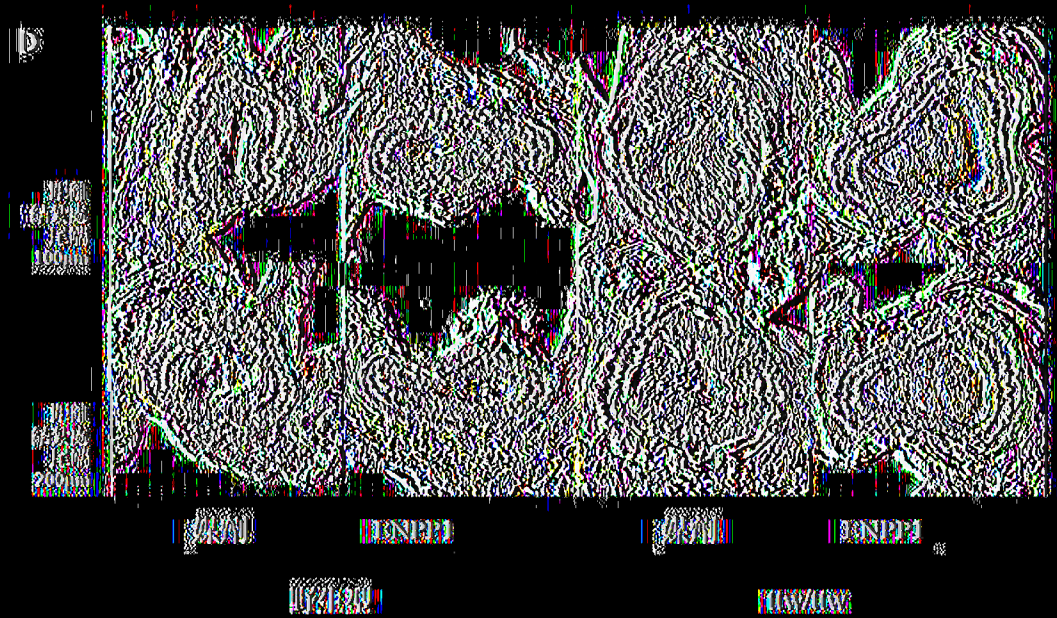
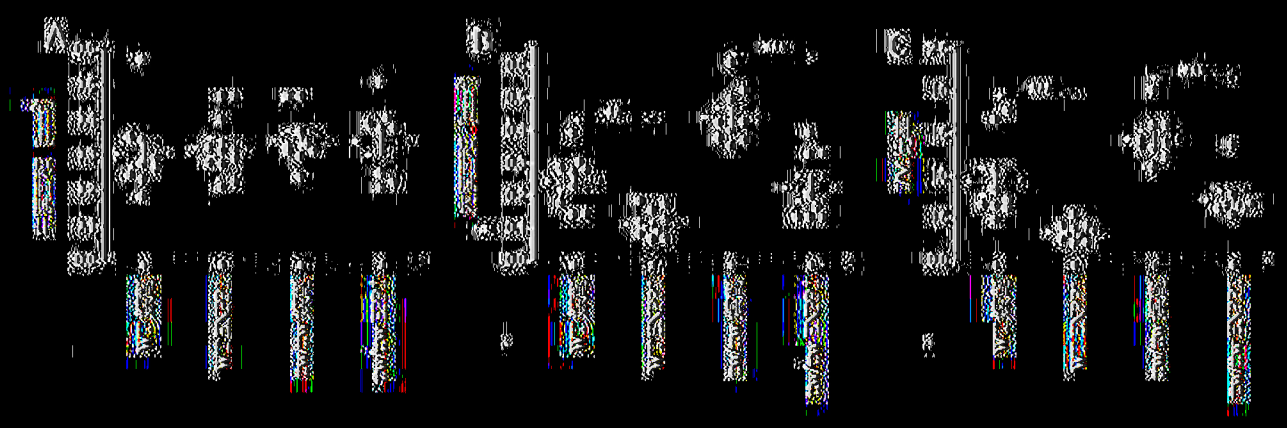


[圖1A-E]



(FIG. 1)

圖 4



(圖5)

