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(54)名稱

用於治療、改善及／或預防特發性瀰漫性骨質增生症(DISH)的方法及組成物

(57)摘要

在一個方面，本揭露內容提供用於體內治療彌漫性特發性骨質增生症(DISH)、強直性脊柱炎及/或脊關節炎的具體劑量的 ENPP1 劑。

The present disclosure provides, in one aspect, specific doses of an ENPP1 agent for in vivo treatment of Diffuse idiopathic skeletal hyperostosis (DISH), Ankylosing Spondylitis, and/or Spondylarthritis.

指定代表圖：

圖 1A

202342103

【發明摘要】

【中文發明名稱】 用於治療、改善及/或預防特發性彌漫性骨質增生症(DISH)的方法及組成物

【英文發明名稱】 METHOD AND COMPOSITIONS FOR TREATMENT, AMELIORATION, AND/OR PREVENTION OF DIFFUSE IDIOPATHIC SKELETAL HYPEROSTOSIS (DISH)

【中文】

在一個方面，本揭露內容提供用於體內治療彌漫性特發性骨質增生症(DISH)、強直性脊柱炎及/或脊關節炎的具體劑量的ENPP1劑。

【英文】

The present disclosure provides, in one aspect, specific doses of an ENPP1 agent for *in vivo* treatment of Diffuse idiopathic skeletal hyperostosis (DISH), Ankylosing Spondylitis, and/or Spondylarthritis.

【指定代表圖】圖1A

【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】 用於治療、改善及/或預防特發性彌漫性骨質增生症(DISH)的方法及組成物

【英文發明名稱】 METHOD AND COMPOSITIONS FOR TREATMENT, AMELIORATION, AND/OR PREVENTION OF DIFFUSE IDIOPATHIC SKELETAL HYPEROSTOSIS (DISH)

【技術領域】

【0001】 與相關申請的交叉引用

【0002】 本案主張 2022 年 3 月 30 日申請之美國臨時專利申請號 63/325,554 的優先權，其內容在此通過引用以其全部內容併入本文。

【0003】 關於聯邦資助的研究和開發的聲明

【0004】 本發明是在國家衛生研究院授予的 DK121326-01、AR080416-01 和 AG067347A1 的政府支持下完成的。政府擁有本發明的某些權利。

【0005】 在一個方面，本發明的領域涉及通過酶療法治療及/或改善 DISH、強直性脊柱炎及/或脊關節炎的問題。

【0006】 序列表

【0007】 該命名為“047162-7377WO1(01806)序列表.xml”的 XML 文件，創建於 2022 年 9 月 29 日，大小為 149KB，現通過引用以其全部內容併入本文。

【先前技術】

【0008】 外核苷酸焦磷酸酶/磷酸二酯酶 1 (ENP1)是一種 2 型跨膜蛋白，其細胞外活性水解細胞外核苷酸，如三磷酸腺苷(ATP)的磷酸二酯鍵，以生成單磷酸腺苷(AMP)和無機焦磷酸鹽(PPi)。由於 PPi 是羥基磷灰石沉積的主要生理性抑制劑，雙等位基因的 ENPP1 缺陷導致

生命早期的異位礦化，在嬰兒期因動脈鈣化和管腔變窄而導致高死亡率(Ziegler et al., Generalized arterial calcification of infancy. In: Adam MP, Ardinger HH, Pagon RA, et al., (eds). Gene Reviews 2014)。存活下來的患者，以及沒有表現出新生兒鈣化的 ENPP1 缺陷個體，在以後的生活中可出現成纖維細胞生長因子 23 (FGF23)介導的低血磷酸鹽性佝僂病(Ferreira et al., Prospective phenotyping of long-term survivors of generalized arterial calcification of infancy (GACI), Genet Med. 2020;23:396-407)。

【0009】 WO2014126965 涉及在包括 ENPP1 缺陷的疾病中病理性鈣化和病理性骨化的治療。ENPP1、組織非特異性鹼性磷酸酶(TNAP)和進行性關節強直蛋白或錨蛋白(ANK)三種蛋白質在調節無機焦磷酸鹽(PPi)和磷酸鹽(Pi)的細胞外平衡中發揮作用。無機焦磷酸鹽(PPi)是由 ENPP1 裂解細胞外核苷酸三磷酸酯(NTPs)或由 Ank 將 PPi 從細胞內轉移到細胞外空間而生成。TNAP 降解 PPi 以生成 Pi。

【0010】 「ENPP1 缺陷」的特徵在於受試者血清及/或血漿中的 ENPP1 酶活性水平降低。ENPP1 缺陷是由編碼 ENPP1 酶的 *ENPP1* 基因的失活突變引起的罕見的遺傳性障礙。如本文其他部分所述，ENPP1 是整合跨膜蛋白，其細胞外結構域具有焦磷酸酶和磷酸二酯酶活性。因此，ENPP1 將細胞外 ATP 轉化為無機焦磷酸鹽(PPi)和 AMP。

【0011】 生物系統中的鈣化是一個複雜的過程，鈣鹽在非循環基質中維持的濃度高於區域循環體液或其他流動液體中的濃度。正常鈣化的主要結果是鈣和相關的無機鹽在專門的細胞間基質中以類似的排列和化學組成的結晶模式的積累，所有這些可能在不同的物種中有所不同。另一方面，病理性鈣化的淨效應是鈣和相關無機鹽的積累，其化學組成或模式多樣性大於正常範圍，這不僅在這些專門的基質中，而且在其他細胞間、細胞外和細胞物質中，從而導致了幾種疾病狀態。

【0012】 特發性彌漫性骨質增生症(DISH)是以不尋常的新骨形成為特徵的骨骼障礙(Resnick 等，Diffuse idiopathic skeletal

hyperostosis (DISH): Forestier's disease with extraspinal manifestations, Radiology. 1975;115:513-524)。新骨的形成最常見於韌帶和腱與骨結合處(肌腱末端區(entheseal area))，但也有普遍的骨骼硬化和骨骼過度生長(骨肥厚)(Pillai & Littlejohn, Metabolic Factors in Diffuse Idiopathic Skeletal Hyperostosis – A Review of Clinical Data. The Open Rheumatology Journal. 2014; 8:116-128)。ENPP1、TNAP 和 ANK 各自與 DISH 相關的作用還不清楚。此外，也不知道這些酶中的一種或多種的缺陷是否是 DISH 表型的一部分。

【發明內容】

【0013】 本發明內容提供治療、改善及/或預防有需要的患者中的特發性彌漫性骨質增生症(DISH)、強直性脊柱炎及/或脊關節炎的方法。在某些實施方式中，方法包括向患者施用治療有效量的式(I)的化合物，或其鹽或溶劑化物，

【0014】 蛋白質-Z-結構域-X-Y (I)，

其中在(I)中：

蛋白質包括 ENPP1 的催化區；

結構域不存在或為選自人類 IgG Fc 結構域(Fc)、人類血清白蛋白(ALB)和其片段的至少一個；

X 和 Z 獨立地不存在或為包括 1-20 個胺基酸的多肽，

Y 不存在或為帶負電荷的骨靶向序列，

從而治療、改善及/或預防患者的 DISH、強直性脊柱炎及/或脊關節炎。

【0015】 在某些實施方式中，化合物缺乏帶負電荷的骨靶向序列。

【0016】 在某些實施方式中，Y 不存在。

【0017】 在某些實施方式中，化合物包括帶負電荷的骨靶向序列。

【0018】 在某些實施方式中，患者具有 ENPP1 單套缺失(haploinsufficiency)。

【0019】 在某些實施方式中，患者沒有 ENPP1 單套缺失。

【0020】 在某些實施方式中，患者不是 ENPP1 缺陷的。

【0021】 在某些實施方式中，患者是 ENPP1 缺陷的。

【0022】 在某些實施方式中，患者通過至少一種選自以下的途徑施用化合物：口服、氣溶膠、吸入、直腸、陰道、透皮、皮下、鼻內、頰、舌下、腸胃外、鞘內、胃內、眼科、肺部和局部。

【0023】 在某些實施方式中，化合物被靜脈內或皮下施用至患者。

【0024】 在某些實施方式中，向患者施用化合物增加患者的細胞外焦磷酸鹽濃度或預防其進一步降低。

【0025】 在某些實施方式中，向患者施用化合物降低患者的跟腱鈣化、脊柱鈣化、髖關節鈣化和雙側鈣化中的一種或多種或預防其進一步增加。

【0026】 在某些實施方式中，結構域包括白蛋白。

【0027】 在某些實施方式中，結構域包括 IgG Fc 結構域。

【0028】 在某些實施方式中，蛋白質缺乏 ENPP1 跨膜結構域。

【0029】 在某些實施方式中，化合物作為醫藥組成物施用至患者，該醫藥組成物進一步包括至少一種醫藥上可接受的載劑。

【0030】 在某些實施方式中，患者是哺乳動物。

【0031】 在某些實施方式中，哺乳動物是人類。

【0032】 在某些實施方式中，蛋白質包括 SEQ ID NO: 1 的胺基酸殘基 99 (PSCAKE……)至 925 (……QED)。

【0033】 在某些實施方式中，蛋白質包括 SEQ ID NO: 3 的胺基酸殘基 1 至 833。

【0034】 在某些實施方式中，蛋白質包括 SEQ ID NO: 2 中描繪的胺基酸序列。

【0035】 在某些實施方式中，蛋白質包括 SEQ ID NO: 3 或 4 或 5 中描繪的胺基酸序列。

【0036】 在某些實施方式中，相對於缺乏結構域的化合物的循環半衰期，該結構域增加了化合物的循環半衰期。

【0037】 在某些實施方式中，患者還被診斷出患有選自以下的疾病或病症：早發性骨質疏鬆症、骨質減少、與年齡有關的骨質減少、OPLL、遺傳性低血磷酸鹽性佝僂病、X 連鎖低磷酸鹽血症、常染色體隱性低血磷酸鹽性佝僂病 2 型、常染色體顯性低血磷酸鹽性佝僂病和低血磷酸鹽性佝僂病。

【0038】 在某些實施方式中，患者沒有被診斷出患有選自以下的疾病或病症：早發性骨質疏鬆症、骨質減少、與年齡有關的骨質減少、OPLL、遺傳性低血磷酸鹽性佝僂病、X 連鎖低磷酸鹽血症、常染色體隱性低血磷酸鹽性佝僂病 2 型、常染色體顯性低血磷酸鹽性佝僂病和低血磷酸鹽性佝僂病。

【0039】 描述

【0040】 在某些實施方式中，本文所考慮的疾病或障礙是特發性彌漫性骨質增生症(DISH)。在某些實施方式中，本文所考慮的疾病或障礙是強直性脊柱炎。在某些實施方式中，本文所考慮的疾病或障礙是脊關節炎。在某些實施方式中，本文考慮的疾病或障礙是特發性彌漫性骨質增生症(DISH)及/或強直性脊柱炎。在某些實施方式中，本文所考慮的疾病或障礙是 DISH 及/或脊關節炎。在某些實施方式中，本發明所考慮的疾病或障礙是強直性脊柱炎及/或脊關節炎。

【0041】 本發明提供了治療、改善、預防有需要的患者中的特發性彌漫性骨質增生症(DISH)、強直性脊柱炎及/或脊關節炎的進一步發展或進展及/或預防有需要的患者中的特發性彌漫性骨質增生症(DISH)、強直性脊柱炎及/或脊關節炎。本發明進一步提供了治療及/或改善有需要的患者中的 DISH、強直性脊柱炎及/或脊關節炎的方法。

【0042】 在一個方面，本揭露內容涉及通過向患有 DISH、強直性脊柱炎及/或脊關節炎的受試者施用治療有效量的 ENPP1 劑來治療、改善、預防 DISH、強直性脊柱炎及/或脊關節炎的進一步發展及/或進展，及/或預防 DISH、強直性脊柱炎及/或脊關節炎。

【0043】 在一個方面，本揭露內容涉及通過向受試者施用治療有效量的 ENPP1 劑來治療、改善、預防受試者中的 ENPP1 缺陷的進一步發展及/或進展，及/或預防受試者中的 ENPP1 缺陷。

【0044】 在一個方面，本揭露內容涉及通過向受試者施用治療有效量的 ENPP1 劑來治療、改善、預防受試者中的 ENPP1 單套缺失的一種或多種症狀的進一步發展及/或進展，及/或預防受試者中的 ENPP1 單套缺失的一種或多種症狀。

【0045】 治療 DISH、強直性脊柱炎及/或脊關節炎包括施用劑量為每千克約 0.1 mg、每千克的受試者約 0.2 mg、每千克的受試者約 0.3 mg、每千克的受試者約 0.4 mg、每千克的受試者約 0.5 mg、每千克的受試者約 0.6 mg、每千克的受試者約 0.7 mg、每千克的受試者約 0.8 mg、每千克的受試者約 0.9 mg、每千克的受試者約 1.0 mg、每千克的受試者約 1.1 mg、每千克的受試者約 1.2 mg、每千克的受試者約 1.3 mg、每千克的受試者約 1.4 mg、每千克的受試者約 1.5 mg、每千克的受試者約 1.6 mg、每千克的受試者約 1.7 mg、每千克的受試者約 1.8 mg、每千克的受試者約 1.9 mg、或每千克的受試者約 2.0 mg 的 ENPP1 劑，從而治療、減少及/或改善 DISH、強直性脊柱炎及/或脊關節炎疾病的一個或多個症狀，其中受試者沒有 ENPP1 缺陷。

【0046】 在一個方面，本揭露內容涉及向患有 DISH、強直性脊柱炎及/或脊關節炎的受試者施用劑量為每千克約 0.1 mg、每千克的受試者約 0.2 mg、每千克的受試者約 0.3 mg、每千克的受試者約 0.4 mg、每千克的受試者約 0.5 mg、每千克的受試者約 0.6 mg、每千克的受試者約 0.7 mg、每千克的受試者約 0.8 mg、每千克的受試者約 0.9 mg、每千克的受試者約 1.0 mg、每千克的受試者約 1.1 mg、每千克的受試

者約 1.2 mg、每千克的受試者約 1.3 mg、每千克的受試者約 1.4 mg、每千克的受試者約 1.5 mg、每千克的受試者約 1.6 mg、每千克的受試者約 1.7 mg、每千克的受試者約 1.8 mg、每千克的受試者約 1.9 mg、或每千克的受試者約 2.0 mg 的 ENPP1 劑，其從而治療、減少及/或改善 DISH、強直性脊柱炎及/或脊關節炎疾病的一個或多個症狀，其中受試者具有 ENPP1 缺陷。

【0047】 在一個方面，本揭露內容涉及向患有 DISH、強直性脊柱炎及/或脊關節炎的受試者施用劑量為每千克約 0.1 mg、每千克的受試者約 0.2 mg、每千克的受試者約 0.3 mg、每千克的受試者約 0.4 mg、每千克的受試者約 0.5 mg、每千克的受試者約 0.6 mg、每千克的受試者約 0.7 mg、每千克的受試者約 0.8 mg、每千克的受試者約 0.9 mg、每千克的受試者約 1.0 mg、每千克的受試者約 1.1 mg、每千克的受試者約 1.2 mg、每千克的受試者約 1.3 mg、每千克的受試者約 1.4 mg、每千克的受試者約 1.5 mg、每千克的受試者約 1.6 mg、每千克的受試者約 1.7 mg、每千克的受試者約 1.8 mg、每千克的受試者約 1.9 mg、或每千克的受試者約 2.0 mg 的 ENPP1 劑，從而治療、減少及/或改善 DISH、強直性脊柱炎及/或脊關節炎疾病的一個或多個症狀，其中受試者沒有 ENPP1 單套缺失。

【0048】 在一個方面，本揭露內容涉及向患有 DISH、強直性脊柱炎及/或脊關節炎的受試者施用劑量為每千克約 0.1 mg、每千克的受試者約 0.2 mg、每千克的受試者約 0.3 mg、每千克的受試者約 0.4 mg、每千克的受試者約 0.5 mg、每千克的受試者約 0.6 mg、每千克的受試者約 0.7 mg、每千克的受試者約 0.8 mg、每千克的受試者約 0.9 mg、每千克的受試者約 1.0 mg、每千克的受試者約 1.1 mg、每千克的受試者約 1.2 mg、每千克的受試者約 1.3 mg、每千克的受試者約 1.4 mg、每千克的受試者約 1.5 mg、每千克的受試者約 1.6 mg、每千克的受試者約 1.7 mg、每千克的受試者約 1.8 mg、每千克的受試者約 1.9 mg、或每千克的受試者約 2.0 mg 的 ENPP1 劑，從而治療、減少及/或改善

DISH、強直性脊柱炎及/或脊關節炎疾病的一個或多個症狀，其中受試者具有 ENPP1 單套缺失。

【0049】 在一個方面，本揭露內容涉及向患有 DISH、強直性脊柱炎及/或脊關節炎的受試者施用劑量為每千克約 0.1 mg、每千克的受試者約 0.2 mg、每千克的受試者約 0.3 mg、每千克的受試者約 0.4 mg、每千克的受試者約 0.5 mg、每千克的受試者約 0.6 mg、每千克的受試者約 0.7 mg、每千克的受試者約 0.8 mg、每千克的受試者約 0.9 mg、每千克的受試者約 1.0 mg、每千克的受試者約 1.1 mg、每千克的受試者約 1.2 mg、每千克的受試者約 1.3 mg、每千克的受試者約 1.4 mg、每千克的受試者約 1.5 mg、每千克的受試者約 1.6 mg、每千克的受試者約 1.7 mg、每千克的受試者約 1.8 mg、每千克的受試者約 1.9 mg、或每千克的受試者約 2.0 mg 的 ENPP1 劑，以恢復受試者血漿及/或組織中的 ENPP1 蛋白及/或活性的生理水平。本文所用的血漿及/或組織中的 ENPP1 蛋白及/或活性的生理水平，是指足以實現和維持人類血清中 PPi 生理水平的 ENPP1 劑的量或濃度。在某些實施方式中，ENPP1 劑是 ENPP1 及/或包含 ENPP1 活性的 ENPP1 構建體。

【0050】 在一個方面，本揭露內容涉及向患有 ENPP1 單套缺失的受試者施用劑量為每千克約 0.1 mg、每千克的受試者約 0.2 mg、每千克的受試者約 0.3 mg、每千克的受試者約 0.4 mg、每千克的受試者約 0.5 mg、每千克的受試者約 0.6 mg、每千克的受試者約 0.7 mg、每千克的受試者約 0.8 mg、每千克的受試者約 0.9 mg、每千克的受試者約 1.0 mg、每千克的受試者約 1.1 mg、每千克的受試者約 1.2 mg、每千克的受試者約 1.3 mg、每千克的受試者約 1.4 mg、每千克的受試者約 1.5 mg、每千克的受試者約 1.6 mg、每千克的受試者約 1.7 mg、每千克的受試者約 1.8 mg、每千克的受試者約 1.9 mg、或每千克的受試者約 2.0 mg 的 ENPP1 劑，以恢復受試者血漿及/或組織中的 ENPP1 蛋白及/或活性的生理水平。本文所用的血漿及/或組織中的 ENPP1 蛋白及/或活性的生理水平，是指足以實現和維持人類血清中 PPi 生理水平

的 ENPP1 劑的量或濃度。在某些實施方式中，ENPP1 劑是 ENPP1 及/或包含 ENPP1 活性的 ENPP1 構建體。

【0051】 在一個方面，本揭露內容涉及增加患有 DISH、強直性脊柱炎及/或脊關節炎的受試者中的循環焦磷酸鹽(PPi)的方法，該方法包括向受試者施用劑量為每千克約 0.1 mg、每千克的受試者約 0.2 mg、每千克的受試者約 0.3 mg、每千克的受試者約 0.4 mg、每千克的受試者約 0.5 mg、每千克的受試者約 0.6 mg、每千克的受試者約 0.7 mg、每千克的受試者約 0.8 mg、每千克的受試者約 0.9 mg、每千克的受試者約 1.0 mg、每千克的受試者約 1.1 mg、每千克的受試者約 1.2 mg、每千克的受試者約 1.3 mg、每千克的受試者約 1.4 mg、每千克的受試者約 1.5 mg、每千克的受試者約 1.6 mg、每千克的受試者約 1.7 mg、每千克的受試者約 1.8 mg、每千克的受試者約 1.9 mg、或每千克的受試者約 2.0 mg 的 ENPP1 劑，從而增加受試者中的循環 PPi。

【0052】 在一個方面，本揭露內容涉及增加患有 ENPP1 單套缺失的受試者中的循環焦磷酸鹽(PPi)的方法，該方法包括向受試者施用劑量為每千克約 0.1 mg、每千克的受試者約 0.2 mg、每千克的受試者約 0.3 mg、每千克的受試者約 0.4 mg、每千克的受試者約 0.5 mg、每千克的受試者約 0.6 mg、每千克的受試者約 0.7 mg、每千克的受試者約 0.8 mg、每千克的受試者約 0.9 mg、每千克的受試者約 1.0 mg、每千克的受試者約 1.1 mg、每千克的受試者約 1.2 mg、每千克的受試者約 1.3 mg、每千克的受試者約 1.4 mg、每千克的受試者約 1.5 mg、每千克的受試者約 1.6 mg、每千克的受試者約 1.7 mg、每千克的受試者約 1.8 mg、每千克的受試者約 1.9 mg、或每千克的受試者約 2.0 mg 的 ENPP1 劑，從而增加受試者中的循環 PPi。

【0053】 在一個方面，本揭露內容涉及改善受試者中的 ENPP1 單套缺失的一個或多個症狀的方法，該方法包括向受試者施用劑量為每千克約 0.1 mg、每千克的受試者約 0.2 mg、每千克的受試者約 0.3 mg、每千克的受試者約 0.4 mg、每千克的受試者約 0.5 mg、每千克的受試

者約 0.6 mg、每千克的受試者約 0.7 mg、每千克的受試者約 0.8 mg、每千克的受試者約 0.9 mg、每千克的受試者約 1.0 mg、每千克的受試者約 1.1 mg、每千克的受試者約 1.2 mg、每千克的受試者約 1.3 mg、每千克的受試者約 1.4 mg、每千克的受試者約 1.5 mg、每千克的受試者約 1.6 mg、每千克的受試者約 1.7 mg、每千克的受試者約 1.8 mg、每千克的受試者約 1.9 mg、或每千克的受試者約 2.0 mg 的 ENPP1 劑，從而改善受試者中的 ENPP1 缺陷的一種或多種症狀或 ENPP1 單套缺失的一種或多種症狀。

【0054】 在一個方面，本揭露內容涉及預防及/或逆轉患有 DISH、強直性脊柱炎及/或脊關節炎的受試者中存在的病理性鈣化及/或骨化塊的進展，或最小化及/或減少患有 DISH、強直性脊柱炎及/或脊關節炎的受試者中存在的病理性鈣化及/或骨化塊，該方法包括向受試者施用劑量為每千克約 0.1 mg、每千克的受試者約 0.2 mg、每千克的受試者約 0.3 mg、每千克的受試者約 0.4 mg、每千克的受試者約 0.5 mg、每千克的受試者約 0.6 mg、每千克的受試者約 0.7 mg、每千克的受試者約 0.8 mg、每千克的受試者約 0.9 mg、每千克的受試者約 1.0 mg、每千克的受試者約 1.1 mg、每千克的受試者約 1.2 mg、每千克的受試者約 1.3 mg、每千克的受試者約 1.4 mg、每千克的受試者約 1.5 mg、每千克的受試者約 1.6 mg、每千克的受試者約 1.7 mg、每千克的受試者約 1.8 mg、每千克的受試者約 1.9 mg、或每千克的受試者約 2.0 mg 的 ENPP1 劑，從而預防及/或逆轉受試者中的病理性鈣化及/或骨化的骨骼塊的進展，或最小化及/或減少受試者中的病理性鈣化及/或骨化的骨骼塊。

【0055】 在上述任何方法的一些實施方式中，方法包括向患者施用治療有效量的 ENPP1 劑。

【0056】 在一些實施方式中，ENPP1 劑是式(I)的化合物，或其鹽或溶劑化物。

W-蛋白質-Z-結構域-X-Y

(I)，

其中在(I)中：

W 不存在或包括允許將化合物輸出到細胞外空間中的信號序列；

蛋白質包括 ENPP1 的催化區；

結構域不存在或為選自人類 IgG Fc 結構域(Fc)、人類血清白蛋白(ALB)和其生物活性片段的至少一個；

X 和 Z 獨立地不存在，或為包括 1-20 個胺基酸的多肽；和

Y 不存在或是「骨靶向」序列基團

其中 m 獨立地是從 1 到 15 的整數，和

其中 n 獨立地是從 1 到 10 的整數。

【0057】 在一些實施方式中，W 不存在。在一些實施方式中，W 包括允許將化合物輸出到細胞外空間中的信號序列。

【0058】 在一些實施方式中，Y 是選由以下的「骨靶向」序列基團：D_m (SEQ ID NO:11)、$(DSS)_n$ (SEQ ID NO:12)、$(ESS)_n$ (SEQ ID NO:13)、$(RQQ)_n$ (SEQ ID NO:14)、$(KR)_n$ (SEQ ID NO:15)、R_m (SEQ ID NO:16)、DSSSEEKFLRRIGRFG (SEQ ID NO:17)、EEEEEEEPRGDT (SEQ ID NO: 18)、APWHLSSQYSRT (SEQ ID NO: 19)、STLPIPHEFSRE (SEQ ID NO: 20)、VTKHLNQISQSY (SEQ ID NO: 116)和 E_m (SEQ ID NO: 117)。

【圖式簡單說明】

【0059】 圖 1A-1B 顯示了患者 1 的脊柱 CT 和骨閃爍顯像圖。圖 1A 表示脊柱 CT 檢測到的脊柱中存在多個壓縮性骨折，顯示為白色箭頭。圖 1B 顯示骨閃爍顯像圖，其揭示肋骨中多個積累。

【0060】 圖 1C-1H 顯示了患者 1 的髖關節、膝關節和跟腱的 X 光照片。圖 1C：右髖關節，圖 1D：左髖關節，圖 1E：右膝關節，圖 1F：左膝關節，圖 1G：右跟腱，圖 1H：左跟腱。沒有異位骨化的跡象。

【0061】 圖 2A-2C 顯示 ENPP1 突變家族家譜，分別對應於患者

1、2 和 3。箭頭表示先證者。

【0062】 圖 3A-3G 顯示了患者 2 的脊柱 CT，髖關節、膝關節和跟腱的 X 光照片。圖 3A：脊柱 CT 顯示脊柱旁韌帶骨化(白色箭頭)和多個壓縮性骨折(白色箭頭)。圖 3B-3C 分別對應於右髖關節(圖 3B)和左髖關節(圖 3C)的 X 光照片。圖片表明沒有觀察到異位骨化的跡象。圖 3D-3E 分別對應於右膝關節(圖 3D)和左膝關節(圖 3E)的 X 光照片。圖片顯示沒有觀察到異位骨化的跡象。圖 3F 和圖 3G 分別對應於右跟腱(圖 3F)和左跟腱(圖 3G)的 X 光照片。在右跟腱中發現了起止點病的跡象(顯示為白色箭頭)。

【0063】 圖 4A-4I 顯示了患者 3 的脊柱 CT，髖關節、膝關節和跟腱的 X 光照片。圖 4A-4C 對應於脊柱 CT，其顯示頸椎(圖 4A)、胸椎(圖 4B)和腰椎(圖 4C)中的多個脊柱旁骨化(白色箭頭)。圖 4D-4E 顯示了 X 光照片中檢測到的右髖關節(圖 4D)和左髖關節(圖 4E)周圍突出的骨化(白色箭頭)。圖 4F-4G 顯示了右膝關節(圖 4F)和左膝關節(圖 4G)的 X 光照片，其沒有異位骨化的跡象。圖 4H-4I 顯示了在右跟腱(圖 4H)和左跟腱(圖 4I)的 X 光照片中檢測到突出的起止點病(白色箭頭)。

【0064】 圖 5A-5G 顯示了患者 1 的兒子的脊柱 CT 和髖關節、膝關節和跟腱的 X 光照片。(圖 5A)脊柱 CT，(圖 5B)右髖關節，(圖 5C)左髖關節，(圖 5D)右膝關節，(圖 5E)左膝關節，(圖 5F)右跟腱，(圖 5G)左跟腱。沒有異位骨化的跡象。

【0065】 圖 6A-6G 顯示患者 3 的一個兒子的脊柱 CT 和髖關節、膝關節和跟腱的 X 光照片。(圖 6A)脊柱 CT，(圖 6B)右髖關節，(圖 6C)左髖關節，(圖 6D)右膝關節，(圖 6E)左膝關節，(圖 6F)右跟腱，(圖 6G)左跟腱。在左跟腱中有輕微的起止點病(enthespathy)(白色箭頭)。

【0066】 圖 7A-7G 為病例 3 的另一個兒子的脊柱 CT 和髖關節、膝關節和跟腱的 X 光照片。圖 7A)脊柱 CT，(圖 7B)右髖關節，(圖 7C)左髖關節，(圖 7D)右膝關節，(圖 7E)左膝關節，(圖 7F)右跟腱，(圖 7G)左跟腱。左腳跟腱有輕微的起止點病(白色箭頭)。

【0067】 圖 8 顯示互補 DNA 的 Sanger 測序證實了患者 3 的 ENPP1 變體的複合雜合性。雖然殖株類型 1 包含 ENPP1 變體 c.536A>G，但另一個 ENPP1 變體 c.1352A>G 位於殖株類型 2 中，表明了複合雜合性。

【0068】 圖 9 顯示了 ENPP1 結構的非限制性示意圖和本變體的位置。ENPP1 由細胞質結構域(CD)、跨膜結構域(TM)和由兩個生長調節素結構域(SMB1 和 SMB2)、催化結構域和核酸酶樣結構域組成的細胞外結構域組成。N179S 和 Y451C 分別位於 SMB2 和催化結構域中。

【0069】 圖 10 顯示了 WT、N179S 和 Y451C 的酶活性的比較。當與 WT ENPP1 相比，N179S 和 Y451C 變體分別顯示出 55%和 70%的酶促反應速度下降。條形圖表示中位數和四分位數值。****: $p<0.0001$。

【0070】 圖 11 顯示了野生型 ENPP1 前體蛋白(SEQ ID NO: 1)的完整的、未加工的胺基酸序列。胞質和跨膜區域以下劃線表示。潛在的 N-糖基化位點以黑體表示。PSCAKE (殘基 99-104；方框內)是可溶性 ENPP1 蛋白部分的起點，其包括 SMB1 (殘基 104-144)和 SMB2 (殘基 145-189)。

【0071】 圖 12 顯示了在每週用指定的皮下劑量的媒劑或 ENPP1 給藥的 WT 和 $Enpp1^{asj}$ 小鼠中的血漿 PPi 的反應(圖 12)。*$P<0.05$，**$P<0.01$；(方差分析，Kruskal-Wallis 檢驗)。

【0072】 圖 13 顯示了在每週用指定的皮下劑量的媒劑或 ENPP1 構建體#1118 和#2000 給藥的 17 週齡的 WT 和 17 週齡的 $Enpp1^{asj}$ 雄性小鼠中的脊柱旁骨贅和關節強直的反應。構建體#1118 從第 3 週開始每週給藥一次，而構建體#2000 從第 5 週開始每週給藥一次。顯微 CT 圖像顯示較佳在構建體#2000 中脊柱旁骨贅和關節強直的衰減，並且在以每週 1 mg/Kg 劑量給藥的 $Enpp1^{asj}$ 雄性和雌性小鼠中都很明顯。

【0073】 圖 14 顯示了在每週用指定的皮下劑量的媒劑或 ENPP1 構建體#1118 和#2000 給藥的 17 週齡的 WT 和 17 週齡的 $Enpp1^{asj}$ 雌

性小鼠中的脊柱旁骨贅和關節強直的反應。構建體#1118 從第 3 週開始每週給藥一次，而構建體#2000 從第 5 週開始每週給藥一次。顯微 CT 圖像顯示較佳在構建體#2000 中脊柱旁骨贅和關節強直的衰減，並且在以每週 1 mg/Kg 劑量給藥的 $Enpp1^{asj}$ 雄性和雌性小鼠中都很明顯。

【0074】 圖 15A-15B 顯示了在每週用指定的皮下劑量的媒劑或 ENPP1 構建體#1118 和#2000 給藥的 17 週齡的 WT 和 17 週齡的 $Enpp1^{asj}$ 小鼠中的聽覺腦幹反應。構建體#1118 從第 3 週開始每週給藥一次，而構建體 2000 構建體從第 5 週開始每週給藥一次。刺激頻率測量表明，每週 2 mg/Kg 劑量的 ENPP1 構建體#1118，以及每週 0.5 和 1 mg/Kg 劑量的 ENPP1 構建體#2000，可以預防低頻(8 kHz)範圍內的聽力損失。也注意到，較佳在每週 1 mg/Kg 劑量給藥的 ENPP1 構建體#2000 中，在高頻範圍(32 kHz)內 ENPP1 缺陷動物的聽力改善。

【0075】 圖 16 顯示了在每週用指定的皮下劑量的媒劑或 ENPP1 構建體#1118 和#2000 的 WT 和 17 週齡的 $ENPP1^{asj}$ 小鼠中的完整的 FGF23 水平。構建體#1118 從第 3 週開始每週給藥一次，而構建體#2000 構建物從第 5 週開始每週給藥一次。數據顯示，當每週以 1 mg/Kg 和 4 mg/Kg 給藥時，ENPP1 構建體#2000 較佳抑制完整的 FGF23。統計學顯著性是通過方差分析 Kruskal-Wallis 測試，然後通過 Dunn 的事後分析來評估與 WT 水平的差異(單因素方差分析)。統計學顯著性用 p 值表示，並附有以下注釋：*$p<0.05$，**$p<0.01$，***$p<0.001$，****$p<0.0001$。

【實施方式】

【0076】 定義

【0077】 本說明書中使用的術語通常在本揭露內容的背景下和每個術語使用的具體背景下具有其在本領域中的普通含義。某些術語在下文或說明書的其他地方進行了討論，以便為從業者描述本揭露內容的組成物和方法以及如何製造和使用它們提供額外的指導。術語的任何使用

範圍或含義將從使用該術語的具體上下文中顯而易見。

【0078】 如本文所用，術語「DISH」是指特發性彌漫性骨質增生症，也被稱為 Forestier 氏病，是一種以不尋常的新骨形成為特徵的骨骼障礙(Resnick et al., Diffuse idiopathic skeletal hyperostosis (DISH)。Forestier's disease with extraspinal manifestations, Radiology. 1975;115:513-524)。DISH 導致體內韌帶和腱鈣化(變硬)及/或在脊柱周圍和骨骼區域出現新的骨骼生長(骨化塊)。這些鈣化的區域在一些實例中還可以形成骨刺(異常的新骨生長)，其可引起疼痛、僵化和活動性下降。新骨的形成最常見於韌帶和腱與骨結合處(肌腱末端區)，但肌腱末端鈣化與脊柱周圍骨化塊之間的關係尚不清楚。還有普遍的骨骼硬化和骨骼過度生長(骨質增生症)(Pillai & Littlejohn, Metabolic Factors in Diffuse Idiopathic Skeletal Hyperostosis - A Review of Clinical Data, The Open Rheumatology Journal. 2014; 8:116-128)。該疾病的另一個方面是由於異常的骨骼生長而形成大的、流動的骨贅。這些骨化多見於軸向骨骼，其中胸區是主要位置。另外，周邊的肌腱端，如髕周韌帶、跟腱插入處、足底筋膜、肩部、鷹嘴和掌指關節也可以有鈣化。在一些實例中，鈣化見於髖、膝蓋、腳踝、腳、肩部、手和肋骨(Helfgott, Diffuse idiopathic skeletal hyperostosis (DISH). UpToDate. June 7, 2017)。DISH 的共同特性及/或症狀包括前縱韌帶的局灶性和彌漫性鈣化和骨化，脊柱旁結締組織和纖維環的鈣化，周邊纖維環纖維(peripheral annulus fibrosus fiber)的退化，纖維組織的前外側延伸，血管過多，慢性炎症細胞浸潤，椎體前表面上骨膜新骨形成，掌指關節骨化，胸椎、腰椎及/或頸椎區域疼痛，神經根病，多關節疼痛，單關節滑膜炎及/或吞咽困難。

【0079】 DISH 表現為腱和韌帶中鈣鹽的堆積(鈣化)和異常的新骨生長(骨化)，但原因不明(Mader et al., Diffuse idiopathic skeletal hyperostosis: clinical features and pathogenic mechanisms，Nat Rev Rheumatol. December 2013; 9(12):741-50& Nascimento et al.,

Diffuse idiopathic skeletal hyperostosis: A review, Surgical Neurology International. 2014; 5(Suppl 3):S122-S125)。形成 DISH 的常見危險因素包括但不限於大腰圍、BMI/肥胖、高胰島素血症、糖尿病、高尿酸血症、血脂紊亂、高血壓、冠狀動脈疾病和痛風。DISH 可以是無症狀的，在這些情況下，通常根據放射學圖像進行診斷。

【0080】 DISH 是與衰老有關的進行性肌肉骨骼疾病。在兩家大型中西部醫院人群中，50 歲以上的男性和女性中 DISH 的發病率分別為 25%和 15%。此外，在日本人群中高達 6.3%，在北美有 25%的退行性頸椎病患者在稱為 OPLL 的病症中在脊柱後縱韌帶中出現進行性鈣化。在肌腱端中進行性鈣沉積導致脊柱旁腫塊不斷增長引起的椎管狹窄和脊髓壓迫。由此產生的脊髓病往往是嚴重的疼痛和虛弱。治療通常由使用 NSAID 的保守性慢性疼痛管理組成，因為沒有有效的療法來預防導致症狀過程的進行性骨化，而且對導致啟動和促進異位礦化的因素知之甚少。手術減壓用於在急性病例中提供短期緩解，但是 OPLL 中的肌腱端進展在手術(椎板成形術)後與保守管理的患者相比發生得更快(分別為 70%和 24%)，因此，除了症狀嚴重的病例外，不鼓勵進行手術干預。

【0081】 如本文所用，患有 DISH 的受試者，是指被診斷為 DISH 的受試者。DISH 的診斷基於放射學及/或臨床結果，並由 Resnick 和 Niwayana 定義。胸椎和腰椎的放射線照相術是診斷 DISH 的單一最有用成像方式。計算機斷層成像(CT)掃描可用於評估併發症，如骨折，或由對氣管、食道和靜脈的壓力作用引起的症狀。這可以將該實體與強直性脊柱炎或 OPLL 區分開來(Artner et al., Diffuse idiopathic skeletal hyperostosis: current aspects of diagnostics and therapy, 2012, Orthopade. 2012 Nov;41(11):916-22; Olivieri et al., Diffuse idiopathic skeletal hyperostosis may give the typical postural abnormalities of advanced Ankylosing Spondylitis Rheumatology 2007 Nov 1;46(11):1709-11)。主要沿至少 4 個相鄰椎骨(跨越 3 個椎間盤空間)的前外側(前縱韌帶)存在流動的鈣化和骨化，並保留椎間盤

高度，表明 DISH。在 DISH 患者的放射照片和 CT 圖像上可見的脊柱和脊柱外的特徵(Radswiki & Baba, Diffuse idiopathic skeletal hyperostosis. Reference article, Radiopaedia.org)如下。

【0082】 非限制性脊柱特徵：

- 流動的骨化：沿著至少四個相鄰的椎骨的前部或右前外側有花狀的(florid)流動骨化
- 盤空間通常保存良好
- 關節強直在胸椎比頸椎或腰椎更常見
    - 經常不完整
    - 流動的骨化中可以有突出的盤材料的交錯區
- 無骶髂關節炎或切面關節強直，儘管可能存在骶髂關節前橋、後橋、肌腱末端橋 10。

非限制性脊柱外特徵：

- 髂脊、坐骨結節和大轉子的起止點病
- 經常出現附屬骨架的骨刺形成(鷹嘴、跟骨、髕骨韌帶)。
- 「鬚狀」的邊緣骨刺(enthesophytes)

【0083】 非限制性的臨床特徵：

- 疼痛
- 活動範圍減小
- 一些患者中脊柱骨折的風險增加

【0084】 在一些實例中，DISH 會出現症狀，主要的臨床特徵包括疼痛、僵化和活動力(活動範圍)下降、吞咽困難(由骨贅壓迫引起)、食道梗阻、聲音嘶啞、頸椎病、寰樞椎半脫位、椎管狹窄、後縱韌帶骨化、脊髓損傷、呼吸困難、異物感、脊髓受壓引起的神經系統表現、高膽固醇血症(導致心血管併發症)及/或周圍關節病變中的一種或多種。

【0085】 「肌腱端(起止點，enthesis)」是腱或韌帶與骨附接的部位，其結構分為四個區域：密集的纖維結締組織區，由成纖維細胞類型細胞(腱細胞(tenocytes))填充，並且由 I 型和 III 型膠原蛋白和飾膠蛋

白聚糖組成；未礦化的纖維軟骨，由纖維軟骨細胞填充，並且由 I 型和 II 型膠原蛋白和聚集蛋白聚糖組成；礦化的纖維軟骨，由肥大軟骨細胞填充，並且由 II 型和 X 型膠原蛋白和聚集蛋白聚糖組成；以及骨，由成骨細胞、骨細胞和破骨細胞填充，並且由 I 型膠原蛋白組成(Calejo et al., Enthesis tissue engineering: biological requirements meet at the interface, Tissue Eng Part B Rev. 2019;25(4):330-356)。因此，肌腱端代表了一種肌肉骨骼結構，其可以在兩種截然不同的組織——腱或韌帶(順應性軟組織)和骨骼(剛性硬組織)之間實現平穩過渡(Calejo et al., Enthesis tissue engineering: biological requirements meet at the interface, Tissue Eng Part B Rev. 2019;25(4):330-356)。在這個界面上的突然過渡會導致區域之間的應力集中，增加失敗的風險；相反，在肌腱端之上的組成和結構的逐漸過渡減輕應力集中。(Genin et al., Functional grading of mineral and collagen in the attachment of tendon to bone, Biophys J. 2009;97(4):976-985)。從腱朝向骨骼，可見膠原纖維排列逐漸減少和礦物質含量增加，這產生了組織僵化的梯度(Genin et al., Functional grading of mineral and collagen in the attachment of tendon to bone, Biophys J. 2009;97(4):976-985)。肌腱端礦化的降低導致該結構的強度下降(Deymier et al., Micro-mechanical properties of the tendon-to-bone attachment, Acta Biomater. 2017;1(56):25-35)，而礦化的纖維軟骨擴張的動物模型也表現出肌腱端強度下降(Marinovich et al., The role of bone sialoprotein in the tendon-bone insertion, Matrix Biol. 2016;52–54:325-338)。因此，必須適當地調節礦化，以實現肌腱端的最佳機械性能。

【0086】 如本文所用，「強直性脊柱炎」是指一種關節炎，其特徵在於脊柱關節的長期炎症，通常是在脊柱與骨盆的連接處。受影響的區域可能包括其他關節，如肩或髖，可能出現眼睛和腸道問題以及背部疼痛。受影響區域的關節活動性一般會隨著時間的推移而惡化。

【0087】 儘管強直性脊柱炎的病因不明，但據認為它涉及遺傳和環境因素的組合。許多受影響的人有特殊的人類白細胞抗原，稱為 HLA-B27 抗原。其基本機制被認為是自身免疫性或自體炎性。診斷通常基於症狀，並有醫學影像和血液測試的支持。強直性脊柱炎是一種血清陰性的脊柱關節病，意味著測試顯示沒有類風濕因子(RF)抗體的存在。強直性脊柱炎尚無已知的治癒方法。治療可能包括藥物治療、運動、物理療法，以及在極少數情況下的手術。使用的藥物包括 NSAID、類固醇、DMARD(例如柳氮磺吡啶)和生物製劑(如 TNF 抑制劑)。所有人類中大約有 0.1%和 0.8%的人受到影響，其中發病通常發生在年輕的成年人中。男性和女性同等地受到影響；然而，女性比男性更可能出現炎症而不是融合。

【0088】 如本文所用，「脊關節炎」或「SpA」的特徵在於軸向骨骼(骶髂關節炎、脊柱炎)、周圍關節和肌腱端的炎症。骨骼外的表現可以發生，如前葡萄膜炎、銀屑病和炎症性腸病。HLA-B27 是主要的遺傳風險因素。整個 SpA 組在全球的發病率為 0.1%至 1.9%，在不同國家和種族之間存在差異。非甾體抗炎藥(通常稱為 NSAID)通過減輕疼痛和腫脹為大多數患者提供症狀緩解。被稱為生物製劑的其他藥物(包括抗 TNF 藥物(TNF 阻斷劑)和抗 IL-17 藥物(IL-17 阻斷劑))對 NSAID 反應不夠好的患者有效。

【0089】 「ENPP1 缺陷」的特徵在於受試者血清及/或血漿中 ENPP1 酶活性水平減少。ENPP1 缺陷是罕見的遺傳性障礙，由編碼 ENPP1 酶的 ENPP1 基因的失活突變引起。ENPP1 是整合跨膜蛋白，其細胞外結構域具有焦磷酸酶和磷酸二酯酶活性。ENPP1 將細胞外 ATP 轉化為無機焦磷酸鹽(PPi)和 AMP。

【0090】 相對於 ENPP1 多肽的「酶促活性的」，或如本文所用，相對於 ENPP1 多肽的「酶活性的」定義為具有將 ATP 水解為 AMP 和 PPi 及/或將 AP3A 水解為 ATP 的活性。ENPP1 易於將 ATP 水解為 AMP 和 PPi。使用 ATP 作為基質確定 ENPP1 的穩態 Michaelis-Menten

酶常數。可以通過酶促反應的 HPLC 分析證明 ENPP1 裂解 ATP，並通過使用 ATP、AMP 和 ADP 標準品確認基質和反應產物的身份。在存在 ENPP1 的情況下，ATP 基質隨時間降解，並具有酶促產物 AMP 的積累。使用不同濃度的 ATP 基質，在存在 ATP 的情況下導出 ENPP1 的初始速率(rate velocity)，並將數據擬合到曲線上以得出酶速率常數。在生理 pH 值下，NPP1 的動力學速率常數為 K_m= 2 μM 和 k_{cat}= 3.4± 0.4 s^{-1}。

【0091】 如本文所使用的術語「血漿焦磷酸鹽(PPi)水平」是指動物血漿中存在的焦磷酸鹽的量。在某些實施方式中，動物包括大鼠、小鼠、貓、犬、人類、牛和馬。由於自血小板的釋放，有必要測量血漿而不是血清中的 PPi。有幾種測量 PPi 的方法，其中之一是使用尿苷-二磷酸葡萄糖(UDPG)焦磷酸化酶的酶法試驗(Lust & Seegmiller, 1976, Clin. Chim. Acta 66:241-249; Cheung & Suhadolnik, 1977, Anal. Biochem. 83:61-63)，具有修改。