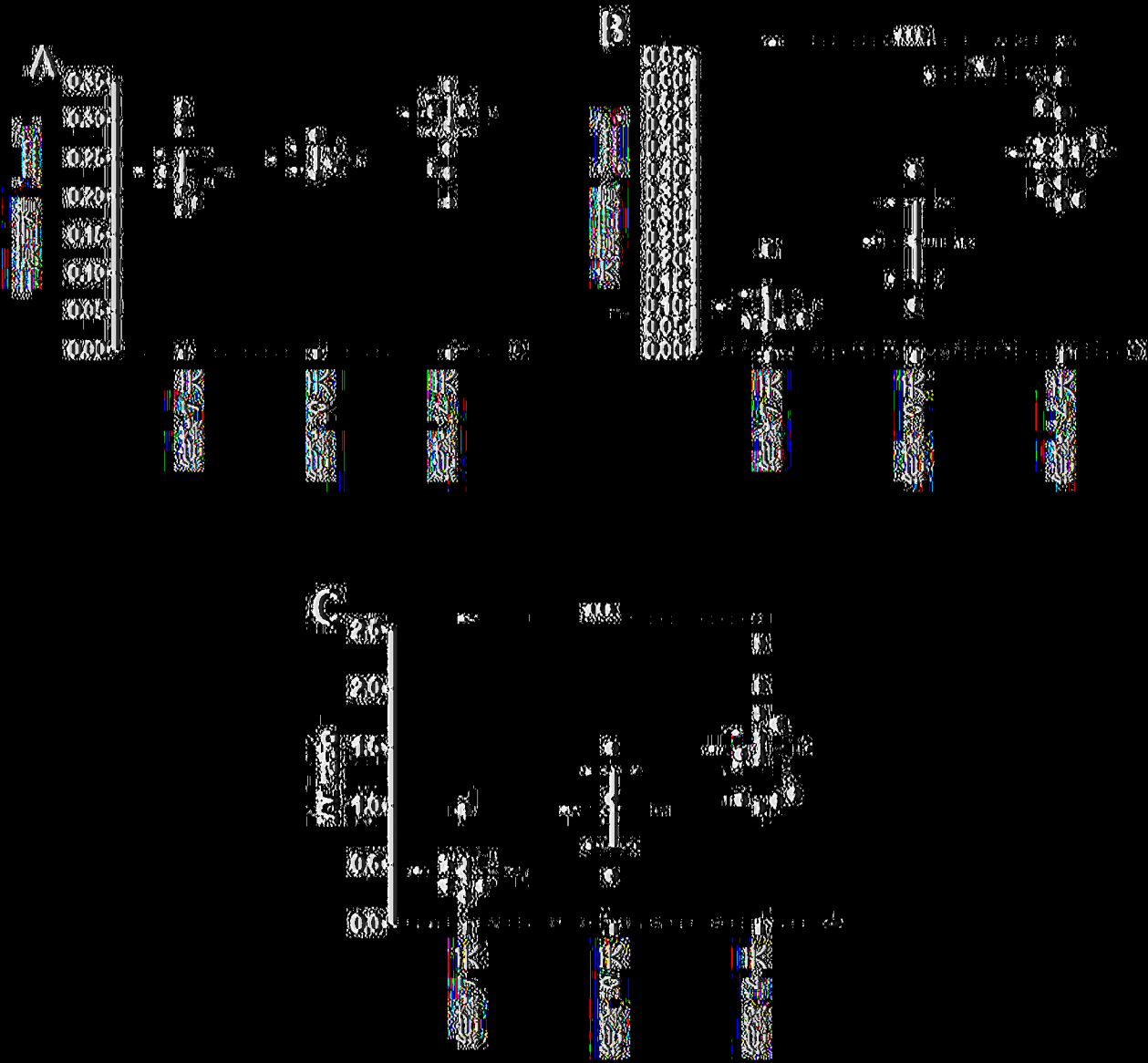
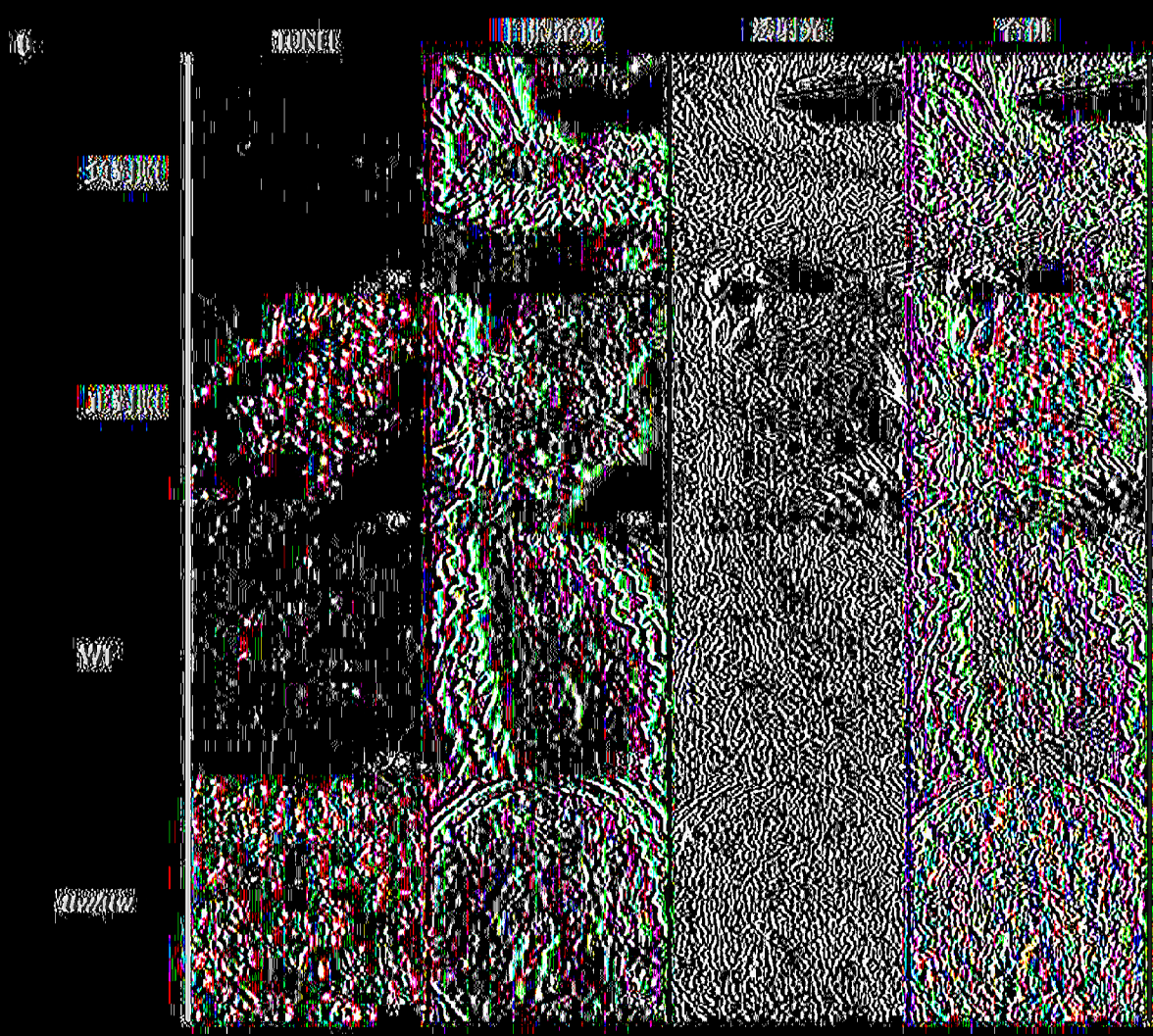