【0092】 通常情況下，健康人受試者的血漿 PPi 水平範圍在約 1 μM 到 3 μM 之間，在一些情況下在 1-2 μM 之間。血漿中 ENPP1 的正常水平是指健康受試者中維持血漿焦磷酸鹽(PPi)正常水平所需的 ENPP1 蛋白的量。健康人的 PPi 的正常水平對應於 2-3 μM。患有 ENPP1 缺陷的受試者表現出低 PPi 水平，其範圍比正常水平至少低 10%、比正常水平至少低 20%、比正常水平至少低 30%、比正常水平至少低 40%、比正常水平至少低 50%、比正常水平至少低 60%、比正常水平至少低 70%、比正常水平至少低 80%及其組合。在患有 GACI 的患者中，發現 PPi 水平低於 1 μM，在一些情況中低於可檢測的水平。在患有 PXE 的患者中，PPi 水平低於 0.5μM (Arterioscler Thromb Vasc Biol. 2014 Sep; 34(9):1985-9; Braddock et al., Nat Commun. 2015; 6: 10006)。

【0093】 如本文所用，術語「病理性鈣化」是指鈣鹽在身體的軟組織、分泌和排泄通道中的異常沉積導致其變硬。有兩種類型：發生在垂

死和死亡組織中的營養不良性鈣化，以及轉移性鈣化，其特徵在於細胞外鈣水平升高(高鈣血症)，超過細胞和組織的體內平衡能力。鈣化可以涉及細胞以及細胞外基質組分，例如基底膜中的膠原蛋白和動脈壁中的彈性纖維。容易發生鈣化的一些組織的實例包括：胃粘膜——胃的內部上皮層，腎臟和肺，角膜，體動脈和肺靜脈。

【0094】 本文所用的術語「病理性骨化」是指在非骨系統的組織中，或在通常不表現成骨性質的結締組織中產生骨的病理性狀況。根據受影響的組織或器官的性質，骨化分為三種類型：軟骨內骨化是發生在軟骨中並取代軟骨的骨化；膜內骨化是發生結締組織中並取代結締組織的骨的骨化；化生性骨化(metaplastic ossification)是在正常的軟體結構中發展出骨性物質；也叫異養骨化。

【0095】 ENPP1 的「缺陷」是指其中受試者血漿中的 ENPP1 低於或等於正常水平的 5%-10%的病症。健康人受試者中 ENPP1 的正常水平大約在 10 至 30 ng/mL 之間(Am J Pathol. 2001 Feb; 158(2): 543–554)。

【0096】 「異位鈣化」是指以鈣鹽在組織中的病理性沉積或軟組織中骨骼生長為特徵的病症。

【0097】 「軟組織的異位鈣化」是指不適當的生物礦化，通常由軟組織中發生的導致軟組織硬化損失的磷酸鈣、羥基磷灰石、草酸鈣和磷酸八鈣組成。「動脈鈣化」是指發生在動脈和心臟瓣膜中導致動脈硬化及/或變窄的異位鈣化。動脈鈣化與動脈粥樣硬化斑塊的負擔和心肌梗塞的風險增加、周圍血管疾病的缺血性發作增加，以及血管成形術後解剖的風險增加有關。

【0098】 「靜脈鈣化」是指發生在靜脈中的異位鈣化，它減少了靜脈的彈性並限制了血流，然後可導致血壓升高和冠狀動脈缺陷。

【0099】 「脈管鈣化」是指礦物在脈管系統中的病理性沉積。它有多種形式，包括內膜鈣化和內側鈣化，但也可在心臟瓣膜中發現。脈管鈣化與動脈粥樣硬化、糖尿病、某些遺傳性病症和腎臟疾病(具體是

CKD)有關。脈管鈣化的患者處於不良心血管事件的更高風險下。脈管鈣化影響著多種多樣的患者。特發性嬰兒動脈鈣化是罕見的脈管鈣化形式，其中新生兒的動脈鈣化。

【0100】 「腦鈣化」(BC)是指非特異性的神經病理學，其中鈣和其他礦物在血管壁和組織實質中的沉積發生，導致神經元死亡和神經膠質增生。腦鈣化通常與多種慢性和急性腦部障礙有關，包括唐氏綜合症、路易體病、阿爾茨海默病、帕金森病、血管性癡呆、腦腫瘤及/或多種內分泌病症。

【0101】 心臟組織鈣化是指鈣的沉積物(可能包括其他礦物質)在心臟組織例如主動脈組織和冠狀動脈組織中的積累。

【0102】 如本文所用，「礦物質骨障礙(MBD)」是指以異常激素水平導致人類血液中鈣和磷水平失衡為特徵的障礙。礦物質和骨障礙通常發生在患有 CKD 的人，並影響大多數接受透析的具有腎衰竭的人。

【0103】 如本文所用，術語「早發性骨質疏鬆症」是指骨質疏鬆症的開始階段，其通常以背痛、彎腰姿勢及/或緩慢的骨量缺失為特徵。常見原因包括低鈣飲食、吸煙、與年齡有關的激素變化。

【0104】 「骨質減少」是以骨密度下降為特徵的骨骼病症，它導致骨骼變弱和骨折的風險增加。骨軟化是骨骼障礙，其特徵在於新形成的骨骼的礦化程度下降。骨軟化是由嚴重的維生素 D 缺陷(可能是營養性的，也可能是由遺傳性綜合徵引起的)和導致非常低血磷酸鹽水平的病症引起的。骨軟化和骨質減少二者都會增加斷骨的風險。骨軟化的症狀包括骨痛和肌肉無力、骨骼壓痛、行走困難和肌肉痙攣。

【0105】 如本文所用，「與年齡有關的骨質減少」是指其中骨礦物質密度低於正常的病症。一般來說，骨質減少患者的骨礦物質密度 T 分數在-1.0 和-2.5 之間。骨質減少如果不加以治療，就會進展成骨質疏鬆症，其中骨骼會變得很脆，極易發生骨折。

【0106】 如本文所用，「後縱韌帶骨化(OPLL)」是指導致後縱韌帶異位鈣化的骨肥厚(過度骨骼生長)病症。後縱韌帶連接並穩定脊柱的

骨骼。增厚或鈣化的韌帶可能會壓迫脊髓，產生脊髓病。脊髓病的症狀包括行走困難以及腸道和膀胱控制困難。OPLL 也可能導致神經根病，或壓迫神經根。頸神經根病的症狀包括頸部、肩部、手臂或手的疼痛、刺痛或麻木。OPLL 與 DISH 不同，因為對於 OPL，骨化只發生在後縱韌帶，而不像骨化也發生在胸區和前縱韌帶的 DISH。

【0107】 OPLL 引起的臨床症狀和體徵可分類為：(1)脊髓病，或脊髓損傷，伴有上下肢運動和感覺失調、痙攣和膀胱功能障礙；(2)頸神經根病，伴有上肢疼痛和感覺失調；(3)軸性不適，頸部周圍疼痛和僵化。OPLL 早期最常見的症狀包括手的感覺遲鈍和刺痛感，以及笨拙。隨著神經功能缺損的進展，可能出現下肢症狀，如步態失調。OPLL 在側位普通放射線片上檢測到，磁共振成像(MRI)和計算機斷層成像(CT)已明確顯示了頸部 OPLL 的診斷和形態學細節。

【0108】 OPLL 在患有頸椎病的美國人中很普遍，在亞洲人群中甚至更為廣泛。脊髓病和活動力下降隨著年齡的增長而逐漸加重，目前還沒有有效的措施預防導致脊髓病和僵化的脊柱旁骨化的金展。目前療法集中於緩解症狀，雖然手術在短期內可能有幫助，但隨後起止點病的快速進展和症狀的復發往往使這種方法複雜化。

【0109】 患有進展迅速的 OPLL 的患者顯示出循環 FGF23 的升高 (Kawaguchi, Y., et al., Serum biomarkers in patients with ossification of the posterior longitudinal ligament (OPLL): Inflammation in OPLL. PLoS One, 2017. 12(5): p. e0174881; Kawaguchi, Y., et al., Increase of the Serum FGF-23 in Ossification of the Posterior Longitudinal Ligament. Global Spine J, 2019. 9(5): p. 492-498)，這是罕見障礙 X 連鎖低磷酸鹽血症(XLH)和常染色體隱性低血磷酸鹽性佝僂病(ARHR)的核心發現，這兩種疾病也表現出與 DISH 和 OPLL 類似的起止點病。這些發現表明，FGF23 (或所得的低磷酸鹽血症)在起止點病的發病機制中起著致病作用，然而，FGF23 升高及/或磷酸鹽降低可能誘發起止點病或脊柱骨化的機制

尚不清楚。

【0110】 如本文所用的「遺傳性低血磷酸鹽性佝僂病」是指與血液中磷酸鹽水平低有關的障礙(低磷酸鹽血症)。磷酸鹽是礦物質，其對骨骼和牙齒的正常形成至關重要。最常見的是，它是由 PHEX 基因的突變引起的。其他可能導致這種病症的基因包括 CLCN5、DMP1、ENPP1、FGF23 和 SLC34A3 基因。遺傳性低血磷酸鹽性佝僂病的其他體徵和症狀可包括顱骨過早融合(顱縫早閉(craniosynostosis))和牙齒畸形。這種障礙還可能導致韌帶和腱與關節附接處的異常骨骼生長(起止點病)。在成人中，低磷酸鹽血症的特徵在於稱為骨軟化的骨骼軟化。另一種罕見類型的障礙被稱為具有高鈣尿症(HHRH)的遺傳性低血磷酸鹽性佝僂病，其中除了低磷酸鹽血症外，這種病症的特徵還在於尿液中高水平鈣的排液(高鈣尿症)。

【0111】 如本文所用，「X 連鎖低磷酸鹽血症(XLH)」，術語 X 連鎖低磷酸鹽血症(XLH)，也稱為 X 連鎖顯性低血磷酸鹽性佝僂病，或 X 連鎖維生素 D 抗性佝僂病，是 X 連鎖顯性形式的佝僂病(或骨軟化)，其與大多數佝僂病的情況不同，因為補充維生素 D 並不能治癒它。它可以導致骨骼畸形，包括身材矮小和膝內翻(弓形腿)。它與 PHEX 基因序列(Xp.22)的突變和隨後的 PHEX 蛋白的失活有關。

【0112】 如本文所用，「常染色體隱性低磷酸鹽血症佝僂病 2 型(ARHR2)」是指以低磷酸鹽血症、佝僂病及/或骨軟化及生長緩慢為特徵的遺傳性腎臟磷酸鹽消耗障礙。常染色體隱性低血磷酸鹽性佝僂病 2 型(ARHR2)是由 ENPP1 基因的純合功能損失突變引起。

【0113】 如本文所用，「常染色體顯性低血磷酸鹽性佝僂病(ADHR)」是指罕見的遺傳性疾病，其中尿液中磷酸鹽的過度損失導致骨骼形成不良(佝僂病)、骨痛和牙齒膿腫。ADHR 是由成纖維細胞生長因子 23 (FGF23)的突變引起的。ADHR 的特徵在於骨骼礦化受損、佝僂病及/或骨軟化、骨化三醇(1,25-二羥基維生素 D3)水平被抑制、腎臟磷酸鹽消耗以及低血清磷酸鹽。FGF23 的突變使該蛋白質更穩定和不

被蛋白酶裂解，從而增強了 FGF23 的生物活性。FGF23 突變體的活性增強減少了近端腎小管細胞頂端表面上的鈉磷共轉運體(sodium-phosphate co-transporter) NPT2a 和 NPT2c 的表現，導致了腎臟磷酸鹽消耗。

【0114】 「低血磷酸鹽性佝僂病」(以前稱為維生素 D 抗性佝僂病)是其中由於血液中磷酸鹽水平低，骨骼變得非常地(painfully)柔軟且容易彎曲的障礙。症狀可能包括腿部彎曲和其他骨骼畸形；骨骼疼痛；關節疼痛；骨骼生長不良；和身材矮小。在一些受影響的嬰兒中，顱骨之間的空間過早地關閉，導致顱縫早閉。大多數患者表現鈣磷代謝異常、牙釉質異常、牙齒萌出延遲和頭長而窄(長頭症(dolichocephaly))。

【0115】 如本文所用，術語「ENPP1 單套缺失」是指其中 ENPP1 基因的一個拷貝失活或缺失，並且剩下的 ENPP1 基因的功能拷貝不足以產生所需的基因產物以保持正常功能的遺傳病症。由於 ENPP1 單套缺失可以但不一定必須以低 PPi 水平和病理性鈣化的形式表現。類似 DISH 或早發性骨質疏鬆症的疾病在某些實施方式中可以與 ENPP1 單套缺失有關，及/或由其引起。

【0116】 對於大多數基因來說，單個拷貝足以支持二倍體生物的正常生長和發育，但被稱為單套缺失(HI)基因的小基因子集表現出對基因劑量降低的極端敏感性。鑒於在生物體的生命週期中，基因失活突變的頻率相對較高，以及基因表現在細胞間的差異性，單套缺失代表了生物體健康的重要障礙。遺傳學中的單套缺失描述了二倍體生物中顯性基因作用的模型，其中基因座處的野生型等位基因的單拷貝與變體等位基因的雜合組合不足以產生野生型表型。單套缺失可能來自於變體等位基因的新發或遺傳的功能損失突變，從而使其產生很少或沒有基因產物。

【0117】 例如，已發現 ENPP1 的 N179S 突變導致 ENPP1 蛋白的功能損失。具有 N179S 突變的單拷貝突變 ENPP1 基因的存在導致 PPi 生產下降。本發明公開了 N179S 突變在某些具有 DISH 或早發性骨質疏鬆症的患者中發現，並在某些實施方式中可作為 DISH 或骨質疏鬆症

存在或未來發展及/或進展的遺傳標誌物。

【0118】 同樣，已發現 ENPP1 的 Y451C 突變導致 ENPP1 蛋白的功能損失。具有 Y451C 突變的單拷貝突變 ENPP1 基因的存在導致 PPi 生產下降。本發明公開了 Y451C 突變在某些具有 DISH 或早發性骨質疏鬆症的患者中發現，並在某些實施方式中可作為 DISH 或骨質疏鬆症存在或未來發展及/或進展的遺傳標誌物。

【0119】 如本文所用，「預處理」是指在開始本文所述的治療方法之前的處理。

【0120】 如本文所用，術語「受試者」是指個體，如哺乳動物，如人類、非人類類靈長類動物(如黑猩猩和其他猿和猴類)、農場動物(如鳥、魚、牛、綿羊、豬、山羊和馬)、家養哺乳動物(如犬和貓)或實驗動物(如齧齒動物，如小鼠、大鼠和豚鼠)。該術語包括任何年齡或性別的受試者。在另一個實施方式中，受試者是哺乳動物，較佳是人類。

【0121】 如果疾病或障礙的症狀的嚴重程度、患者經歷這種症狀的頻率或兩者都減少，則該疾病或障礙得到「緩解」。

【0122】 如本文所用，術語「改變」、「缺陷」、「變異」或「突變」是指細胞中的基因的突變，影響其編碼的多肽的功能、活性、表現(轉錄或翻譯)或構型，包括錯義和無義突變、插入、缺失、移碼和過早終止。

【0123】 「疾病」是動物的健康狀態，其中動物無法維持體內穩態，並且其中如果疾病沒有得到改善，則動物的健康狀況將繼續惡化。

【0124】 動物的「障礙」是一種健康狀態，其中動物能夠維持體內穩態，但其中與沒有該障礙的情況相比，動物的健康狀態不利。如果不治療，障礙不一定會導致動物健康狀況進一步下降。

【0125】 如本文所用，術語「ENPP」或「NPP」是指外核苷酸焦磷酸酶/磷酸二酯酶。

【0126】 如本文所用，術語「ENPP1 蛋白質」或「ENPP1 多肽」是指由 ENPP1 基因編碼的外核苷酸焦磷酸酶/磷酸二酯酶-1 蛋白質。

編碼的蛋白質是 II 型跨膜糖蛋白，並裂解多種基質，其包括核苷酸和核苷酸糖的磷酸二酯鍵以及核苷酸和核苷酸糖的焦磷酸鍵。ENPP1 蛋白質具有跨膜結構域和可溶性細胞外結構域。細胞外結構域進一步細分為生長調節素 B 結構域、催化結構域(SEQ ID NO: 1 的殘基 186 至 586)和核酸酶結構域(SEQ ID NO: 1 的殘基 524 至 885)。野生型 ENPP1 的序列和結構在 Braddock 等人的 PCT 申請公開號 WO 2014/126965 中詳細描述，其通過引用以其整體併入本文。

【0127】 哺乳動物 ENPP1 多肽、突變體或其突變體片段先前已在以下的國際 PCT 申請公開號中公開：Braddock 等人的 WO/2014/126965、Braddock 等人的 WO/2016/187408、Braddock 等人的 WO/2017/087936 和 Braddock 等人的 WO2018/027024，所有這些都通過引用以其整體併入本文。

【0128】 如本文所用，術語「ENPP1 前體蛋白質」是指在 ENPP1 的 N 端具有其信號肽序列的 ENPP1。在蛋白水解後，信號序列(在某些非限制性的實施方式中，在式(I)的化合物中用 W 表示)從 ENPP1 裂解，以提供 ENPP1 蛋白質。在本發明中有用的信號肽序列包括但不限於白蛋白信號序列、天青殺素信號序列(azurocidin signal sequence)、ENPP1 信號肽序列、ENPP2 信號肽序列、ENPP7 信號肽序列及/或 ENPP5 信號肽序列。

【0129】 如本文所用，術語「ENPP1-Fc 構建體」是指與 IgG 分子(較佳地，人類 IgG)的 FcR 結合結構域重組融合及/或化學綴合(包括共價和非共價綴合)的 ENPP1。在某些實施方式中，ENPP1 的 C 端與 FcR 結合結構域的 N 端融合或綴合。

【0130】 如本文所用，術語「Fc」是指人類 IgG (免疫球蛋白)Fc 結構域。考慮將諸如 IgG1、IgG2、IgG3 和 IgG4 的 IgG 亞型用作 Fc 結構域。

【0131】 如本文所用，「Fc 區或 Fc 多肽」是 IgG 分子的一部分，其與通過木瓜蛋白酶消化 IgG 分子獲得的可結晶片段相關。Fc 區包含

通過二硫鍵連接的 IgG 分子的兩條重鏈的 C 端一半。它沒有抗原結合活性，但包含碳水化合物部分以及補體和 Fc 受體(包括 FcRn 受體)的結合位點。Fc 片段包含整個第二恒定結構域 CH2 (根據 Kabat 編號系統，人類 IgG1 的殘基 231-340)和第三恒定結構域 CH3 (殘基 341-447)。術語「IgG 鉸鏈-Fc 區」或「鉸鏈-Fc 片段」是指由 Fc 區(殘基 231-447)和從 Fc 區的 N 端延伸的鉸鏈區(殘基 216-230)組成的 IgG 分子區域。術語「恒定結構域」是指免疫球蛋白分子的一部分，其相對於免疫球蛋白的另一部分，即含有抗原結合位點的可變結構域，具有更保守的胺基酸序列。恒定結構域包含重鏈的 CH1、CH2 和 CH3 結構域以及輕鏈的 CHL 結構域。

【0132】 如本文所用，術語「片段」應用於核酸時，是指較大核酸的子序列。核酸的「片段」可以是至少約 15、50-100、100-500、500-1000、1000-1500 個核苷酸、1500-2500 或 2500 個核苷酸(及其之間的任何整數值)。如本文所用，術語「片段」應用於蛋白質或肽時，是指較大蛋白質或肽的子序列，長度可以至少為約 20、50、100、200、300 或 400 個胺基酸(及其之間的任何整數值)。

【0133】 「分離的」是指從天然狀態改變或移出的。例如，活體動物中天然存在的核酸或多肽不是「分離的」，但與其天然狀態的共存材料部分或完全分開的相同核酸或多肽是「分離的」。分離的核酸或蛋白質可以以實質上純化的形式存在，或可以存在於非天然環境中，例如宿主細胞中。

【0134】 如本文所用，術語「患者」、「個體」或「受試者」是指人類。

【0135】 如本文所用，術語「醫藥組成物」或「組成物」是指在本發明中有用的至少一種化合物與醫藥上可接受的載劑的混合物。該醫藥組成物促進了化合物向患者的施用。本領域中存在多種施用化合物的技術，其包括但不限於皮下、靜脈內、口服、氣霧劑、吸入、直腸、陰道、透皮、鼻內、頰、舌下、腸胃外、鞘內、胃內、眼科、肺部和局部施用。

【0136】 如本文所用，術語「醫藥上可接受的」是指不消除化合物的生物學活性或性質並且相對無毒的材料，例如載劑或稀釋劑，即，該材料可以被施用至個體，而不會引起不良的生物學影響或以有害的方式與組成物中所含的任何組分相互作用；例如，磷酸鹽緩衝鹽水(PBS)

【0137】 如本文所用，術語「血漿焦磷酸鹽(PPi)水平」是指動物血漿中存在的焦磷酸鹽的量。在某些實施方式中，動物包括大鼠、小鼠、貓、犬、人類、奶牛和馬。由於從血小板釋放，有必要測量血漿而不是血清中的 PPi。有多種測量 PPi 的方式，其中一種是通過使用尿苷二磷酸葡萄糖(UDPG)焦磷酸化酶的酶法試驗(Lust 和 Seegmiller，1976，Clin. Chim. Acta 66：241-249；Cheung 和 Suhadolnik，1977，Anal. Biochem 83：61-63)，具有修改。健康受試者的正常 PPi 水平範圍通常為約 1 μm 至約 3 μM，在一些情況下為 1-2 μM 之間。在一些實施方式中，PPi 的「低」水平是指受試者的血漿焦磷酸鹽(PPi)低於或等於正常水平的 2%-5%的狀況(Arthritis and Rheumatism, Vol. 22, No. 8 (August 1979))。

【0138】 患有 ENPP1 表現缺陷的受試者傾向於表現出較低的 PPi 水平，其範圍比正常水平低至少 10%、比正常水平低至少 20%、比正常水平低至少 30%、比正常水平低至少 40%、比正常水平低至少 50%、比正常水平低至少 60%、比正常水平低至少 70%、比正常水平低至少 80%及其組合。在患有 GACI 的患者中，發現 PPi 水平低於 1 μM，在一些情況下低於可檢測的水平。在患有 PXE 的患者中，PPi 水平低於 0.5 Mm (Arterioscler Thromb Vasc Biol. 2014 Sep; 34(9):1985-9; Braddock et al., Nat Commun. 2015; 6: 10006)。

【0139】 如本文所用，術語「多肽」是指由通過肽鍵連接的胺基酸殘基、相關的天然存在的結構變體和合成的非天然存在的其類似物組成的聚合物。

【0140】 如本文所用，術語「PPi」是指焦磷酸鹽。

【0141】 如本文所用，術語「預防」或「防止」是指如果沒有障礙

或疾病發生，則沒有障礙或疾病發展，或如果已經有障礙或疾病發展，則沒有進一步的障礙或疾病發展。還考慮了人類預防與障礙或疾病有關的一些或全部症狀的能力。

【0142】 如本文所用的「樣品」或「生物樣品」是指從受試者分離的生物材料。生物樣品可包含適合於檢測受試者的生理或病理過程的mRNA、多肽或其他標誌物的任何生物材料，並且可包含獲自個體的流體、組織、細胞及/或非細胞材料。

【0143】 如本文所用，「實質上純化的」是指實質上不含其他組分。例如，實質上純化的多肽是已經與其通常以其天然存在狀態締合的其他組分分開的多肽。非限制性實施方式包括 95%的純度、99%的純度、99.5%的純度、99.9%的純度和 100%的純度。

【0144】 如本文所用，術語「治療」或「處理」定義為將治療劑，即在本發明中有用的化合物(單獨或與另一種藥劑組合)應用或施用至患者，或將治療劑應用或施用至來自患者的分離的組織或細胞系(例如，用於診斷或離體應用)，該患者具有疾病或障礙及/或疾病或障礙的症狀，旨在治療、治癒、減輕、緩解、改變、補救、改良、改善、影響及/或預防及/或最小化疾病或障礙及/或疾病或障礙的症狀的進展。基於從藥物基因組學領域獲得的知識，可以具體地定制或修改這樣的治療。

【0145】 如本文所用，術語「預防」、「預防的」和「防止」是指抑制受試者疾病的開始或減少其發生。預防可以是完全的(如受試者中完全沒有病理細胞)或部分的。預防也指對臨床病症的易感性減少。在某些實施方式中，「預防」包括預防疾病或障礙的發作。

【0146】 如本文所用，術語「野生型」是指從天然存在來源分離的基因或基因產物。野生型基因在人群中最常見，並因此被任意設計為人類 ENPP1 基因的「正常」或「野生型」形式。相反，術語「功能等效」是指與野生型基因或基因產物相比，在序列及/或功能性質(即改變的特性)上顯示出改變的 ENNP1 基因或基因產物。可以分離天然存在的突變體；通過與野生型基因或基因產物相比其具有改變的特性(包括改變

的核酸序列)這一事實來對其進行鑒定。

【0147】 如本文所用，術語「功能等效變體」涉及與 ENPP1 (上文定義)的序列實質上同源的多肽，並且保留了 ENPP1 的酶促和生物學活性。確定變體是否保留了原生 ENPP1 的生物學活性的方法是技術人員廣泛瞭解的，包括本申請的實驗部分所使用的任何實驗方法。具體地，由病毒載體遞送的 ENPP1 的功能等效變體被本發明所包括。

【0148】 ENPP1 的功能等效變體是與原生 ENPP1 實質上同源的多肽。「實質上同源的」涉及當蛋白質序列與上述 ENPP1 序列的同一性程度分別為至少 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%時的蛋白質序列。

【0149】 兩個多肽之間的同一性程度是使用計算機算法和本領域技術人員廣泛瞭解的方法來確定的。兩個胺基酸序列之間的同一性較佳通過使用 BLASTP 算法(BLAST Manual, Altschul et al., NCBI NLM NIH Bethesda, Md. 20894, Altschul et al., J. Mol. Biol. 215: 403-410 (1990))確定，但是也可以使用其他類似的算法。使用 BLAST 和 BLAST 2.0，用本文描述的參數來確定序列同一性百分比。執行 BLAST 分析的軟件可通過國家生物技術信息中心公開獲得。

【0150】 ENPP1 的「功能等效變體」可以通過替換多核苷酸內的核苷酸來獲得，這些核苷酸分別考慮用於生產 ENPP1 的宿主細胞中的密碼子偏好。這樣的「密碼子優化」可以經由計算機算法確定，該算法併入了密碼子頻率表，例如 University of Wisconsin Package Version 9.0, Genetics Computer Group, Madison, Wis 提供的密碼子偏好的「Human high.cod」。

【0151】 如本文所用，「約」當指可測量的值，例如數量、時間段等時，意指包括從指定的值(2 mg/kg 或 0.6 mg/kg 或 1.8 mg/kg)的±10%或 5%，在某些實施方式中為±1-5%，在某些實施方式中為±5%，在某些實施方式中為±4%，在某些實施方式中為±4%，在某些實施方式

中為±2%，和在某些實施方式中為±1%的變化，因為這樣的變化對於執行所公開的方法是合適的。

【0152】 本公開方式提供了有代表性的蛋白質序列的實例。所述的蛋白質序列可以通過進行反轉錄和密碼子優化轉換為核酸序列。在技術上有幾種可以進行這種轉換的工具，例如 Expasy (https://www.expasy.org/) 和生物信息學服務器 (www *dot* bioinformatics *dot* org)。

【0153】 範圍：在整個的本揭露內容中，根據本發明的多個方面可以以範圍格式呈現。應當理解，以範圍格式進行的描述僅是為了方便和簡潔，而不應被解釋為對根據本發明範圍的不靈活的限制。因此，應該將範圍的描述視為已明確公開了在該範圍內的所有可能的子範圍以及單個數值。例如，應將例如從 1 到 6 的範圍描述視為已明確公開了子範圍，例如從 1 到 3、從 1 到 4、從 1 到 5、從 2 到 4、從 2 到 6、從 3 到 6 等，以及該範圍內的單個數字，例如 1、2、2.7、3、4、5、5.3 和 6。無論範圍的廣度如何，這都適用。

【0154】 本文描述了較佳的方法和材料，但與本文所述的方法和材料相似或等效的方法和材料也可用於苯公開的方法和組成物的實踐或測試。本文提到的所有出版物、專利申請、專利和其他參考文獻都通過引用以其整體併入本文。

【0155】 具體實施方式

1. ENPP1 劑

【0156】 ENPP1 劑是一種 ENPP1 多肽。本文公開的 ENPP1 多肽包括但不限於 ENPP1 家族的天然存在的多肽以及保留生物活性(例如但不限於 ENPP1 的催化活性)的其任何變體(包括突變體、片段、融合體和肽模擬物形式)。

【0157】 ENPP1 劑可以用下面所示的公式形式表示：

W-蛋白質-Z-結構域-X-Y

(I)，

其中在(I)中：

W 不存在或包括允許將化合物輸出到細胞外空間中的信號序列；

蛋白質包括 ENPP1 的催化區；

結構域不存在或為選自人類 IgG Fc 結構域(Fc)、人類血清白蛋白(ALB)和其生物活性片段的至少一個；

X 和 Z 獨立地不存在或為包括 1-20 個胺基酸的多肽；和

Y 不存在或是選自由以下「骨靶向」序列的序列：D_m (SEQ ID NO:11)、$(DSS)_n$ (SEQ ID NO:12)、$(ESS)_n$ (SEQ ID NO:13)、$(RQQ)_n$ (SEQ ID NO:14)、$(KR)_n$ (SEQ ID NO:15)、R_m (SEQ ID NO:16)、DSSSEEKFLRRIGRFG (SEQ ID NO:17)、EEEEEEEPRGDT (SEQ ID NO: 18)、APWHLSSQYSRT (SEQ ID NO: 19)、STLPIPHEFSRE (SEQ ID NO: 20)、VTKHLNQISQSY (SEQ ID NO: 116)和 E_m (SEQ ID NO: 117)，

其中 m 獨立地是從 1 到 15 的整數，及

其中 n 獨立地是從 1 到 10 的整數。

【0158】 在一些實施方式中，W 不存在。在一些實施方式中，W 包括允許將化合物輸出到細胞外空間的信號序列。

【0159】 在一些實施方式中，ENPP1 劑包括骨靶向結構域。在一些實施方式中，骨靶向結構域是帶負電荷的胺基酸序列。在一些實施方式中，帶負電荷的骨靶向結構域是聚天冬胺酸。

【0160】 術語「ENPP1」或「ENPP1 多肽」是指來自任何物種的外核苷酸焦磷酸酶/磷酸二酯酶 1 蛋白(NPP1/ENPP1/PC-1)和 ENPP1 相關蛋白。ENPP1 蛋白包括形成同型二聚體的 II 型跨膜糖蛋白。ENPP1 蛋白的每個單體包括參與靶向質膜的短的細胞內 N 端結構域、跨膜結構域和包含數個結構域的大的細胞外區域。大的胞外區域包括 SMB1 和 SMB2 結構域，據報道它們參與 ENPP1 二聚化(Gijsbers et al., Biochem. J. 371; 2003: 321-330)。具體來說，SMB 結構域包含八個半胱胺酸殘基，每個排列成四個二硫鍵，並被證明通過共價半胱胺酸分

子間和分子內鍵介導 ENPP1 的同型二聚化。蛋白裂解多種基質，其包括核苷酸和核苷酸糖的磷酸二酯鍵以及核苷酸和核苷酸糖的焦磷酸鍵。ENPP1 蛋白的功能是將核苷酸 5'三磷酸酶水解為相應的單磷酸酯，也水解二腺苷多磷酸酯。ENPP1 蛋白在嘌呤信號傳導中發揮作用，而嘌呤信號傳導參與心血管、神經、免疫、肌肉骨骼、激素和血液學功能的調節。圖 11 顯示了人類 ENPP1 前體蛋白(NCBI 登錄號 NP_006199)的示例性胺基酸序列(SEQ ID NO: 1)。人類 ENPP1 前體蛋白在 ENPP1 的 N 端包括內源性 ENPP1 信號肽序列。本文所述的所有 ENPP1 相關多肽的胺基酸的編號基於圖 2 中提供的人類 ENPP1 前體蛋白序列的編號，除非另有特別指定。在某些實施方式中，ENPP1 前體蛋白進一步包括內源性或異源性的信號肽序列。在蛋白質水解時，信號肽序列從 ENPP1 前體蛋白中裂解出來，以提供成熟的 ENPP1 蛋白。參見，例如，Jansen et al., J Cell Sci.2005;118(Pt 14):3081-9。可與本文公開的多肽一起使用的示例性信號肽序列包括但不限於 ENPP1 信號肽序列、ENPP2 信號肽序列、ENPP7 信號肽序列及/或 ENPP5 信號肽序列。非限制性的加工(成熟)的細胞外 ENPP1 多肽序列在 SEQ ID NO: 2 中顯示。

【0161】 本領域一般都知道，ENPP1 在脊椎動物中是很保守的，其中細胞外結構域的大段序列都是實質上保守的。例如，圖 7A-7B 描繪了人類 ENPP1 細胞外結構與多種 ENPP1 直向同源物相比的多序列比對。ENPP1 與多種核苷酸三磷酸酯(如 ATP、UTP、GTP、TTP 和 CTP)、pNP-TMP、3',5'-cAMP 和 2'-3'-cGAMP 的結合也是高度保守的(例如，見 Kato et al., Proc Natl Acad Sci USA. 2012;109(42):16876-81 和 Mackenzie et al., Bone. 2012;51(5):961-8)。因此，從這些比對中，可以預測對正常 ENPP1 活性很重要的細胞外結構域的關鍵胺基酸位置，也可以預測可能容忍取代而不顯著改變正常 ENPP1 活性的胺基酸位置。因此，根據目前公開的組成物有用的具有酶活性的人類 ENPP1 多肽可以包括另一種脊椎動物 ENPP1 序列中

相應位置處的一個或多個胺基酸，或者可以包括與人類或其他脊椎動物序列中相似的殘基。在相應位置處一個或多個胺基酸的取代可以包括保守的變化或取代，其不可能改變多肽鏈的形狀或改變正常 ENPP1 活性。保守的變化或取代的實例包括用一個疏水殘基如異亮胺酸、纈胺酸、亮胺酸或甲硫胺酸替換另一個，或用一個極性殘基取代另一個，如用精胺酸取代賴胺酸，用谷胺酸取代天冬胺酸，或用穀氨醯胺取代天冬醯胺。例如，ENPP1 多肽包括源自任何已知的 ENPP1 多肽的序列的多肽，其序列與 ENPP1 多肽的序列至少有約 80%的同一性，較佳是至少 85%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%或更大的同一性。

2. ENPP1 的酶活性

【0162】 在結構和生物學特性方面在本領域中已經表徵了 ENPP1 蛋白。在某些實施方式中，本文公開的可溶性 ENPP1 蛋白包括焦磷酸酶及/或磷酸二酯酶活性。例如，在一些實施方式中，ENPP1 蛋白結合核苷酸三磷酸酯(如 ATP、UTP、GTP、TTP 和 CTP)、pNP-TMP、3',5'-cAMP 和 2'-3'-cGAMP；並將核苷酸三磷酸酯轉化為無機焦磷酸鹽[參見，例如 Kato 等，Proc Natl Acad Sci USA. 2012;109(42):16876-81; Li et al., Nat Chem Biol. 2014;10(12):1043-8; Jansen et al., Structure. 2012;20(11):1948-59；和 Onyedibe et al., Molecules. 2019;24(22)]。

【0163】 「酶活性的」或「生物活性的」ENPP1 多肽表現出焦磷酸酶及/或磷酸二酯酶活性(例如，能夠結合 ATP 及/或將其水解為 AMP 和 PPi，及/或結合 AP3a 及/或將其水解為 ATP)。例如，ENPP1 蛋白的焦磷酸酶/磷酸二酯酶結構域水解細胞外核苷酸三磷酸酯，以產生無機焦磷酸鹽(PPi)，並且一般是可溶的。這種活性可以使用以前描述的 pNP-TMP 試驗來測量(Saunders et al., 2008, Mol. Cancer Ther. 7(10):3352-62; Albright et al., 2015, Nat Comm. 6:10006)。在某些

實施方式中，可溶性 ENPP1 多肽對基質 ATP 的 k_{cat} 值大於或等於約 3.4 (±0.4)s^{-1} 酶$^{-1}$，其中 k_{cat} 是通過測量多肽水解 ATP 的速率確定的。在某些實施方式中，可溶性 ENPP1 多肽對基質 ATP 的 K_M 值小於或等於約 2 μM，其中 K_M 是通過測量多肽水解 ATP 速率確定的。除了本文的教導外，這些參考文獻也為如何生成保留一種或多種生物活性(如將核苷酸轉化為無機焦磷酸鹽)的可溶性 ENPP1 蛋白質提供了充分的指導。

3. 可溶性 ENPP1

【0164】 在一個實施方式中，本揭露內容涉及 ENPP1 劑，如但不限於 ENPP1 多肽。如本文所述，術語可溶性 ENPP1 多肽包括 ENPP1 蛋白的任何天然存在的細胞外結構域以及保留了生物活性(例如，酶活性)的其任何變體(包括突變體、片段和肽模擬物形式)。可溶性 ENPP1 多肽的實例包括，例如，ENPP1 細胞外結構域(SEQ ID NO: 2)。在某些實施方式中，可溶性 ENPP1 多肽除了 ENPP1 多肽的細胞外結構域之外，進一步包括信號序列。示例性的信號序列包括 ENPP1 多肽的原生信號序列，或來自另一種蛋白質的信號序列，如 hENPP7 信號序列。國際專利申請公開號 WO 2012/125182、WO 2014/126965、WO 2016/187408、WO 2018/027024、WO 2020206302 和 WO 2020/047520 中提供了變體可溶性 ENPP1 多肽的實例，其所有內容以其整體通過引用併入本文。

4. ENPP1 融合蛋白

【0165】 在一些實施方式中，ENPP1 多肽是融合蛋白，其包括 ENPP1 多肽結構域和一個或多個異源蛋白部分(即與 ENPP1 異源的多肽結構域)。如果胺基酸序列在 SEQ ID NO: 1 所表示的 ENPP1 的形式中沒有唯一地發現，則被理解為與 ENPP1 異源。在一些實施方式中，異源蛋白部分包括免疫球蛋白的 Fc 結構域。在一些實施方式中，免疫

球蛋白的 Fc 結構域是 IgG1 免疫球蛋白的 Fc 結構域。在某些實施方式中，可溶性 ENPP1 多肽在 C 端與人類免疫球蛋白 1 (IgG1)、人類免疫球蛋白 2 (IgG2)、人類免疫球蛋白 3 (IgG3)及/或人類免疫球蛋白 4 (IgG4)的 Fc 結構域融合。在其他實施方式中，可溶性 ENPP1 多肽在 N 端與人類免疫球蛋白 1 (IgG1)、人類免疫球蛋白 2 (IgG2)、人類免疫球蛋白 3 (IgG3)及/或人類免疫球蛋白 4 (IgG4)的 Fc 結構域融合。在一些實施方式中，Fc 結構域的存在改善了半衰期、可溶性、減少了免疫原性，並增加了可溶性 ENPP1 多肽的活性。在某些實施方式中，原生人類 IgG 蛋白的部分(IgG1、IgG2、IgG3 和 IgG4)可用於 Fc 部分(例如 ENPP1-Fc)。例如，本揭露內容提供的融合蛋白包括與包含免疫球蛋白恒定結構域的多肽融合的 ENPP1，所述恒定結構域例如源自人類 IgG1、IgG2、IgG3 及/或 IgG4 的 CH1、CH2 或 CH3 結構域。Fc 片段可包括原生 IgG 的區域，如鉸鏈區(根據 Rabat 編號系統，人類 IgG1 的殘基 216-230)、整個第二恒定結構域 CH2(殘基 231-340)和第三恒定結構域 CH3(殘基 341-447)。如本文所用，術語「ENPP1-Fc 構建體」是指 ENPP1 的可溶性形式(例如，ENPP1 多肽的細胞外結構域)，其與 IgG 分子(較佳為人類 IgG)的 FcR 結合結構域重組融合及/或化學綴合(包括共價和非共價綴合)。在某些實施方式中，ENPP1 的 C 端與 FcR 結合結構域的 N 端融合或綴合。

【0166】 可用於人類 IgG1 的 Fc 部分(G1Fc)的胺基酸序列的實例是 SEQ ID NO: 6 (表 1)。部分地，本揭露內容提供了包括以下、基本由以下組成或由以下組成的多肽：與 SEQ ID NO: 6 具有 70%、75%、80%、85%、86%、87%、88%、89%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%或 100%同一性的胺基酸序列。

【0167】 在一些實施方式中，異源蛋白部分包括選自以下的一個或多個結構域：聚組胺酸、FLAG 標籤、Glu-Glu、谷胱甘肽 S-轉移酶(GST)、硫氧還蛋白、蛋白 A、蛋白 G、免疫球蛋白重鏈恒定區(Fc)、麥芽糖結合蛋白(MBP)或人類血清白蛋白。融合結構域可以被選擇，以

賦予所期望的性質。例如，一些融合結構域對通過親和層析分離融合蛋白特別有用。為了親和純化的目的，使用相關的親和層析基質，如谷胱甘肽、澱粉酶、鎳或鈷綴合的樹脂。許多這樣的基質以「套組」形式提供，如 Pharmacia GST 純化系統和 QIAexpress™ 系統(Qiagen)，可供(HIS_6)融合伴侶使用。作為另一個實例，可以選擇融合結構域，以促進 ENPP1 多肽的檢測。這種檢測結構域的實例包括多種熒光蛋白(如 GFP)以及「表位標籤」，這通常是短肽序列，特異性抗體對其是可用的。特異性單株抗體可容易可用的熟知的表位標籤包括 FLAG、流感病毒血凝素(HA)和 c-myc 標籤。在一些實施方式中，融合結構域具有蛋白酶裂解位點，例如因子 Xa 或凝血酶，這使得相關的蛋白酶部分地消化融合蛋白，從而將重組蛋白從其中釋放出來。然後，通過隨後的層析分離，可以將釋放的蛋白質從融合結構域中分離出來。

5. 連接子

【0168】 在一些實施方式中，ENPP1 融合蛋白進一步包括定位在 ENPP1 多肽結構域和一個或多個異源蛋白部分(例如，Fc 免疫球蛋白結構域)之間的連接子(Z)。在某些實施方式中，可溶性 ENPP1 多肽直接或間接地與 Fc 結構域融合。在一些實施方式中，可溶性 ENPP1 融合蛋白包括 Fc 結構域和 ENPP1 多肽之間的連接子。在一些實施方式中，連接子可以是包括 1-200 個胺基酸的胺基酸間隔區。合適的肽間隔區是本領域已知的，例如包括含有撓性胺基酸殘基如甘胺酸、丙胺酸和絲胺酸的肽連接子。

【0169】 在一些實施方式中，連接子包括聚甘胺酸連接子或 Gly-Ser 連接子。在一些實施方式中，間隔區可包含下述的基序，例如多個或重複基序：GA (SEQ ID NO: 21)、GS (SEQ ID NO: 22)、GG (SEQ ID NO: 23)、GGA (SEQ ID NO: 24)、GGS (SEQ ID NO: 25)、GGG (SEQ ID NO: 26)、GGGA (SEQ ID NO: 27)、GGGS (SEQ ID NO: 28)、GGGG (SEQ ID NO: 29)、GGGGA (SEQ ID NO: 30)、GGGGS

(SEQ ID NO: 31)、GGGGG (SEQ ID NO: 32)、GGAG (SEQ ID NO: 33)、GGSG (SEQ ID NO: 34)、AGGG (SEQ ID NO: 35)、SGGGG (SEQ ID NO: 36)或 SGGG (SEQ ID NO: 37)。在一些實施方式中，間隔區可包含 2 至 12 個胺基酸，包括 GA 或 GS 的基序，例如 GA、GS、GAGA (SEQ ID NO: 38)、GSGS (SEQ ID NO: 39)、GAGAGA (SEQ ID NO: 40)、GSGSGS (SEQ ID NO: 41)、GAGAGAGA (SEQ ID NO: 42)、GSGSGSGS (SEQ ID NO: 43)、GAGAGAGAGA (SEQ ID NO: 44)、GSGSGSGSGS (SEQ ID NO: 45)、GAGAGAGAGAGA (SEQ ID NO: 46)和 GSGSGSGSGSGS (SEQ ID NO: 47)。在一些實施方式中，間隔區可包含 3 至 12 個胺基酸，包括 GGA 或 GGS 的基序，例如 GGA、GGS、GGAGGA (SEQ ID NO: 48)、GGSGGS (SEQ ID NO: 49)、GGAGGAGGA (SEQ ID NO: 50)、GGSGGSGGS (SEQ ID NO: 51)、GGAGGAGGAGGA (SEQ ID NO: 52)和 GGSGGSGGSGGS (SEQ ID NO: 53)。在還有一些實施方式中，間隔區可包含 4 至 12 個胺基酸，包括 GGAG (SEQ ID NO: 54)、GGSG (SEQ ID NO: 55)的基序，例如 GGAG (SEQ ID NO: 56)、GGSG (SEQ ID NO: 57)、GGAGGGAG (SEQ ID NO: 58)、GGSGGGSG (SEQ ID NO: 59)、GGAGGGAGGGAG (SEQ ID NO: 60)和 GGSGGGSGGGSG (SEQ ID NO: 61)。在一些實施方式中，間隔區可包含 GGGGA (SEQ ID NO: 62)或 GGGGS (SEQ ID NO: 63)的基序，例如 GGGGAGGGGAGGGGA (SEQ ID NO: 64)和 GGGGSGGGGSGGGGS (SEQ ID NO: 65)。在本發明的一些實施方式中，異源蛋白部分(例如，Fc 結構域單體、野生型 Fc 結構域、具有胺基酸取代的 Fc 結構域(例如，可減少二聚化的一個或多個取代)、白蛋白結合肽、纖連蛋白結構域或人類血清白蛋白))和可溶性 ENPP1 多肽之間的胺基酸間隔區可以是 GGG、GGGA (SEQ ID NO: 27)、GGGG (SEQ ID NO: 29)、GGGAG (SEQ ID NO: 66)、GGGAGG (SEQ ID NO: 67)或 GGGAGGG (SEQ ID NO: 68)。