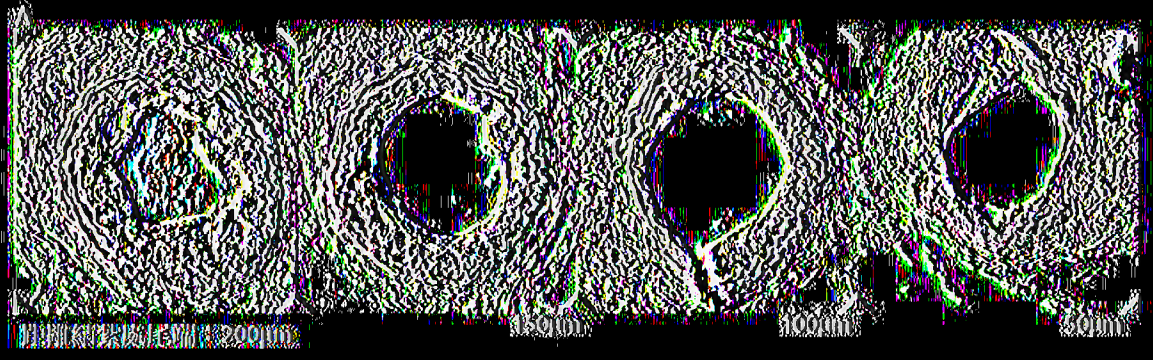
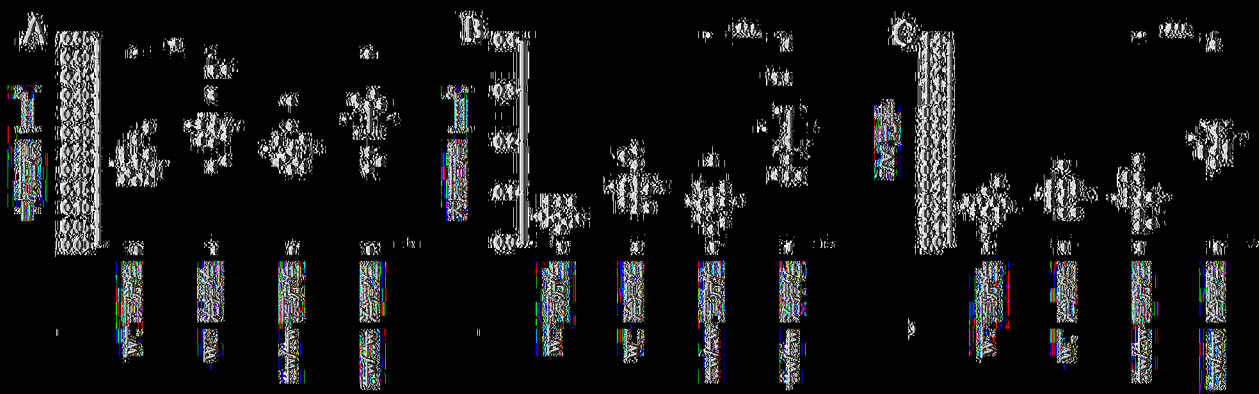