【0170】 在一些實施方式中，間隔區也可包含除甘胺酸、丙胺酸和絲胺酸以外的胺基酸，例如，LIN (SEQ ID NO: 69)、TGGGG (SEQ ID NO: 70)、AAAL (SEQ ID NO: 71)、AAAK (SEQ ID NO: 72)、AAAR (SEQ ID NO: 73)、EGKSSGSGSESKST (SEQ ID NO: 74)、GSAGSAAGSGEF (SEQ ID NO: 75)、AEAAAKEAAAKA (SEQ ID NO: 76)、KESGSVSSEQLAQFRSLD (SEQ ID NO: 77)、GENLYFQSGG (SEQ ID NO: 78)、SACYCELS (SEQ ID NO: 79)、RSIAT (SEQ ID NO: 80)、RPACKIPNDLKQKVMNH (SEQ ID NO: 81)、GGSAGGSGSGSSGGSSGASGTGTAGGTGSGSGTGSG (SEQ ID NO: 82)、AAANSSIDLISVPVDSR (SEQ ID NO: 83)、GGSGGGSEGGGSEGGGSEGGGSEGGGSEGGGSGGGS (SEQ ID NO: 84)、NSS (SEQ ID NO: 87)、ESS (SEQ ID NO: 88)、RQQ (SEQ ID NO: 89)、KR (SEQ ID NO: 90)、$(R)_m$; m=0-15 (SEQ ID NO: 91)、DSSSEEKFLRRIGRFG (SEQ ID NO: 92)、EEEEEEEPRGDT (SEQ ID NO: 93)、APWHLSSQYSRT (SEQ ID NO: 94)、STLPIPHEFSRE (SEQ ID NO: 95)、VTKHLNQISQSY (SEQ ID NO: 96)、$(E)_m$; m=1-15 (SEQ ID NO: 97)、RSGSGGS (SEQ ID NO: 98)、$(D)_m$; m=1-15 (SEQ ID NO: 99)、LVIMSLGLGLGLGLRK (SEQ ID NO: 100)、VIMSLGLGLGLGLRK (SEQ ID NO: 101)、IMSLGLGLGLGLRK (SEQ ID NO: 102)、MSLGLGLGLGLRK (SEQ ID NO: 103)、SLGLGLGLGLRK (SEQ ID NO: 104)、LGLGLGLGLRK (SEQ ID NO: 105)、GLGLGLGLRK (SEQ ID NO: 106)、LGLGLGLRK (SEQ ID NO: 107)、GLGLGLRK (SEQ ID NO: 108)、LGLGLRK (SEQ ID NO: 109)、GLGLRK (SEQ ID NO: 110)、LGLRK (SEQ ID NO: 111)、GLRK (SEQ ID NO: 112)、LRK (SEQ ID NO: 113)、RK (SEQ ID NO: 114)或$(K)_m$; m=1-15 (SEQ ID NO: 115)。在一些實施方式中，間隔區可包含 EAAAK (SEQ ID NO: 85)的基序，例如多個或重複的基序。在一些實施方式中，間隔區可包含富含

堅果糖序列的基序，例如多個或重複的基序，所述富含堅果糖序列例如(XP)n，其中 X 可以是任何胺基酸(例如 A、K 或 E)，n 是 1-5，以及 PAPAP(SEQ ID NO: 86)。

【0171】 肽間隔區的長度和使用的胺基酸可以根據所涉及的兩種蛋白質和最終蛋白質融合多肽所需的撓性程度來調整。間隔區的長度可以調整，以確保適當的蛋白質折疊並避免聚集體形成。

【0172】 在一些實施方式中，融合蛋白(如免疫球蛋白 Fc 融合蛋白)的不同元件可以以與所期望功能一致的任何方式排列。例如，可溶性 ENPP1 多肽結構域可以置於異源蛋白部分的 C 端，或可選的，異源蛋白部分可以置於可溶性 ENPP1 多肽結構域的 C 端。可溶性 ENPP1 多肽結構域和異源蛋白部分可以直接或間接地連接在融合蛋白中，另外的結構域或胺基酸序列可以包括在任一結構域的 C 端或 N 端或結構域之間。較佳的融合蛋白包括 SEQ ID NO: 3-5 中任何一個列出的胺基酸序列。

【0173】 在一些實施方式中，本揭露內容的可溶性 ENPP1 多肽含有一個或多個異源部分。任選地，可溶性 ENPP1 多肽包括選自以下的一個或多個異源部分：糖基化的胺基酸、PEG 化的胺基酸、法尼基化的胺基酸、乙醯化的胺基酸、生物素化的胺基酸、與脂質部分綴合的胺基酸和與有機衍生劑綴合的胺基酸。在一些實施方式中，本文公開的可溶性 ENPP1 多肽被進一步修飾。這種修飾包括但不限於乙醯化、羧化、糖基化、磷酸化、脂化和醯化。因此，可溶性 ENPP1 多肽可能含有非胺基酸元件，如聚乙二醇、脂類、多糖或單糖和磷酸鹽。這種非胺基酸元件對可溶性 ENPP1 多肽功能的影響可按本文對其他可溶性 ENPP1 多肽的描述進行測試。當本揭露內容的多肽在細胞中通過裂解多肽的新生形式產生時，翻譯後加工對於蛋白質的正確折疊及/或功能也可能是重要的。不同的細胞(如 CHO、HeLa、MDCK、293、WI38、NIH-3T3 或 HEK293)對這種翻譯後活性有特定的細胞機器和特徵機構，可選擇不同的細胞以確保可溶性 ENPP1 多肽的正確修飾和加工。

【0174】 如本文所用，多肽序列和參考序列之間的「同一性」百分比定義為在比對序列並引入間隙(如果有必要的話)以達到最大的序列同一性百分比之後，多肽序列中與參考序列中的胺基酸殘基相同的胺基酸殘基的百分比。為確定胺基酸序列同一性百分比的目的而進行的比對可以通過本領域技術人員的多種方式實現，例如，使用公開可得的計算機軟件，例如 BLAST、BLAST-2、ALIGN、MEGALIGN (DNASTAR)、CLUSTALW 或 CLUSTAL OMEGA 軟件。在一些實施方式中，使用 CLUSTAL OMEGA 軟件進行比對。本領域的技術人員可以確定比對序列的適當參數，包括在被比較的序列的全長上實現最大的比對所需的任何算法。

6. 確定可溶性

【0175】 在一些實施方式中，可溶性 ENPP1 多肽的活性也可以在基於細胞或體內的試驗中進行測試。例如，可以測量可溶性 ENPP1 多肽對無機焦磷酸鹽(PPi)產生的影響。具體來說，ENPP1 蛋白的焦磷酸酶/磷酸二酯酶結構域水解細胞外核苷酸三磷酸酯以產生無機焦磷酸鹽(PPi)，並且通常是可溶的。這種活性可以使用 pNP-TMP 試驗以及基於 HPLC 的 ATP 水解試驗來測量，如前所述(Saunders et al., Mol. Cancer Ther. 7(10):3352-62; Albright et al., 2015, Nat Comm. 6:10006)。可以評估可溶性 ENPP1 多肽對參與 ENPP1 相關疾病例如 ARHR2 的基因表現的影響(例如成纖維細胞生長因子 23 在成骨細胞和破骨細胞的轉錄)。這可以根據需要在一種或多種核苷酸三磷酸酯或其他 ENPP1 基質的存在下進行，細胞可以被轉染以便產生可溶性 ENPP1 多肽。同樣，可溶性 ENPP1 多肽可被施用至小鼠或其他動物，並且對 ENPP1 相關疾病的影響可使用本領域公認的方法進行評估。

【0176】 在一些實施方式中，根據本文所述方法使用的 ENPP1 多肽是分離的多肽。如本文所用，分離的蛋白質或多肽是指已經與其自然環境的組分分開的蛋白質或多肽。在一些實施方式中，本發明內容的多

肽被純化到大於 95%、96%、97%、98%或 99%的純度，如通過例如電泳(例如 SDS-PAGE、等電聚焦(IEF)、毛細管電泳)或層析(例如離子交換或反相 HPLC)分析確定的。評估純度的方法在本領域是熟知的[參見，例如，Flatman et al., 2007, J. Chromatogr. B 848:79-87]。在一些實施方式中，根據本文所述的方法使用的可溶性 ENPP1 多肽是重組多肽。

7. ENPP1 生產

【0177】 本揭露內容的 ENPP1 多肽可以通過多種本領域已知的技術生產。例如，可以使用標準的蛋白質化學技術合成本揭露內容的多肽，如 Bodansky, Principles of Peptide Synthesis, Springer Verlag, Berlin (1993)和 Grant G. A. (ed.), Synthetic Peptides: A User's Guide, W. H. Freeman and Company, New York (1992)中描述的。此外，自動多肽合成儀是商業上可購的(例如 Advanced ChemTech Model 396；Milligen/Biosearch 9600)。可選地，本揭露內容的多肽，包括其片段或變體，可以使用多種表現系統[例如大腸桿菌、中國倉鼠卵巢(CHO)細胞、COS 細胞、杆狀病毒、畢赤酵母]重組生產，這在本領域是熟知的。該蛋白可以在貼壁細胞或懸浮細胞中生產。在一些實施方式中，融合蛋白在 CHO 細胞中表現。為了建立穩定的細胞系，將編碼 ENPP1 構建體的核酸序列選殖到適當的載體中，以用於大規模的蛋白質生產。在某些實施方式中，可通過使用例如蛋白酶，例如胰蛋白酶、嗜熱菌蛋白酶、糜蛋白酶、胃蛋白酶或配對鹼性胺基酸轉化酶(PACE)消化重組產生的全長 ENPP1 多肽來生產本揭露內容的修飾的或未修飾的多肽。計算機分析(使用商業上可售的軟件，例如 MacVector, Omega, PCGene, Molecular Simulation, Inc.)可以用來鑒定蛋白酶水解裂解位點。可選地，這種多肽可以使用化學裂解法(例如溴化氰、羥胺等)從重組生成的全長 ENPP1 多肽中產生。

8. 表現系統

【0178】 已知許多表現系統並且可用於生產 ENPP1 融合蛋白，包括細菌(例如大腸桿菌和枯草芽孢桿菌)、酵母(例如釀酒酵母、乳酸克魯維酵母和巴斯德畢赤酵母)、絲狀真菌(例如麴黴)、植物細胞、動物細胞和昆蟲細胞。所期望的蛋白質可以以常規方式產生，例如從插入宿主染色體中或游離質體上的編碼序列產生。

【0179】 可以用任何通常的方式(例如電穿孔)，用期望蛋白質的編碼序列轉化酵母。通過電穿孔轉化酵母的方法在 Becker 和 Guarente，1990，Methods Enzymol. 194:182 中公開。成功轉化的細胞，即含有本揭露內容的 DNA 構建體的細胞，可以通過熟知的技術進行鑒定。例如，引入表現構建體所產生的細胞可以生長以生產 ENPP1 多肽。可以收穫細胞並進行裂解，並使用諸如 Southern，1975，J. Mol. Biol. 98:503 及/或 Berent et al., 1985，Biotech 3:208 中描述的方法檢查細胞的 DNA 含量，以檢測 DNA 的存在。可選地，可以使用抗體檢測上清液中蛋白質的存在。

【0180】 有用的酵母質體載體包括 pRS403-406 和 pRS413-416，並且通常可從 Stratagene Cloning Systems, La Jolla, CA, USA 獲得。質體 pRS403、pRS404、pRS405 和 pRS406 是酵母整合質體(Yip)，並且併入了酵母選擇性標記 I-11S3、TRP1、LEU2 和 IJRA3。質體 pRS413-416 是酵母著絲粒質體(Yeast Centromere plasmid，YCp)。

【0181】 已經開發了多種方法來通過互補的粘性末端將 DNA 與載體可操作地連接。例如，可以將互補的均聚物束(homopolymer tract)添加到 DNA 區段中以插入到載體 DNA 中。然後通過互補的均聚物尾之間的氫鍵將載體和 DNA 區段連接起來以形成重組 DNA 分子。

【0182】 含有一個或多個限制性位點的合成連接子提供了將 DNA 區段連接到載體的可選方法。通過內切核酸酶限制性消化生成的 DNA 區段用噬菌體 T4 DNA 聚合酶或大腸桿菌 DNA 聚合酶 I 處理，這些酶是去除具有其 3'-5'-外切核酸酶活性的突出的 3'-單鏈末端，並利用其聚合活性填充凹入的 3'-末端的酶。

【0183】 這些活性的組合因此生成了平端 DNA 區段。然後在能夠催化平端 DNA 分子的連接的酶(例如，噬菌體 T4 DNA 連接酶)的存在下，將平端區段與大量莫耳過量的連接子分子一起培養。結果是，反應的產物是在其末端帶有聚合連接子序列的 DNA 區段。這些 DNA 區段可以用適當的限制性內切酶裂解，並連接至表現載體，該表現載體已被產生與 DNA 區段末端相容的末端的酶裂解。

【0184】 然後建立單個穩定轉染的細胞的殖株，並篩選期望 ENPP1 融合蛋白的高表現殖株。可以在 96 孔板中以高通量方式使用如前所述的合成酶基質 pNP-TMP (Albright et al., 2015，Nat. Commun. 6:10006)完成篩選 ENPP1 蛋白表現的單細胞殖株。通過篩選鑒定高表現殖株後，蛋白質生產可以在搖瓶或生物反應器中完成，如在 Albright et al., 2015, Nat. Commun. 6:10006 中描述的。

9. ENPP1 純化

【0185】 ENPP1 的純化可以使用本領域已知的標準純化技術組合來完成。純化後，可以將 ENPP1-Fc 透析至補充有 Zn^{2+}和 Mg^{2+}的濃縮至 5 和 7 mg/ml 之間的 PBS (PBSplus)，並以 200-500 pl 的等分試樣在-80℃下冷凍。就在使用前可以將等分部分融化，並通過在 PBSplus 中稀釋可以將溶液的比活性調節至 31.25 au/ml (或約 0.7 mg/ml，這取決於製劑)。

10. 施用途徑和頻率

【0186】 多肽可以急性或慢性地施用至受試者。在某些實施方式中，在大約兩天后、四天后、一週後或一個月後的適當時間間隔後對受試者施用本文公開的可溶性 ENPP1 多肽或 ENPP1 融合多肽的第二劑量，或甚至更少的頻率，如每幾個月一次或甚至一年一次或更少。劑量的頻率對技術人員來說是顯而易見的，並取決於任何數量的因素，例如，但不限於，被治療疾病的類型和嚴重程度，以及患者的類型和年齡。

【0187】 可以選擇劑量的量或頻率以使血漿 PPi 的穩態水平保持在恒定或穩態水平，及/或使血漿 PPi 的持續水平接近正常 PPi 水平(2-3 μM)或高於正常 PPi 水平(比其高 30-50%)，並且不返回到受試者在施用本文公開的第一劑量構建體之前的較低 PPi 水平。

【0188】 可選地，ENPP1 劑可以以每 2 天，或每 4 天，每週或每月的適當時間間隔施用，以達到 ENPP1 的酶活性的恒定水平。

【0189】 可選地，通過監測受試者的疾病或障礙的一個或多個症狀，以每 2 天、或每 4 天、或每週或每月的適當時間間隔施用根據本揭露內容的 ENPP1 劑。

【0190】 在不希望受理論約束的情況下，相信將血漿 PPi 的穩態濃度維持在正常水平減少及/或預防受試者的病理性鈣化的進展。

【0191】 在某些實施方式中，多肽被局部、區域、腸胃外或全身地施用至受試者。在一些實施方式中，多肽被皮下施用。

【0192】 如本文所用，製劑的「腸胃外施用」包括特徵在於以受試者組織的物理破壞和通過組織中的該破壞施用 ENPP1 劑的任何施用途徑。因此，腸胃外施用包括但不限於通過注射組成物、通過手術切口施加組成物、通過穿透組織的非手術傷口施加組成物等來施用 ENNP1 劑。具體地，考慮腸胃外施用包括但不限於皮下、靜脈內、腹膜內、肌內、胸骨內(intrastemal)注射和腎透析輸注技術。

【0193】 施用方案可能會影響有效量的構成。例如，可以在一個給定的時間段(每天)或依次施用幾個分割的劑量以及交錯的劑量，也可以連續輸注劑量，或可以是彈丸注射。此外，ENPP1 劑的所述劑量的選擇可通過治療或預防情況的緊迫性來指示。

【0194】 對患者，例如哺乳動物(即人類)施用本揭露內容的組成物(例如可溶性 ENPP1 多肽及其融合蛋白)，可使用已知的程序，以有效來治療患者的疾病或障礙的劑量和時間段來進行。為達到治療效果所需的 ENPP1 劑的所述劑量的有效量可根據以下因素而變化，例如所採用的具體化合物的活性；施用時間；化合物的排泄率；治療持續時間；與

化合物組合使用的其他藥物、化合物或材料；被治療的患者的疾病或障礙狀態、年齡、性別、體重、狀況、一般健康情況和先前的病史，以及醫學領域中熟知的類似因素。可以調整劑量方案以提供最佳的治療反應。選定劑量是基於治療性化合物的生物活性來確定的，而生物活性又取決於半衰期和治療性化合物曲線的血漿時間下面積。

11. 預防性施用

【0195】 通過本文公開內容，本領域的技術人員將理解，預防受試者的疾病或障礙包括向受試者施用 ENPP1 多肽作為疾病或障礙的預防性措施。

【0196】 活性成分(例如，可溶性 ENPP1 多肽及其融合蛋白)、醫藥上可接受的載劑以及本文公開的製劑中的任何另外的成分的相對數量將有所不同，這取決於被治療的受試者的身份、大小和病症，並進一步取決於組成物被施用的途徑。舉例來說，組成物可包括約 0.1%至約 100% (w/w)之間的活性成分。

12. ENPP1 多肽序列

表 1: 序列

SEQ ID NO	序列	描述
1	1 MERDGCAGGG SRGGEGGRAP REGPAGNGRD RGRSHAAEAP GDPQAAASLL 51 APMDVGEEPL EKAARARTAK DPNTYKVLSL VLSVCVLTTI LGCIFGLKPS 101 CAKEVKSCKG RCFERTFGNC RCDAACVELG NCCLDYQETC IEPEHIWTCN 151 KFRCGEKRLT RSLCACSDDC KDKGDCCINY SSVCQGEKSW VEEPCESINE 201 PQCPAGFETP PTLLFSLDGF RAEYLHTWGG LLPVISKLKK CGTYTKNMRP 251 VYPTKTFPNH YSIVTGLYPE SHGIIDNKMY DPKMNASFSL KSKEKFNPEW 301 YKGEPIWVTA KYQGLKSGTF FWPGSDVEIN GIFPDIYKMY NGSVPFEERI 351 LAVLQWLQLP KDERPHFYTL YLEEPDSSGH SYGPVSSEVI KALQRVDGMV 401 GMLMDGLKEL NLHRCLNLIL ISDHGMEQGS CKKYIYLNKY LGDVKNIKVI 451 YGPAARLRPS DVPDKYYSFN YEGIARNLSC REPNQHFKPY LKHFLPKRLH 501 FAKSDRIEPL TFYLDPQWQL ALNPSERKYC GSGFHGSDNV FSNMQALFVG 551 YGPGFKHGIE ADTFENIEVY NLMCDLLNLT PAPNNGTHGS LNHLLKNPVY 601 TPKHPKEVHP LVQCPFTRNP RDNLGCSCNP SILPIEDFQT QFNLTVAEEK 651 IIKHETLPYG RPRVLQKENT ICLLSQHQFM SGYSQDILMP LWTSYTVDRN 701 DSFSTEDFSN CLYQDFRIPL SPVHKCSFYK NNTKVSYGFL SPPQLNKNSS 751 GIYSEALLTT NIVPMYQSFQ VIWRYFHDTL LRKYAEERNG VNVVSGPVFD 801 FDYDGRCDSL ENLRQKRRVI RNQEILIPTH FFIVLTSCKD TSQTPLHCEN 851 LDTLAFILPH RTDNSESCVH GKHDSSWVEE LLMLHRARIT DVEHITGLSF 901 YQQRKEPVSD ILKLKTHLPT FSQED	野生型 ENPP1 前體蛋白的完全的、未加工的胺基酸序列

2	1 PSCAKEVKSC KGRCFERTFG NCRCDAACVE LGNCCLDYQE TCIEPEHIWT 51 CNKFRCGEKR LTRSLCACSD DCKDKGDCCI NYSSVCQGEK SWVEEPCESI 101 NEPQCPAGFE TPPTLLFSLD GFRAEYLHTW GGLLPVISKL KKCGTYTKNM 151 RPVYPTKTFP NHYSIVTGLY PESHGIIDNK MYDPKMNASF SLKSKEKFNP 201 EWYKGEPIWV TAKYQGLKSG TFFWPGSDVE INGIFPDIYK MYNGSVPFEE 251 RILAVLQWLQ LPKDERPHFY TLYLEEPDSS GHSYGPVSSE VIKALQRVDG 301 MVGMLMDGLK ELNLHRCLNL ILISDHGMEQ GSCKKYIYLN KYLGDVKNIK 351 VIYGPAARLR PSDVPDKYYS FNYEGIARNL SCREPNQHFK PYLKHFLPKR 401 LHFAKSDRIE PLTFYLDPQW QLALNPSERK YCGSGFHGSD NVFSNMQALF 451 VGYGPGFKHG IEADTFENIE VYNLMCDLLN LTPAPNNGTH GSLNHLLKNP 501 VYTPKHPKEV HPLVQCPFTR NPRDNLGCSC NPSILPIEDF QTQFNLTVAE 551 EKIIKHETLP YGRPRVLQKE NTICLLSQHQ FMSGYSQDIL MPLWTSYTVD 601 RNDSFSTEDF SNCLYQDFRI PLSPVHKCSF YKNNTKVSYG FLSPPQLNKN 651 SSGIYSEALL TTNIVPMYQS FQVIWRYFHD TLLRKYAEER NGVNVVSGPV 701 FDFDYDGRCD SLENLRQKRR VIRNQEILIP THFFIVLTSC KDTSQTPLHC 751 ENLDTLAFIL PHRTDNSESC VHGKHDSSWV EELLMLHRAR ITDVEHITGL 801 SFYQQRKEPV SDILKLKTHL PTFSQED	加工的(成熟的)細胞外ENPP1多肽序列
3	FTAGLKPSCAKEVKSCKGRCFERTFGNCRCDAACVELGNCCLDYQETCIEPEHIWTCNKF RCGEKRLTRSLCACSDDCKDKGDCCINYSSVCQGEKSWVEEPCESINEPQCPAGFETPPT LLFSLDGFRAEYLHTWGGLLPVISKLKKCGTYTKNMRPVYPTKTFPNHYSIVTGLYPESH GIIDNKMYDPKMNASFSLKSKEKFNPEWYKGEPIWVTAKYQGLKSGTFFWPGSDVEINGI FPDIYKMYNGSVPFEERILAVLQWLQLPKDERPHFYTLYLEEPDSSGHSYGPVSSEVIKA LQRVDGMVGMLMDGLKELNLHRCLNLILISDHGMEQGSCKKYIYLNKYLGDVKNIKVIYG PAARLRPSDVPDKYYSFNYEGIARNLSCREPNQHFKPYLKHFLPKRLHFAKSDRIEPLTF YLDPQWQLALNPSERKYCGSGFHGSDNVFSNMQALFVGYGPGFKHGIEADTFENIEVYNL MCDLLNLTPAPNNGTHGSLNHLLKNPVYTPKHPKEVHPLVQCPFTRNPRDNLGCSCNPSI LPIEDFQTQFNLTVAEEKIIKHETLPYGRPRVLQKENTICLLSQHQFMSGYSQDILMPLW TSYTVDRNDSFSTEDFSNCLYQDFRIPLSPVHKCSFYKNNTKVSYGFLSPPQLNKNSSGI YSEALLTTNIVPMYQSFQVIWRYFHDTLLRKYAEERNGVNVVSGPVFDFDYDGRCDSLEN LRQKRRVIRNQEILIPTHFFIVLTSCKDTSQTPLHCENLDTLAFILPHRTDNSESCVHGK HDSSWVEELLMLHRARITDVEHITGLSFYQQRKEPVSDILKLKTHLPTFSQEDLIN**DKTH** **TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV** **HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR** **EPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF** **FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK**	ENPP1-連接子-hIgG1 Fc構建體
4	GLKPSCAKEVKSCKGRCFERTFGNCRCDAACVELGNCCLDYQETCIEPEHIWTCNKFRCG EKRLTRSLCACSDDCKDKGDCCINYSSVCQGEKSWVEEPCESINEPQCPAGFETPPTLLF SLDGFRAEYLHTWGGLLPVISKLKKCGTYTKNMRPVYPTKTFPNHYSIVTGLYPESHGII DNKMYDPKMNASFSLKSKEKFNPEWYKGEPIWVTAKYQGLKSGTFFWPGSDVEINGIFPD IYKMYNGSVPFEERILAVLQWLQLPKDERPHFYTLYLEEPDSSGHSYGPVSSEVIKALQR VDGMVGMLMDGLKELNLHRCLNLILISDHGMEQGSCKKYIYLNKYLGDVKNIKVIYGPAA RLRPSDVPDKYYSFNYEGIARNLSCREPNQHFKPYLKHFLPKRLHFAKSDRIEPLTFYLD PQWQLALNPSERKYCGSGFHGSDNVFSNMQALFVGYGPGFKHGIEADTFENIEVYNLMCD LLNLTPAPNNGTHGSLNHLLKNPVYTPKHPKEVHPLVQCPFTRNPRDNLGCSCNPSILPI EDFQTQFNLTVAEEKIIKHETLPYGRPRVLQKENTICLLSQHQFMSGYSQDILMPLWTSY TVDRNDSFSTEDFSNCLYQDFRIPLSPVHKCSFYKNNTKVSYGFLSPPQLNKNSSGIYSE ALLTTNIVPMYQSFQVIWRYFHDTLLRKYAEERNGVNVVSGPVFDFDYDGRCDSLENLRQ KRRVIRNQEILIPTHFFIVLTSCKDTSQTPLHCENLDTLAFILPHRTDNSESCVHGKHDS SWVEELLMLHRARITDVEHITGLSFYQQRKEPVSDILKLKTHLPTFSQEDLIN**DKTHTCP** **PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA** **KTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ** **VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY** **SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK**	ENPP1-連接子-hIgG1 Fc構建體
5	PSCAKEVKSCKGRCFERTFGNCRCDAACVELGNCCLDYQETCIEPEHIWTCNKFRCGEKR LTRSLCACSDDCKDKGDCCINYSSVCQGEKSWVEEPCESINEPQCPAGFETPPTLLFSLD GFRAEYLHTWGGLLPVISKLKKCGTYTKNMRPVYPTKTFPNHYSIVTGLYPESHGIIDNK MYDPKMNASFSLKSKEKFNPEWYKGEPIWVTAKYQGLKSGTFFWPGSDVEINGIFPDIYK MYNGSVPFEERILAVLQWLQLPKDERPHFYTLYLEEPDSSGHSYGPVSSEVIKALQRVDG MVGMLMDGLKELNLHRCLNLILISDHGMEQGSCKKYIYLNKYLGDVKNIKVIYGPAARLR PSDVPDKYYSFNYEGIARNLSCREPNQHFKPYLKHFLPKRLHFAKSDRIEPLTFYLDPQW QLALNPSERKYCGSGFHGSDNVFSNMQALFVGYGPGFKHGIEADTFENIEVYNLMCDLLN LTPAPNNGTHGSLNHLLKNPVYTPKHPKEVHPLVQCPFTRNPRDNLGCSCNPSILPIEDF QTQFNLTVAEEKIIKHETLPYGRPRVLQKENTICLLSQHQFMSGYSQDILMPLWTSYTVD RNDSFSTEDFSNCLYQDFRIPLSPVHKCSFYKNNTKVSYGFLSPPQLNKNSSGIYSEALL TTNIVPMYQSFQVIWRYFHDTLLRKYAEERNGVNVVSGPVFDFDYDGRCDSLENLRQKRR VIRNQEILIPTHFFIVLTSCKDTSQTPLHCENLDTLAFILPHRTDNSESCVHGKHDSSWV EELLMLHRARITDVEHITGLSFYQQRKEPVSDILKLKTHLPTFSQEDLIN**DKTHTCPPCP**	ENPP1-連接子-hIgG1 Fc構建體

	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYT LPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	
6	DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	人類 IgG1 Fc
118	X- PSCAKEVKSCKGRCFERTFGNCRCDAACVELGNCCLDYQETCIEPEHIWTCNKFRCGEKR LTRSLCACSDDCKDKGDCCINYSSVCQGEKSWVEEPCESINEPQCPAGFETPPTLLFSLD GFRAEYLHTWGGLLPVISKLKKCGTYTKNMRPVYPTKTFPNHYSIVTGLYPESHGIIDNK MYDPKMNASFSLKSKEKFNPEWYKGEPIWVTAKYQGLKSGTFFWPGSDVEINGTFPDIYK MYNGSVPFEERILAVLQWLQLPKDERPHFYTLYLEEPDSSGHSYGPVSSEVIKALQRVDG MVGMLMDGLKELNLHRCLNLILISDHGMEQGSCKKYIYLNKYLGDVKNIKVIYGPAARLR PSDVPDKYYSFNYEGIARNLSCREPNQHFKPYLKHFLPKRLHFAKSDRIEPLTFYLDPQW QLALNPSERKYCGSGFHGSDNVFSNMQALFVGYGPGFKHGIEADTFENIEVYNLMCDLLN LTPAPNNGTHGSLNHLLKNPVYTPKHPKEVHPLVQCPFTRNPRDNLGCSCNPSILPIEDF QTQFNLTVAEEKIIKHETLPYGRPRVLQKENTICLLSQHQFMSGYSQDILMPLWTSYTVD RNDSFSTEDFSNCLYQDFRIPLSPVHKCSFYKNNTKVSYGFLSPPQLNKNSSGIYSEALL TTNIVPMYQSFQVIWRYFHDTLLRKYAEERNGVNVVSGPVFDFDYDGRCDSLENLRQKRR VIRNQEILIPTHFFIVLTSCKDTSQTPLHCENLDTLAFILPHRTDNSESCVHGKHDSSWV EELLMLHRARITDVEHITGLSFYQQRKEPVSDILKLKTHLPTFSQED**RSDKTHTCPPCPA PELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK**-Y	BL-1118 (長效)
119	X- PSCAKEVKSCKGRCFERTFGNCRCDAACVELGNCCLDYQETCIEPEHIWTCNKFRCGEKR LTRSLCACSDDCKDKGDCCINYSSVCQGEKSWVEEPCESINEPQCPAGFETPPTLLFSLD GFRAEYLHTWGGLLPVISKLKKCGTYTKNMRPVYPTKTFPNHYSIVTGLYPESHGIIDNK MYDPKMNASFSLKSKEKFNPEWYKGEPIWVTAKYQGLKSGTFFWPGSDVEINGIFPDIYK MYNGSVPFEERILAVLQWLQLPKDERPHFYTLYLEEPDSSGHSYGPVSSEVIKALQRVDG MVGMLMDGLKELNLHRCLNLILISDHGMEQGSCKKYIYLNKYLGDVKNIKVIYGPAARLR PSDVPDKYYSFNYEGIARNLSCREPNQHFKPYLKHFLPKRLHFAKSDRIEPLTFYLDPQW QLALNPSERKYCGSGFHGSDNVFSNMQALFVGYGPGFKHGIEADTFENIEVYNLMCDLLN LTPAPNNGTHGSLNHLLKNPVYTPKHPKEVHPLVQCPFTRNPRDNLGCSCNPSILPIEDF QTQFNLTVAEEKIIKHETLPYGRPRVLQKENTICLLSQHQFMSGYSQDILMPLWTSYTVD RNDSFSTEDFSNCLYQDFRIPLSPVHKCSFYKNNTKVSYGFLSPPQLNKNSSGIYSEALL TTNIVPMYQSFQVIWRYFHDTLLRKYAEERNGVNVVSGPVFDFDYDGRCDSLENLRQKRR VIRNQEILIPTHFFIVLTSCKDTSQTPLHCENLDTLAFILPHRTDNSESCVHGKHDSSWV EELLMLHRARITDVEHITGLSFYQQRKEPVSDILKLKTHLPTFSQEDRS**DKTHTCPPCPA PELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK**-Y	BL-782

對於 SEQ ID NO:118 和 119：

X=輸出序列

Y=骨靶向標籤或終止密碼子(即沒有胺基酸，如通過*標記的)

【0197】 骨靶向序列的非限制性實例包括但不限於 DDDDDDDD 及/或 EEEEEEEE。

【0198】 非粗體、非下劃線字體=連接子區域，其可以是多種長度等。連接子的胺基酸組成可以是可變的。在某些非限制性的實施方式中，

連接子區域可以包括殘基，如組胺酸，以阻止非特異性蛋白酶裂解(即HS 或 HG 而不是 RS 或 RG)。

【0199】

粗體字體=人類 IgG1(在 BL-1118 中優化，其中 M883Y S885T T887E 突變以粗斜體字突出顯示)

下劃線字體=人類 ENPP1 的細胞外結構域(在 BL-1118 中優化，其中 I256T 的取代用粗體下劃線突出顯示)

SEQ ID NO: 7 *(小鼠 ENPP1- NCBI 登錄號 NP_001295256.1)*

```
  1 MERDGDQAGH GPRHGSAGNG RELESPAAAS LLAPMDLGEE PLEKAERARP AKDPNTYKVL
 61 SLVLSVCVLT TILGCIFGLK PSCAKEVKSC KGRCFERTFS NCRCDAACVS LGNCCLDFQE
121 TCVEPTHIWT CNKFRCGEKR LSRFVCSCAD DCKTHNDCCI NYSSVCQDKK SWVEETCESI
181 DTPECPAEFE SPPTLLFSLD GFRAEYLHTW GGLLPVISKL KNCGTYTKNM RPMYPTKTFP
241 NHYSIVTGLY PESHGIIDNK MYDPKMNASF SLKSKEKFNP LWYKGQPIWV TANHQEVKSG
301 TYFWPGSDVE IDGILPDIYK VYNGSVPFEE RILAVLEWLQ LPSHERPHFY TLYLEEPDSS
361 GHSHGPVSSE VIKALQKVDR LVGMLMDGLK DLGLDKCLNL ILISDHGMEQ GSCKKYVYLN
421 KYLGDVNNVK VVYGPAARLR PTDVPETYYS FNYEALAKNL SCREPNQHFR PYLKPFLPKR
481 LHFAKSDRIE PLTFYLDPQW QLALNPSERK YCGSGFHGSD NLFSNMQALF IGYGPAFKHG
541 AEVDSFENIE VYNLMCDLLG LIPAPNNGSH GSLNHLLKKP IYNPSHPKEE GFLSQCPIKS
601 TSNDLGCTCD PWIVPIKDFE KQLNLTTEDV DDIYHMTVPY GRPRILLKQH RVCLLQQQQF
661 LTGYSLDLLM PLWASYTFLS NDQFSRDDFS NCLYQDLRIP LSPVHKCSYY KSNSKLSYGF
721 LTPPRLNRVS NHIYSEALLT SNIVPMYQSF QVIWHYLHDT LLQRYAHERN GINVVSGPVF
781 DFDYDGRYDS LEILKQNSRV IRSQEILIPT HFFIVLTSCK QLSETPLECS ALESSAYILP
841 HRPDNIESCT HGKRESSWVE ELLTLHRARV TDVELITGLS FYQDRQESVS ELLRLKTHLP
901 IFSQED
```

SEQ ID NO: 8 *(牛 ENPP1- NCBI 登錄號 NP_001193141.1)*

```
  1 MERDSCAGGG SRGGEGGRGP REGLAGNGRD PGPGRAAEAS GEPQAAASLL APMDLGEEPL
```

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 61 ERAARARPAK DPNTYKVLSL VLSVCVLTTI LGCIFGLKPS CAKEIKSCKG RCFERTFGNC
121 RCDAACVDLG NCCLDYQETC IEPERIWTCT KFRCGEKRLS RSLCSCSDDC KDKGDCCINH
181 GSVCRGEKSW AEEECDSIDE PQCPAGFETP PTLLFSLDGF RAEYLHTWGG LLPVISKLKT
241 CGTYTKNMRP VYPTKTFPNH YSIVTGLYPE SHGIIDNNIY DPQMNANFAL KNKEKFNPEW
301 YKGEPIWLTA KYQGLKTGTF FWPGSDVKIN GIFPDIYKIY NVSVPFEERI LAILKWLQLP
361 KDERPHFYTL YLEEPDSSGH SYGPVSSEVI RALQRVDNMV GMLMDGLKEL NLHRCLNLIL
421 ISDHGMEQGS CKKYVYLNKY LGDTKDYKVV YGPAARLRPS DVPDKYYSFD YEGIAKNLSC
481 QEPNQHFKPY LKHFLPKRLH FAKNDRIERL TFYLDPQWQL ALNPSERKYC GGGFHGSDNT
541 FLNMQALFIG YGPGFKHSTE VDSFENIEVY NLMCDLLNLT PAPNNGTHGS LNHLLSNPVY
601 TPKHPKEVRP LVQCPFTRAP RESLDCSCDP SILPIVDFQT QLNLTMAEEK TIKRGALPYG
661 RPRVLQNSTV CLLYQHQFVS GYSRDILMPL WTSYTIGRND SFSTEDFSNC LYQDLRIPLS
721 PVHKCSFYKN NAKLSYGLLS PPQLHKGSSQ VYSEALLTTN IVPMYQSFQV IWHYLHGTLL
781 QRYAEERNGL NVVSGPVFDS DYDGRYDSLE TLKQNSKIIR NLEVLIPTHF FLVLTSCKNT
841 SQTPLQCENL DAMAFILPHK TDNSESCAHG KHESLWVEEL LKLHTARITD VEHITGLSFY
901 QERKEPISDI LKLKTHLPTF NQED
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SEQ ID NO: 9 *(兔 ENPP1- NCBI 登錄號 NP_001162404.1)*

```
  1 MERDGCAGGG SRGGEGGRAP REGPAGNSRD PGRSHAAEAP GNPQAAASLL APMDVGEEPL
 61 EKAARARTAK DPNTYKVLSL VLSVCVLTTI LGCIFGLKPS CAKEVKSCKG RCFERTFGNC
121 RCDAACVELG NCCLDYQETC IEPEHIWTCN KFRCGEKRLT RSLCACSDDC KDQGDCCINY
181 SSVCQGEKSW VEEPCESINE PQCPAGFETP PTLLFSLDGF RAEYLHTWGG LLPVISKLKK
241 CGTYTKNMRP VYPTKTFPNH YSIVTGLYPE SHGIIDNKMY DPKMNASFSL KSKEKFNPEW
301 YKGEPIWVTA KYQGLKSGTF FWPGSDVEIN GIFPDIYKMY NGSVPFEERI LAVLQWLQLP
361 KDERPHFYTL YLEEPDSSGH SYGPVSSEVI KALQRVDNMV GMLMDGLKEL NLHRCLNLIL
421 VSDHGMEQGS CKKYIYLNKY LGDVKNIKVI YGPAARLRPS DVPDKYYSFN YEGIARNLSC
481 REPNQHFKPY LKHFLPKRLH FAKSDRIEPL TFYLDPQWQL ALNPSERKYC GSGFHGSDNI
541 FSNMQALFVG YGPGFKHGIE VDTFENIEVY NLMCDLLNLT PAPNNGTHGS LNHLLKNPVY
601 TPKHPKEVHP LIQCPFTRNP RDNLGCSCNP SILPIEDFQT QFNLTVAEEK NIKHETLPYG
```

661 RPRVLQKKNT ICLLSQHQFM SGYSQDILMP LWTSYTVDRN DSFSTEDFSN CLYQDFRISL

721 SPVHKCSFYK NNTKVSYGFL SPPQLNKNSR GIYSEALLTT NIVPMYQSFQ VIWRYFHDTL

781 LRKYAEERNG VNVVSGPVFD FDYDGRYDSL EILRQKRRVI RNQEILIPTH FFIVLTSCKD

841 ASQTPLHCEN LDTLAFILPH RTDNSESCLH GKHESSWVEE LLMLHRARIT DVEHITGLSF

901 YQQRKEPVSD ILKLKTHLPT FSQED

SEQ ID NO: 10 *(狒狒 ENPP1- NCBI 登錄號 NP_001076211.2)*

1 MERDGCAGGG SQGGGKGGRG PREGLAGNGR DPSHGQASEA PGDPQAAASL LAPMDLGEEP

61 LEKAAGARPA KDPNTYKVLS LVLSVCVLTT ILGCIFGLKP SCAKEVKSCK GRCFERTFGN

121 CRCDVACVDL GNCCLDYQET CIEPERIWTC NKFRCGEKRL SRSLCACSDD CKERGDCCIN

181 YSAVCQGEKS WVEETCENIN EPQCPEGFEM PPTLLFSLDG FRAEYLHTWG GLLPVISKLK

241 KCGTYAKNMR PVYPTKTFPN HYSIVTGLYP ESHGIIDNKM YDPKMNASFS LKSKEKFNPE

301 WYKGEPIWLT AKYQGLRSGT FFWPGSDVKI NGIFPDIYKI YNGSVPFEER ILAILKWLRL

361 PKDERPHFYT LYLEEPDSSG HSYGPVSSEV IKALQRVDNM VGMLMDGLKE LNLHQCLNLI

421 LISDHGMEQG SCKKYIYLNK YLGDTKNIKV IYGPAARLRP SDVPEKYYSF NYENIARNLS

481 CREPNQHFKP YLKHFLPKRL HFAKSDRIEP LTFYLDPQWQ LALSPSERKY CGSGFHGSDN

541 VFSNMQALFV GYGPGFQHGI EVDSFENIEV YNLMCDLLNL TPAPNNGTHG SLNHLLKNPI

601 YTPKHPKEVQ PSVQCPLAGS PRDSLGCSCN PSILPIVDFQ TQFNLTTAEE KNINRASLPY

661 GRPRLLQKKS SVCLLYQHQF VSGYSHDVLM PLWTSYTVNR NDSFSTEDFS NCLYQDLRIS

721 FSPIHNCSFY KNNAKLSYGF LSPPQLSKDS SQIYSEALLT SNIVPMYQSF QVIWRYFHDT

781 LLQRYAEERN SINVVSGPVF DSDYDGRYDS SEALKRNRRV IRNQEILIPT HFFIVITSCK

841 NTSQTPLQCD NLDPLAFILP HRSDNSESCV HEKRESSWIE ELLMMHRARI MDVEHITGLS

901 FYQERKEPVS DILKLKTHLP TVSQED

SEQ ID NO: 118 (構建體 1118–可溶性 ENPP1-Fc)

MRGPAVLLTVALATLLAPGAGAPSCAKEVKSCKGRCFERTFGNCRCDAACVELGNCCLDYQETCIEPEHIWTC

NKFRCGEKRLTRSLCACSDDCKDKGDCCINYSSVCQGEKSWVEEPCESINEPQCPAGFETPPTLLFSLDGFRA

EYLHTWGGLLPVISKLKKCGTYTKNMRPVYPTKTFPNHYSIVTGLYPESHGIIDNKMYDPKMNASFSLKSKEK

FNPEWYKGEPIWVTAKYQGLKSGTFFWPGSDVEINGTFPDIYKMYNGSVPFEERILAVLQWLQLPKDERPHFY
TLYLEEPDSSGHSYGPVSSEVIKALQRVDGMVGMLMDGLKELNLHRCLNLILISDHGMEQGSCKKYIYLNKYL
GDVKNIKVIYGPAARLRPSDVPDKYYSFNYEGIARNLSCREPNQHFKPYLKHFLPKRLHFAKSDRIEPLTFYL
DPQWQLALNPSERKYCGSGFHGSDNVFSNMQALFVGYGPGFKHGIEADTFENIEVYNLMCDLLNLTPAPNNGT
HGSLNHLLKNPVYTPKHPKEVHPLVQCPFTRNPRDNLGCSCNPSILPIEDFQTQFNLTVAEEKIIKHETLPYG
RPRVLQKENTICLLSQHQFMSGYSQDILMPLWTSYTVDRNDSFSTEDFSNCLYQDFRIPLSPVHKCSFYKNNT
KVSYGFLSPPQLNKNSSGIYSEALLTTNIVPMYQSFQVIWRYFHDTLLRKYAEERNGVNVVSGPVFDFDYDGR
CDSLENLRQKRRVIRNQEILIPTHFFIVLTSCKDTSQTPLHCENLDTLAFILPHRTDNSESCVHGKHDSSWVE
ELLMLHRARITDVEHITGLSFYQQRKEPVSDILKLKTHLPTFSQEDRSDKTHTCPPCPAPELLGGPSVFLFPP
KPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*

SEQ ID NO: 119 (構建體 2000–骨靶向的 ENPP1-Fc)

MRGPAVLLTVALATLLAPGAGAPSCAKEVKSCKGRCFERTFGNCRCDAACVELGNCCLDYQETCIEPEHIWTC
NKFRCGEKRLTRSLCACSDDCKDKGDCCINYSSVCQGEKSWVEEPCESINEPQCPAGFETPPTLLFSLDGFRA
EYLHTWGGLLPVISKLKKCGTYTKNMRPVYPTKTFPNHYSIVTGLYPESHGIIDNKMYDPKMNASFSLKSKEK
FNPEWYKGEPIWVTAKYQGLKSGTFFWPGSDVEINGTFPDIYKMYNGSVPFEERILAVLQWLQLPKDERPHFY
TLYLEEPDSSGHSYGPVSSEVIKALQRVDGMVGMLMDGLKELNLHRCLNLILISDHGMEQGSCKKYIYLNKYL
GDVKNIKVIYGPAARLRPSDVPDKYYSFNYEGIARNLSCREPNQHFKPYLKHFLPKRLHFAKSDRIEPLTFYL
DPQWQLALNPSERKYCGSGFHGSDNVFSNMQALFVGYGPGFKHGIEADTFENIEVYNLMCDLLNLTPAPNNGT
HGSLNHLLKNPVYTPKHPKEVHPLVQCPFTRNPRDNLGCSCNPSILPIEDFQTQFNLTVAEEKIIKHETLPYG
RPRVLQKENTICLLSQHQFMSGYSQDILMPLWTSYTVDRNDSFSTEDFSNCLYQDFRIPLSPVHKCSFYKNNT
KVSYGFLSPPQLNKNSSGIYSEALLTTNIVPMYQSFQVIWRYFHDTLLRKYAEERNGVNVVSGPVFDFDYDGR
CDSLENLRQKRRVIRNQEILIPTHFFIVLTSCKDTSQTPLHCENLDTLAFILPHRTDNSESCVHGKHDSSWVE
ELLMLHRARITDVEHITGLSFYQQRKEPVSDILKLKTHLPTFSQEDRSDKTHTCPPCPAPELLGGPSVFLFPP
KPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE

YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY

KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKDDDDDDDD*

【0200】 實驗實施例

【0201】 通過參考以下實驗實施例，進一步詳細描述本揭露內容。提供這些實施例只是為了說明，並不意味著是限制性的，除非有特別說明。因此，本揭露內容絕不應被解釋為僅限於以下實施例，而應被解釋為包括由於本文提供的教導而變得明顯的任何和所有變化。

【0202】 無需進一步描述，相信本領域的普通技術人員可以利用前面的描述和下面的說明性實施例，製造和利用本揭露內容的化合物並實踐所要求保護的方法。因此，下面的工作實施例具體指出了本揭露內容的較佳實施方式，而不應被理解為以任何方式限制本揭露內容的其餘部分。

【0203】 現對以下實施例中採用的材料和方法進行描述。

【0204】 人類受試者

【0205】 回顧性地收集患者的數據，包括實驗室數據、X 光照片、計算機斷層掃描(CT)和骨礦物質密度(BMD)，並報告具有 ENPP1 突變的患者的骨骼和生物化學數據。

【0206】 突變分析

【0207】 對與遺傳性低血磷酸鹽性佝僂病、成骨不全症(OI)和骨質疏鬆症-假性神經膠質瘤綜合症(OPPG)(表 2)相關的基因進行了突變分析，利用 Kazusa DNA 研究所的 MiSeq Sequencing 系統進行了下一代測序，如之前報道的(Fujiki et al., 2018)。如之前所報道的(Fujiki 等，2018)，或通過使用表 2 所列出的引物，在先證者的家庭成員中對檢測到的 ENPP1 變體進行直接測序。通過矽學(in silico)工具 PolyPhen-2、SIFT 和 Mutation Taster (Adzhubei et al., 2010；Kumar et al., 2009；Schwarz et al., 2010)評估檢測到的變體的致病性。