圖6

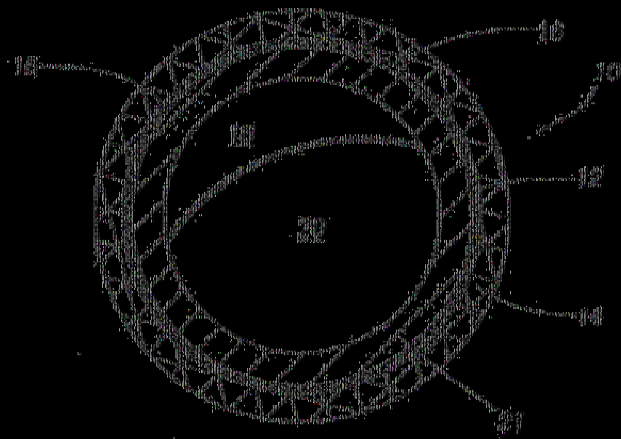


[(圖)]

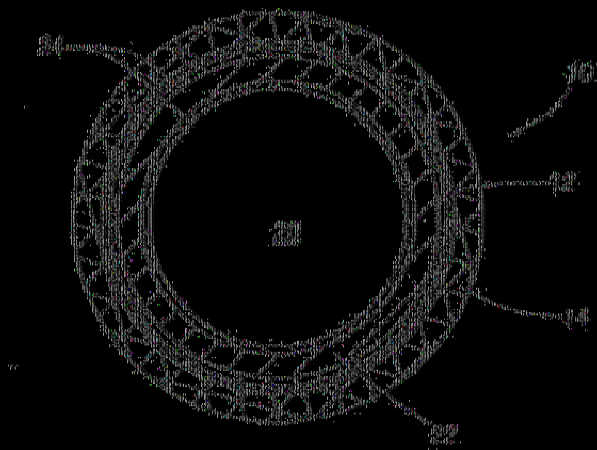


[(圖)8]

9A



9B



[(圖9)]