表 2. 本案例系列中測試的基因(A)和用於 ***ENPP1*** 基因變體的靶向序列的引物(B)。

(A) 本報告中測試的基因	基因
與 OI 和 OPPG 相關的基因	*BMP1, COL1A1, COL1A2, CRTAP, FKBP10, IFITM5, P3H1, PPIB, SERPINF1, SERPINH1, SP7, TMEM38B, WNT1, CREB3L1, SPARC, TENT5A, MBTPS2, MESD*
與低血磷酸鹽性佝僂病相關的基因	*PHEX, FGF23, DMP1, ENPP1, FAM20C, FGFR1, PTH1R, SLC34A3, SLC9A3R1, CLCN5, OCRL, CYP27B1, CYP2R1, VDR, HNRNPC, CYP3A4, NF1, SLC34A1*

(B)用於 ***ENPP1*** 基因变体的靶向序列的引物

變體	寡核苷酸序列	方向	產物大小
ENPP1 c.536A>G	GGATCATACTCAGGAAGACAGC	正向	321
	TGGCCAATAGCCATGACTCC	反向	

OI，成骨不全症；OPPG，骨質疏鬆症-假性神經膠質瘤綜合症

【0208】 **補體 DNA 的選殖**

【0209】 在患者 3 的病例中，使用逆轉錄和聚合酶鏈反應(RT-PCR)，來自外周血單核細胞的總 RNA 被用於合成 ENPP1 cDNA。ENPP1 cDNA 和 pT7blue T-載體(Merck, Darmstadt, Germany)在轉化到大腸桿菌中之前進行連接。用 QIAprep Spin Miniprep 套組(Qiagen, Redwood City, CA, USA)對擴增的載體進行純化，並在兩個等位基因中進行測序。

【0210】 **完整的 FGF23 的測量**

【0211】 根據製造商的方案，通過 Determinar CL FGF23(CL)測量完整的 FGF23 (Minaris Medical, Tokyo, Japan)。CL 是夾心化學發光酶免疫測定法(CLEIA)，使用抗人類 FGF23 小鼠單株抗體。使用這種方法，FGF23 的參考範圍為 16.1-49.3 pg/ml，其中 FGF23 相關的低磷酸鹽血症的截止值為 30 pg/ml (Ito et al., 2021；Kato et al., 2021)。

【0212】 **血漿 PPi 的測量**

【0213】 收集參與者的血漿以測量血漿焦磷酸鹽(PPi)濃度。血漿分離後，樣品經由離心過濾通過 30kDa 膜(PALL, Port Washington, NY, USA)以去除血小板，並在采血後 1 小時內冷凍於-80℃，供單次使用。血漿[PPi]的測量使用 ATP 硫酸化酶進行，如前所述，稍作修改(Jansen et al., 2013；Jansen et al., 2014)。發光信號通過 EnSpire 多模式平板閱讀器(PerkinElmer, Waltham, MA, USA)在室溫下讀取。最終的血漿[PPi]通過來自適當對照的背景減去[PPi]而標準化。使用 ATP 硫酸化酶法檢測健康兒童和青少年的[PPi]參考範圍最近被報道為 2,360 到 4,440 (Bernhard et al., 2022)。這些值與之前報告的健康成人的標準範圍(O'Neill et al., 2010)相似。

【0214】 **ENPP1 的酵素動力學試驗**

【0215】 使用 Quikchange II-XL 位點定向誘變法(Agilent Technologies, Santa Clara, CA, USA)將人類突變工程化到 hENPP1-Fc 結構體中。序列驗證後，使用 Lipofectamine 2000 (Thermo Fisher Scientific, Waltham, MA, USA)將構建體轉染到 CHO-K1 細胞中。轉染 48 小時後，將 10 μL 上清液與 90 μL 含有 250 mM Tris pH 8.0、500 mM NaCl、0.05% Triton X-100 和 1 mM 胸苷 50-單磷酸鹽對硝基苯基的試驗緩衝液混合。從發色基質中釋放出對硝基苯基的速度被報告為 OD405 nM/分鐘的變化，每個構建體至少有 5 次重複，並相對於 WT%標準化。

【0216】 統計分析

【0217】 PPi 水平以平均值±標準偏差(SD)表示。用方差分析來分析 WT 和突變之間的 ENPP1 的酵素動力學試驗的比較。顯著性被設定為 $P<0.05$。數據分析經由 Windows 的 GraphPad Prism version 6.05 (GraphPad Software, San Diego, CA, USA)進行。

【0218】 **實施例 1：鑒定患者的 ENPP1 單套缺失**

【0219】 患者 1 是一名 47 歲的男性，具有上肢和下肢的骨折史。他是個應酬飲者，有 20 包年的吸煙史。他沒有輸尿管結石或吸收不良綜合症史，沒有與骨質疏鬆症有關的治療史，也沒有骨質疏鬆症的家族史。46 歲時，他出現背痛，被診斷為脊柱壓縮性骨折，在背痛一個月後開始還出現了膝關節、腕關節和踝關節疼痛。他被轉到當地醫院，腰部和股骨近側雙能 X 射線吸收儀(DEXA)顯示 T 分數分別為-3.8 和-2.6。脊柱的 CT 掃描顯示第 7 和第 11 胸椎處的壓縮性骨折(圖 1A)。

【0220】 骨閃爍顯像圖顯示肋骨有多個攝取點(uptake)，表明有多處骨折(圖 1B)。在髖關節和膝關節、跟腱或脊柱旁韌帶中沒有檢測到異位骨化的跡象(圖 1C-1H)。該患者被診斷患有早發性骨質疏鬆症，並進行了實驗室檢查以排除繼發性骨質疏鬆症和骨軟化。雖然在當地一家醫院檢測到低-正常的血清磷，同時血清鹼性磷酸酶和骨鹼性磷酸酶略有升高，但在另一家醫院沒有檢測到血清鈣、磷或 FGF23 的異常(補充表 1)。

【0221】 其他內分泌功能檢查，如促甲狀腺激素、游離睾酮和皮質醇(早晨測量)都在正常範圍內(補充表 1)。因此，他被轉到 University of Tokyo Hospitals 作進一步評估，並重新評估了血液化學成分(表 3)。實驗室數據顯示，正常血清白蛋白水平，正常校正鈣(8.8 mg/dL)，低正常血清磷(2.7 mg/dL，參考區間 2.7-4.6 mg/dL)，正常 FGF23 (28 pg/mL，參考區間 16.1-49.3 pg/mL)，以及低 25 羥基維生素 D(7.2 ng/mL)。

【0222】 考慮 OI 或 OPPG 輕度表型的診斷，並對與 OI 或 OPPG 相關的基因進行了突變分析(表 2)，但沒有鑒定出致病變體。基於在最

初醫院測量的血清分析物(補充表 1)和在我們醫院的低-正常血清磷存在，接下來考慮輕度低血磷酸鹽性佝僂病的診斷，並對相關基因進行突變分析，揭示了 ENPP1 中存在錯義變體(c.536A>G，p.Asn179Ser [N179S])(表 3)。接下來在 18 歲的患者的兒子中進行了檢測的 ENPP1 變體的直接測序，揭示了相同的雜合 ENPP1 變體(圖 2A)。儘管該兒子表現出低-正常的 BMD——腰部(-1.6)和股骨近側(-0.8)的低 Z 分數，但他在脊柱、髖關節、膝關節或跟腱中沒有自發性骨折或異位骨化的歷史(圖 5A-5G 和表 3)。

【0223】 患者 2 是 77 歲的女性，其被診斷患有特發性彌漫性骨質增生症(DISH)，當她遭受脊柱中的壓縮性骨折時被轉到 University of Tokyo hospital。評估時，通過 CT 觀察到脊柱旁韌帶的骨化和多個脊柱壓縮性骨折(圖 3A)。此外，在跟腱中檢測到了輕微的異位骨化(圖 3F)，但髖關節和膝關節是完整的(圖 3B、3C、3D 和 3E)。脊柱 CT 檢測到的骨化沒有進行組織學評估。患者的生化譜顯示，低-正常血清磷(3.1 mg/dL，參考區間 2.7-4.6 mg/dL)，高-正常 FGF23(43.3pg/mL，參考區間 16.1-49.3 pg/mL)。由於脊柱旁韌帶和跟腱存在異位骨化，考慮遺傳性 FGF23 相關的低磷酸鹽血症的診斷(具體為 ARHR 或 XLH)。對與遺傳性低血磷酸鹽性佝僂病相關基因的測試(表 2)揭示了 ENPP1 存在雜合錯義變體(c.1352A>G，p.Tyr451Cys[Y451C])(表 3)。

【0224】 患者 3 是 54 歲的女性，到附近醫院就診，主訴髖關節、膝關節和背部疼痛。她隨後出現了前/後縱韌帶骨化(OALL/OPLL)，被診斷為 DISH，雙側髖關節周圍有骨贅，雙側跟腱中有起止點病(圖 4A-4I)。實驗室數據顯示，低-正常血清磷酸鹽(2.9 mg/dL)和高-正常血清 FGF23 (38.4pg/mL，參考範圍 16.1-49.3pg/mL)。生化譜與異位脊柱旁骨化的發現相結合，得出了 FGF23 相關的低磷酸鹽血症的結論，並且基因分析(表 2)揭示了與患者 1 和 2 相同的 ENPP1 變體(c.536A>G 和 c.1352A>G)(表 3)。接下來對她的兒子(19 歲和 23 歲)進行了 Sanger 測序，揭示兩人都有 c.1352A>G 的雜合 ENPP1 變體(圖 2C)。值得注

意的是，這兩個年輕人都表現出鈣化的跟腱起止點病，而在脊柱或髖中不存在異位骨化(圖 6A-6G 和 7A-7G)。

補充表 1. 轉診前病例 1 的生化和激素數據

	RI，成人	**病例 1**
血清鈣 (mg/dL)	8.8 - 10.1	9.4
血清磷酸鹽 (mg/dL)	2.7 - 4.6	2.8
eGFR (mL/分鐘/1.73m^2)		
25(OH)D (ng/mL)		< 4.0
1,25(OH)$_2$D (pg/mL)	20 - 60	39.7
ALP (U/L)	38 - 113	152
BAP (μg/L)	3.7 - 20.9	25.6
TRACP-5b (mU/dL)	170 - 590	594
iPTH (pg/mL)	25.8 - 75.7	36
FGF23 (pg/mL)	16.1 - 49.3	28
TSH (μIU/mL)	0.38 - 4.31	2.46
游離睾酮 (pg/mL)	4.7 - 21.6	5.6
皮質醇(μg/dL)	4.5 - 21.1	6.0

縮略語：RI，參考區間；eGFR，估計的腎小球濾過率；25(OH)D，25-羥基維生素 D；1,25(OH)$_2$D，1,25-二羥基維生素；ALP，鹼性磷酸酶；BAP，骨鹼性磷酸酶；TRACP-5b，抗酒石酸酸性磷酸酶 5b；iPTH，完整的副甲狀腺激素；FGF23，成纖維細胞生長因子 23；TSH，促甲狀腺激素。

表3. 具有單等位基因ENPP1變體或復合染合ENPP1變體的成人中人口、臨床和生化數據，c.536A>G or c.1352A>G.

	RI, 成人	病例 1	病例 1的兒子	病例 2	病例 3	病例 3的兒子 (Ⅲ-2)	病例 3的兒子 (Ⅲ-3)
ENPP1 變體		c.536A>G, 雜合	c.536A>G, 雜合	c.1352A>G 雜合	c.536 A>G/ c.1352 A>G	c.1352 A>G 雜合	c.1352 A>G 雜合
蛋白質變化		p.Asn179Ser	p.Asn179Ser	p.Tyr451Cys	p.Asn179Ser / p.Tyr451Cys	p.Tyr451Cys	p.Tyr451Cys
人口數據							
年齡 (年)/性別		48/M	18/M	78/F	54/F	23/M	19/M
身高 (cm/SD)		166/-0.9	177/ 1.2	146/-0.9	155/-0.4	167/-0.4	164/-2.0
臨床數據							
異位骨化							
脊柱旁韌帶		否	否	是	是	否	否
髖關節		否	否	否	是	否	否
膝關節		否	否	否	否	否	否
跟腱		否	否	是	是	是	是
BMD(T分數/Z分數)							
股骨近側		-2.6/-2.3	NA / -0.8	-3.5 / -1.3	-0.2 / -0.7	NE	NE
腰部		-3.8/-2.6	NA / -1.6	-3.3 / -0.8	3.6 / 2.9	NE	NE
生化數據							
血清鈣 (mg/dL)	8.8 - 10.1	8.8	9.9	9.6	9.3	9.6	10.0

血清磷酸鹽 (mg/dL)	2.7 - 4.6	2.7	3.7	3.1	2.9	3.4	3.2
血漿 PP_i (nM)	2360 - 4440	1646 ± 36	NE	1748 ± 45	1866 ± 82	1585 ± 56	1153 ± 31
eGFR (mL/min/1.73m²)		76.8	99	96.4	84.2	84.4	129.1
25(OH)D(ng/mL)		7.2	18.1	9.5	9.2	15.0	10.1
$1.25(OH)_2D$(pg/mL)	20 - 60	40	31	26	48.1	68.3	65.9
BAP(μg/L)	3.7 - 20.9	13.5	13.9	NE	19.1	12.5	26.5
TRACP-5b(mU/dL)	170 - 590(M) 120 - 420(F)	450	308	245	289	228	430
iPTH (pg/mL)	25.8 - 75.7	35	35	29	106	37.1	21.4
FGF23 (pg/mL)	16.1 - 49.3	28.0	34.0	43.3	38.4	39.0	43.2
TPR (%)	>80	93	93	NE	96	97	97
TmP/GFR (mg/dL)	2.3 - 4.3	2.5	3.6	NE	2.8	3.3	3.1

縮寫 ：RI， 參考區間 ：M，男；F，女；SD， 標準偏差 ；BMD,骨礦物質密度 ；NA， 不適用 ；NE，未檢測；PP_i，焦磷酸鹽；eGFR，估計的腎小球濾過率；25(OH)D，25-羥基維生素D；$1.25(OH)_2D$,1,25-二羥基維生素；BAP,骨鹼性磷酸酶 ；TRACP-5b， 抗酒石酸酸性磷酸酶 5b；iPTH，完整的甲狀旁腺激素；FGF23, 成纖維細胞生長因子 23; TPR， 管狀磷鹽重吸收

【0225】 實施例 2：**ENPP1** 單套缺失在患者中影響的表徵

【0226】 *選殖患者 3 中的 ENPP1 的互補 DNA*

【0227】 對 ENPP1 的互補 DNA 進行選殖和測序，以評估兩個 ENPP1 變體是位於同一等位基因還是相反的等位基因中。每個等位基因的序列數據揭示病例 3 具有 ENPP1 變體的複合雜合性(圖 8)。

【0228】 *對檢測到的 ENPP1 變體的致病性的矽學預測*

【0229】 在本病例中檢測到的 N179S 和 Y451C 的等位基因頻率在基因組聚集數據庫(GnomAD)中被報道分別為 0.00010 和 0.00016。然而，在由 Tohoku Medical Megabank Organization (ToMMo)構建的 3552 名普通日本人個體的全基因組參考組中，N179S 和 Y451C 的等位基因頻率被報道分別為 0.0071 和 0.0055 (表 4)。Asn 179 位於生長調節素 B 結構域 2 (SMB2)中，其對蛋白質二聚化和穩定性至關重要，而 Tyr 451 在催化結構域中(圖 9)，Asn 179 和 Tyr 451 在所有物種中都是高度保守的。方法中描述的矽學工具的組合將 N179S 和 Y451C 突變標記為致病性的(表 4)。

表4. ENPP1 變體的等位基因頻率和矽學預測 ,c.536A>G orc.1352A>G.

	等位基因頻率		矽學預測		
變體	GnomAD	ToMMo	PolyPhen-2	SIFT	Mutation Taster
c.536 A>G	0.00010	0.0071	可能有害	有害	引起疾病
c.1352 A>G	0.00016	0.0055	可能有害	有害	多態性

【0230】 *血漿 PPi 的測量*

【0231】 對三個先證者(病例 1-3)及其家庭成員的血漿 PPi 進行了測量。具有雜合 ENPP1 變體的患者表現出在 1,000 至 2,000 nM 之間的血漿 PPi 水平(表 3)，而患有雙等位基因 ENPP1 變體的患者中的血漿 PPi 表現出類似的 1,866 nM 的濃度。

【0232】 ***ENPP1 的酵素動力學試驗***

【0233】 為了進一步評估突變對 ENPP1 催化活性的影響，與 WT ENPP1 同工型相比，在體外試驗中一起對所有變體的酶促率進行了評估。與 WT ENPP1 相比，N179S 和 Y451C 變體分別降低了 ENPP1 的催化率 55%和 70% (圖 10)。因此，根據 ACMG 指南，N179S 和 Y451C 變體被分類為「可能致病的」(N179S：PM1+PP3+PS3，Y451C：PM1+PS3)。

【0234】 *選定結果*

【0235】 結果表明，在原發受試者(患者 1-3)中存在兩例單等位基因 ENPP1 缺陷和一例複合雙等位基因雜合 ENPP1 缺陷的臨床表現，在這些受試者的子女中還存在另外三例 ENPP1 單套缺失。

【0236】 患者 1 表現為早發性骨質疏鬆症，而患者 2 表現為脊柱骨質增生症和 DISH 的推定診斷，並被另外發現有骨質疏鬆症(由脊柱中的壓縮性骨折證明，圖 1A-1B 和 3A-3G)。患者 3 擁有複合雜合 ENPP1 突變，其由患者 1 和 2 中存在的單個突變組成，使得患者是 ENPP1 純合缺陷的，患者表現出突出的脊柱旁韌帶骨化，以及髖關節周圍的鈣化和雙側跟腱鈣化起止點病(圖 4A-4I)。

【0237】 此外，所有擁有從原發患者那裡繼承的單等位基因 ENPP1 變體的兒童都在令人驚訝的年輕年紀時表現出肌肉骨骼疾病，如患者 1 的 18 歲兒子的低骨量(腰椎的 Z 得分為-1.6)和患者 3 的 19 歲和 23 歲兒童的跟腱鈣化起止點病。基因型與表型的分離進一步支持了 ENPP1 缺陷在本研究中描述的骨骼障礙的發病機制中起核心作用的觀點。

【0238】 此前，對擁有誘導 GACI 的純合 ENPP1 突變的家族的評估報告，單倍性不足 ENPP1 攜帶者無症狀，但擁有低鈣血症和低磷酸鹽血症的血清生化指標，表明 ENPP1 可能在鈣和磷酸鹽體內穩態中發揮作用(Kotwal et al., 2020)。相反，Oheim 等人報告了在患有早發性骨質疏鬆症的成年男性中的 ENPP1 單套缺失，這種表型也存在於稱為 $ENPP1^{asj/asj}$ 的 ENPP1 純合缺陷小鼠中(Oheim et al., 2020)，這支持

了 ENPP1 調節哺乳動物骨量的觀點。事實上，患者 1 和她 18 歲的兒子的骨骼表型支持 ENPP1 單套缺失與早發性骨質疏鬆症的關聯。

【0239】 該研究將 ENPP1 單套缺失的關聯擴展到 DISH 患者。DISH 是全身性疾病，其特徵在於韌帶和肌腱端的骨化，尤其是在胸椎周圍。DISH 患者有時會遭受疼痛和運動範圍減少，並增加脊柱骨折的風險(Mader et al., 2013)。雖然發病機制不明，但 DISH 與年齡較大(50 歲以上)、男性、肥胖、高血壓和糖尿病有關(Kuperus 等，2020)。

【0240】 在患者 2 的病例中，她的年齡超過 50 歲，但不存在 DISH 的其他風險因素，相反，發現該患者為 ENPP1 單倍性不足。鑒於人類和小鼠的臨床和臨床前研究將純合 ENPP1 缺陷與脊柱韌帶骨化相關聯(Okawa 等，1998；Nakamura 等，1999；Saito 等，2011；Hirao 等，2016)，導致血漿 PPi 降低的 ENPP1 活性受損是該患者中存在的進行性脊柱旁骨化和鈣化起止點病的一個風險因素。

【0241】 所描述的兩個 ENPP1 變體(N179S 和 Y451C)都位於 ENPP1 區域的高度保守序列中，其對二聚化和穩定性(Asn 179)以及催化活性(Tyr 451)非常重要。此外，N179S 和 Y451C 被多個矽學工具發現是有害的(表 4)，但迄今尚未被報告為致病性的。

【0242】 此外，與 WT 水平相比，N179S 和 Y451C 分別降低酶活性 55%和 70%，這與 ENPP1 的其他致病性變體中存在的殘餘酶活性相似(Kotwal et al., 2020；Oheim et al., 2020；Rutsch et al., 2003；Stella et al., 2016；Thumbiger-Math et al., 2018)。綜上所述，這些發現支持一個或多個 ENPP1 變體 N179S 及/或 Y451C 負責三個先證者中存在骨骼表型和異位骨化。

【0243】 雖然 ENPP1 調節肌肉骨骼礦化的機制尚不完全理解，即是通過催化作用還是不依賴催化的蛋白信號傳導，但患者 1 和 2 中所述的患者都表現出低血漿[PPi](分別為 1,646 nM 和 1,748 nM，參考範圍為 2,360 - 4,440 nM)，這與 ENPP1 的催化活性在觀察到的異常表型中的作用一致。ENPP1 和 ABCC6 缺陷都會導致低血漿 PPi 水平

(Lorenz-Depiereux et al., 2010；Levy-litan et al., 2010；Rutsch et al., 2001；Nitschke et al., 2012；Le Saux et al., 2000)。ENPP1 單套缺失患者中的血漿 PPi 水平介於無 ENPP1 缺陷和純合 ENPP1 缺陷患者的 PPi 水平之間(Kotwal et al., 2020；Oheim et al., 2020)。我們的患者中的 PPi 水平也落在 1,000 至 2,000 nM 的範圍內，但出乎意料的是，具有複合雜合 ENPP1 缺陷的患者 3 的 PPi 濃度與單倍性不足 ENPP1 患者相似，這表明有補償機制參與(Kotwal et al., 2020)。

【0244】 此外，在患者 3 中觀察到繼發性副甲狀腺功能亢進，這一發現也在其他具有純合 ENPP1 缺陷的患者(Kotwal 等，2020，和 Capelli 等，2015)和 ENPP1 缺陷的小鼠模型中觀察到。在由 FGF23 升高誘發的其他障礙中，PTH 也會升高，如 Hyp 小鼠和具有 XLH 和 ARHR 的人類，其由於 FGF23 的作用導致維生素 D 活化受損而出現繼發性副甲狀腺功能亢進(Carpenter JBMR，2011)。類似的機制可能解釋了病例 3 中的繼發性副甲狀腺功能亢進，該患者被指出維生素 D 缺陷，以及純合 ENPP1 缺陷的其他病例(Kotwal et al., 2020)。由於患者 3 中描述的患者沒有出現骨軟化，因此，用天然維生素 D 而不是活性維生素 D 治療將適合於改善和預防繼發性副甲狀腺功能亢進症的惡化。

【0245】 雖然研究中的患者呈現出正常的完整 FGF23，但在其低度正常血清磷水平的背景下，該水平被解釋為升高，這就提出了遺傳誘導的磷酸鹽消耗性障礙的可能性。在這方面，ARHR2 的原始報告中所描述的大多數患者在低血清磷的背景下具有高-正常或輕微升高的完整 FGF23。在 Levy-Litan 對 3 名佝僂病患者的描述中，3 人中有 2 人具有高-正常的完整的 FGF23(50 pg 和 47 pg，正常參考範圍為 10-50 pg)，(Levy-Litan 等，2010)，Lorenz-Depiereux 報告的 7 名 ARHR2 患者中有 5 人的完整 FGF23 處於正常範圍的上限或重複測量時略有升高。在低磷酸鹽值和患者表現出的嚴重佝僂病表型的背景下，這些範圍也同樣被解釋為高。

【0246】 在不希望受到任何理論限制的情況下，本研究表明

ENPP1 單套缺失比純合 ENPP1 缺陷誘導更大的 FGF23 升高，在正常或低-正常血清磷(2.7-3.1 mg/dL，參考範圍為 2.7-4.6 mg/dL)的情況下，完整 FGF23 的正常和高-正常水平引起了對基因誘導的低磷酸鹽血症的懷疑，並開始進行基因測試。該研究表明，在罕見的代謝性障礙如 ARHR、XLH 和低血磷酸鹽性腫瘤鈣化症的患有鈣化起止點病患者中(Okawa et al., 1998；Nakamura et al., 1999；Saito et al., 2011 年；Hirao et al., 2016 年；Maulding et al., 2021 年；Rutsch et al., 2001 年；Cheng et al., 2005 年；Albright et al., 2015 年)，以及在快速進展形式 OPL 患者的一般醫療人群中(Albright et al., 2015 年；Ferreira et al., 2021 年)，增加的循環 FGF23 和低磷酸鹽血症發生。相反，鈣化起止點病與不依賴 FGF23 的低血磷酸鹽性佝僂病形式如 SLC34A3 缺陷無關(Kotwal et al., 2020)。因此，FGF23 似乎與起止點病的發展有密切關係。

【0247】 先前在 ENPP1 缺陷小鼠全骨中進行的轉錄組分析報告 Enpp1 的失活突變增加了 Fgf23 轉錄，並減少了 Wnt10b 和 Wnt16 轉錄(Maulding et al., 2021)，這表明 ENPP1 缺陷部分地通過受損的 Wnt 信號傳導誘導了異常的骨骼礦化。患者 1 沒有表現出明顯的具有升高 FGF23 水平的低血磷酸鹽性佝僂病，而且骨吸收標誌物抗酒石酸酸性磷酸酶 5b (TRACP-5b)處於正常範圍，表明骨質疏鬆症的發展沒有高骨轉換，這一發現與缺陷的 Wnt 信號傳導誘導的合成代謝缺陷一致。因此，人類的觀察結果與 ENPP1 缺陷的小鼠模型的轉錄組分析所建議的骨質疏鬆機制一致(Maulding et al., 2021)。

【0248】 最後，重要地是注意該研究中描述的變體的等位基因頻率的差異。在患者 2 中檢測到的等位基因(Y451C)的頻率在日本人中(ToMMo：0.0055)比在所有其他種族中(GnomAD：0.00016)高約 30 倍。鑒於觀察到單等位基因 ENPP1 Y451C 突變與 OPL 有關，這種變體頻率的差異可能解釋了日本的 OPLL 發病率(1.8-4.1%)比美國(0.12%)和德國(0.1%)高 10-40 倍(Stapleton et al., 2011)。

【0249】 實施例 3：**ENPP1** 融合蛋白的生成和對 **DISH** 模型小鼠的治療

【0250】 **ENPP1** 的生成

【0251】 ENPP1 融合蛋白的一個實例是 ENPP1-Fc。然而，ENPP1-Fc 的例證也可適用於如本文闡述的其他 ENNPP1 融合蛋白(如 ENPP1-白蛋白)。

【0252】 ENPP1-Fc 是重組融合蛋白，其含有與 IgG1 的 Fc 片段(rhENPP1-Fc)結合的人類 ENPP1 (可溶性 ENPP1)的細胞外結構域。ENPP1-Fc 的重組細胞外結構域包含其催化活性，與原生 ENPP1 酶相同。ENPP1-Fc 是在 CHO 細胞中經由補料批式細胞培養過程生產的重組人類蛋白，其不含動物來源的組分。ENPP1-Fc 二聚體的分子量約為 290 kDa；ENPP1-Fc 是高度糖基化的，pI 為約 6.0。與內源性 ENPP1 一樣，ENPP1-Fc 的主要基質是 ATP，它被裂解為 AMP 和 PPi。

【0253】 在具體實施方式中，可溶性 ENPP1 蛋白經由連接子(包括亮胺酸、異亮胺酸和天冬醯胺)與帶有連接子的人類 Fc 結構域融合。三個 ENPP1-Fc 構建體在表 1 中顯示為 SEQ ID NO：3、4 和 5，如從 CHO 細胞中純化的。

【0254】 ENPP1-Fc 的純化可通過一系列柱層析步驟實現，其例如包括以下三種或更多種，以任何順序進行：蛋白 A 層析法、Q 瓊脂糖凝膠層析法、苯基瓊脂糖凝膠層析法、尺寸排阻層析法和陽離子交換層析法。純化可以通過病毒過濾和緩衝液交換來完成。蛋白純化後，可以使用 pNP-TMP 作為發色基質來評估 ENPP1-Fc 蛋白的催化活性。

【0255】 用 **ENPP1** 劑治療 **DISH** 模型小鼠

【0256】 最成熟的脊柱起止點病(DISH)小鼠模型是 Enpp1 缺陷的小鼠，被稱為 ttw (「趾尖行走小鼠」(*tip toe walking mice*))。ttw 小鼠表現出嚴重的脊髓病和廣泛的脊柱旁韌帶鈣化和骨贅形成。為了評估 PPi 與起止點病的嚴重程度之間的關係，我們對 23 週齡的 $Enpp1^{asj}$ 小鼠的跟腱進行了檢查，這些小鼠以普通飼料飼養。

【0257】 在皮下亞毫克計量後，用媒劑(PBS)或能夠使血漿[PPi]正常化的人類 ENPP1-Fc 向動物給藥超過一週。ENPP1-Fc 的施用方案、放射線分析和組織學實驗概述於 Ferreira et al., Musculoskeletal Comorbidities and Quality of Life in ENPP1-Deficient Adults and the Response of Enthesopathy to Enzyme Replacement Therapy in Murine Models. J Bone Miner Res, 2021)。任選地，可使用含有骨靶向結構域的 ENPP1 劑(例如但不限於 ENPP1-Fc)重複實驗，以更好地遞送和更高的療效。

【0258】 在第 2-23 週之間，以每週 0.3 mg/kg 向 $Enpp1^{asj}$ 小鼠施用 ENPP1 劑(例如但不限於 ENPP1-Fc)，並測量給藥 $Enpp1^{asj}$ 小鼠中的血漿 PPi。注意到相對於 WT 對來說，PPi 顯著增加，但沒有完全正常化(分別為 1358 vs 2235 nM，表 6)。

表 6 23 週齡的 $Enpp1^{WT}$ 和給藥的及未給藥的 $Enpp1^{asj/asj}$ 小鼠的血漿分析物

參數	單位	**$Enpp1^{wt}$ + PBS**	**$ENPP1^{asj}$ + PBS**	**$Enpp1^{asj}$ + BL-1118**
鈣	mg/dL	6.6 ± 0.5	7.0 ± 0.8	6.9 ± 0.4
磷酸鹽	mg/dL	6.4 ± 0.9	5.7 ± 0.5	5.5 ± 0.8
PTH	pg/ml	137 ± 80	229 ± 89	**524 ± 248*(↑)**
FGF23	pg/ml	172 ± 28	**439 ± 215*(↑)**	**614 + 167***(↑)**
PPi	nM	2235±621	**51 ± 22****(↓)**	**1358 ± 268**(↓)**

【0259】 對跟腱中的起止點病進行組織學分析，並使用定制的 MATLAB 軟件對茜素紅染色切片的顯微照片中的紅色像素進行量化。經媒劑處理的 $Enpp1^{asj}$ 小鼠的跟腱預計會在整個腱的長度上出現實質上的鈣化，而經 ENPP1-Fc 處理的 $Enpp1^{asj}$ 小鼠的腱鈣化預計會被抑制。

【0260】 在不受理論約束的情況下，起止點病可以依賴於血漿

PPi，並且可以通過用例如 ENPP1 劑(例如 ENPP1-Fc)的酶類生物製劑升高血漿 PPi 來預防起止點病。研究結果表明，在劑量擴大後，可能會達到完全抑制起止點病。

【0261】 **PPi 對 DISH 模型小鼠的影響**

【0262】 為了評估血漿 PPi 對 DISH 小鼠模型中的骨贅形成、脊柱融合和骨化的影響，在第 3-17 週之間用媒劑或 1 mg/kg ENPP1-Fc 向 $Enpp1^{asj}$ 小鼠給藥，並通過顯微 CT 分析其脊柱。圖 12：用 ENPP1-Fc 給藥的小鼠表現出較高的血漿 PPi 水平(約 10 μm)，其比 WT 水平高數倍。

【0263】 在用 ENPP1 劑(例如 ENPP1-Fc)治療的 DISH 小鼠模型中，存在血漿 PPi 的升高和脊柱旁骨化的減少將表明，對患有 DISH 的人類受試者的這種 ENPP1 施用也會減輕脊柱旁骨贅、關節強直和脊柱融合。

【0264】 **實施例 4：治療方案**

【0265】 以下列選定的劑量之一施用 ENPP1 劑(例如，但不限於 ENPP1、ENPP1-X、ENPP1-Fc 及/或 ENPP1-Fc-X，其中 X 是如本文其他部分所述的骨靶向標籤)：0.2 mg/kg、0.3 mg/kg、0.4 mg/kg、0.5 mg/kg、0.6 mg/kg、0.7 mg/kg、0.8 mg/kg、0.9 mg/kg、1.0 mg/kg、1.1 mg/kg、1.2 mg/kg、1.3 mg/kg、1.4 mg/kg、1.5 mg/kg、1.6 mg/kg、1.7 mg/kg、1.8 mg/kg、1.9 mg/kg、2.0 mg/kg、2.1 mg/kg、2.2 mg/kg、2.3 mg/kg、2.4 mg/kg、2.5 mg/kg、2.6 mg/kg、2.7 mg/kg、2.8 mg/kg、2.9 mg/kg、3.0 mg/kg、3.1 mg/kg、3.2 mg/kg、3.3 mg/kg、3.4 mg/kg、3.5 mg/kg、3.6 mg/kg、3.7 mg/kg、3.8 mg/kg、3.9 mg/kg、4.0 mg/kg、4.1 mg/kg、4.2 mg/kg、4.3 mg/kg、4.4 mg/kg、4.5 mg/kg、4.6 mg/kg、4.7 mg/kg、4.8 mg/kg、4.9 mg/kg、5.0 mg/kg、5.1 mg/kg、5.2 mg/kg、5.3 mg/kg、5.4 mg/kg、5.5 mg/kg、5.6 mg/kg、5.7 mg/kg、5.8 mg/kg、5.9 mg/kg、6.0 mg/kg、6.1 mg/kg、6.2 mg/kg、6.3 mg/kg、6.4 mg/kg、6.5 mg/kg、6.6 mg/kg、6.7 mg/kg、6.8 mg/kg、6.9 mg/kg、7.0 mg/kg、

7.1 mg/kg、7.2 mg/kg、7.3 mg/kg、7.4 mg/kg、7.5 mg/kg、7.6 mg/kg、7.7 mg/kg、7.8 mg/kg、7.9 mg/kg、8.0 mg/kg、8.1 mg/kg、8.2 mg/kg、8.3 mg/kg、8.4 mg/kg、8.5 mg/kg、8.6 mg/kg、8.7 mg/kg、8.8 mg/kg、8.9 mg/kg、9.0 mg/kg、9.1 mg/kg、9.2 mg/kg、9.3 mg/kg、9.4 mg/kg、9.5 mg/kg、9.6 mg/kg、9.7 mg/kg、9.8 mg/kg、9.9 mg/kg、10.0 mg/kg 及/或其分數或倍數。施用為皮下注射(SC)，每兩個月至少一次或兩次、每月至少一次或兩次、每月三次、每週至少一次或兩次。

【0266】 ENPP1 劑的第一劑量可在第 1 天施用。在第 8 天及其後，以選定計量的 ENPP1 劑 mg/kg 的劑量每週兩次向受試者施用 ENPP1 劑。劑量可在每個給藥日的大約同一時間施用。注射部位是交替進行的，其中在過去 2 週內的任何過去注射部位的 2 英寸範圍內沒有注射部位。

【0267】 ENPP1 劑的選定劑量是 0.2 mg/kg、0.3 mg/kg、0.4 mg/kg、0.5 mg/kg、0.6 mg/kg 或 1.8 mg/kg SC 之一。通過 SC 的 ENPP1 劑的另一選定劑量是以下之一：0.2 mg/kg、0.3 mg/kg、0.4 mg/kg、0.5 mg/kg、0.6 mg/kg、0.7 mg/kg、0.8 mg/kg、0.9 mg/kg、1.0 mg/kg、1.1 mg/kg、1.2 mg/kg、1.3 mg/kg、1.4 mg/kg、1.5 mg/kg、1.6 mg/kg、1.7 mg/kg、1.8 mg/kg、1.9 mg/kg、2.0 mg/kg、2.1 mg/kg、2.2 mg/kg、2.3 mg/kg、2.4 mg/kg、2.5 mg/kg、2.6 mg/kg、2.7 mg/kg、2.8 mg/kg、2.9 mg/kg、3.0 mg/kg、3.1 mg/kg、3.2 mg/kg、3.3 mg/kg、3.4 mg/kg、3.5 mg/kg、3.6 mg/kg、3.7 mg/kg、3.8 mg/kg、3.9 mg/kg、4.0 mg/kg、4.1 mg/kg、4.2 mg/kg、4.3 mg/kg、4.4 mg/kg、4.5 mg/kg、4.6 mg/kg、4.7 mg/kg、4.8 mg/kg、4.9 mg/kg、5.0 mg/kg、5.1 mg/kg、5.2 mg/kg、5.3 mg/kg、5.4 mg/kg、5.5 mg/kg、5.6 mg/kg、5.7 mg/kg、5.8 mg/kg、5.9 mg/kg、6.0 mg/kg、6.1 mg/kg、6.2 mg/kg、6.3 mg/kg、6.4 mg/kg、6.5 mg/kg、6.6 mg/kg、6.7 mg/kg、6.8 mg/kg、6.9 mg/kg、7.0 mg/kg、7.1 mg/kg、7.2 mg/kg、7.3 mg/kg、7.4 mg/kg、7.5 mg/kg、7.6 mg/kg、7.7 mg/kg、7.8 mg/kg、7.9 mg/kg、8.0 mg/kg、8.1 mg/kg、8.2 mg/kg、8.3 mg/kg、8.4 mg/kg、8.5 mg/kg、8.6 mg/kg、8.7 mg/kg、

8.8 mg/kg、8.9 mg/kg、9.0 mg/kg、9.1 mg/kg、9.2 mg/kg、9.3 mg/kg、9.4 mg/kg、9.5 mg/kg、9.6 mg/kg、9.7 mg/kg、9.8 mg/kg、9.9 mg/kg、10.0 mg/kg 及/或其分數或倍數。ENPP1 劑的第一劑量可在第 1 天施用。第一劑量後，可對受試者觀察 7 天，以監測安全性並收集 PK 樣品。在第 8 天和此後，受試者每週兩次接受選定的劑量。在醫療專家認為合適的情況下，繼續以選定的劑量施用 ENPP1 劑。

【0268】 受試者可以在 29 天的時間段內接受 8 劑量的 ENPP1 劑，例如，對於劑量的量為 0.2 mg/kg、0.6 mg/kg 和 1.8 mg/kg，導致每 29 天分別暴露 1.6 mg、4.8 mg 和 14.4 mg。或者受試者可以接受多於或少於 8 個劑量，如醫療專家認為合適的情況下。

【0269】 與內源性 ENPP1 酶一樣，ENPP1 劑裂解 ATP 以生成 AMP 和 PPi，從而增加血漿 PPi 水平，並轉化為 AMP，CD73 迅速將其轉化為腺苷。替換內源性人類酶旨在改正固有的缺陷，並允許改善健康狀況和減輕與 ENPP1 基線患者、臨床醫生和照顧者結果有關的臨床併發症。

【0270】 **實施例 5：對具有 ENPP1 單套缺失的患者的治療**

【0271】 通過在第 1 天皮下注射，並從第 8 天開始每週兩次使用如下的選定劑量對被鑒定為具有 ENPP1 單套缺失的患者施用 ENPP1 劑。

表 7.

1	0.2 mg/kg
2	0.6 mg/kg
3	1.8 mg/kg

【0272】 ENPP1 劑以 0.2 mg/kg、0.6 mg/kg 或 1.8 mg/kg SC 之一的選定劑量施用，每週至少兩次，時間段由醫療專家確定。根據需要，監測患者對酶置換的反應，如由專業醫師確定的，例如，通過跟蹤 ENPP1 缺陷的一個或多個症狀的減少，及/或使用本文提供的指導。

【0273】 **實施例 6：對診斷患有 DISH 的患者的治療**

【0274】 DISH 通常涉及脊柱周圍腱和韌帶的鈣化。一旦腱和韌帶變硬，這些組織的一部分就會變成骨頭。這通常發生在組織與骨的連接處。因此，會出現骨刺，這是沿骨頭邊緣發展的骨骼向外生長。DISH 通常影響背部和頸部的上半部分，即胸椎和頸椎。然而，DISH 也可以影響肩、肘、手、膝蓋、髖、腳跟及/或腳踝。

【0275】 在某些實施方式中，用 ENPP1 劑治療被診斷患有 DISH 的受試者，選定劑量為 0.2 mg/kg、0.6 mg/kg 或 1.8 mg/kg 之一，SC、IV 及/或 IP 施用 ENPP1 劑，每週至少兩次，時間段由醫療專家確定。

【0276】 在某些實施方式中，用 ENPP1 劑治療被診斷患有 DISH 的受試者，選定劑量為 0.2 mg/kg、0.3 mg/kg、0.4 mg/kg、0.5 mg/kg、0.6 mg/kg、0.7 mg/kg、0.8 mg/kg、0.9 mg/kg、1.0 mg/kg、1.1 mg/kg、1.2 mg/kg、1.3 mg/kg、1.4 mg/kg、1.5 mg/kg、1.6 mg/kg、1.7 mg/kg、1.8 mg/kg、1.9 mg/kg、2.0 mg/kg、2.1 mg/kg、2.2 mg/kg、2.3 mg/kg、2.4 mg/kg、2.5 mg/kg、2.6 mg/kg、2.7 mg/kg、2.8 mg/kg、2.9 mg/kg、3.0 mg/kg、3.1 mg/kg、3.2 mg/kg、3.3 mg/kg、3.4 mg/kg、3.5 mg/kg、3.6 mg/kg、3.7 mg/kg、3.8 mg/kg、3.9 mg/kg、4.0 mg/kg、4.1 mg/kg、4.2 mg/kg、4.3 mg/kg、4.4 mg/kg、4.5 mg/kg、4.6 mg/kg、4.7 mg/kg、4.8 mg/kg、4.9 mg/kg、5.0 mg/kg、5.1 mg/kg、5.2 mg/kg、5.3 mg/kg、5.4 mg/kg、5.5 mg/kg、5.6 mg/kg、5.7 mg/kg、5.8 mg/kg、5.9 mg/kg、6.0 mg/kg、6.1 mg/kg、6.2 mg/kg、6.3 mg/kg、6.4 mg/kg、6.5 mg/kg、6.6 mg/kg、6.7 mg/kg、6.8 mg/kg、6.9 mg/kg、7.0 mg/kg、7.1 mg/kg、7.2 mg/kg、7.3 mg/kg、7.4 mg/kg、7.5 mg/kg、7.6 mg/kg、7.7 mg/kg、7.8 mg/kg、7.9 mg/kg、8.0 mg/kg、8.1 mg/kg、8.2 mg/kg、8.3 mg/kg、8.4 mg/kg、8.5 mg/kg、8.6 mg/kg、8.7 mg/kg、8.8 mg/kg、8.9 mg/kg、9.0 mg/kg、9.1 mg/kg、9.2 mg/kg、9.3 mg/kg、9.4 mg/kg、9.5 mg/kg、9.6 mg/kg、9.7 mg/kg、9.8 mg/kg、9.9 mg/kg、10.0 mg/kg 及/或其分數或倍數之一，SC、IV 及/或 IP 施用 ENPP1 劑，每週至少兩次，時間段由醫療專家確定。

【0277】 根據需要，監測 DISH 患者對酶置換的反應，如由專業醫師確定的，例如，通過跟蹤 DISH 的一個或多個症狀的減少、使用本文提供的指導。

【0278】 可選地，懷疑有 DISH 風險的受試者通過施用選定劑量的 ENPP1 劑來治療。在某些實施方式中，發展 DISH 的常見風險因素包括但不限於大腰圍、BMI/肥胖、高胰島素血症、糖尿病、高尿酸血症、血脂紊亂、高血壓、冠狀動脈疾病及/或痛風。DISH 可以是無症狀的，在那些情況下，通常根據放射學圖像進行診斷。在某些實施方式中，DISH 與年齡較大(50 歲以上)、男性、肥胖、高血壓及/或糖尿病有關。

【0279】 可選地，具有 DISH 的放射學證據但缺乏該疾病的臨床表現的受試者可以用 ENPP1 劑治療，以預防或最小化脊柱骨折的增加、活動能力下降、脊髓病及/或疼痛，這些都是與 DISH 有關的已知表型。

【0280】 在整個說明書的背景下，下面的實施例為確定治療方案和療效提供了指導。

【0281】 **實施例 7：與骨健康有關的生物標誌物**

【0282】 除低血漿 PPi 外，ENPP1 缺陷的患者的生化特徵在於低血清磷酸鹽、高尿磷酸鹽、低腎 TmP/GFR、正常鈣(Ca)、低-正常尿 Ca、正常 25-羥基維生素 D(25 OH D)、低-正常 1,25(OH)2D、高 BAP、高完整 FGF23、正常及/或升高的 PTH (IOF 2019)。

【0283】 表 8 中敘述了可在某些實施方式中作為治療患者的骨骼健康的另外決定因素的生物標誌物。

表 8. 臨床中間物和生物標誌物

	實驗室	樣品類型
主要藥效學標誌物	焦磷酸鹽(PPi)	血漿或血清
	無機磷酸鹽	血漿或血清
	FGF23 (完整的)	血漿或血清
	TmP/GFR	血清肌酐、血清磷酸鹽、尿磷酸鹽
	ALP, BALP, CTx, P1NP	血清、血漿、尿液

【0284】 **實施例 8：用 ENPP1 劑的治療的療效**

【0285】 可以通過測量血漿 PPi 以及測量其他血漿分析物，如 FGF23、Pi、FGF23、Pi、TmP/GFR、血清鹼性磷酸酶(ALP)、骨特異性 ALP (BALP)、I 型膠原的羧基末端交聯端肽(CTx)及/或 1 型前膠原 N 端前肽(P1NP)來評估治療療效。這些分析物測量可作為與 ENPP1 缺陷有關的 PD 標誌物，以確定 ENPP1 劑的療效。這些分析物的變化可被描述為從基線開始的變化，並在治療過程中以時間依賴的方式。可以評估 PK 和 PD 參數的劑量線性度。

【0286】 血漿 PPi 水平、FGF23 水平和每肌酐清除率的尿磷排泄量從基線的變化可以用成對差異的 t 檢驗來分析。

【0287】 **實施例 9：藥物濃度的測量**

【0288】 此外，可從患者獲得血樣，以測量血漿中的 ENPP1 劑濃度，並在第一劑量後(即單次劑量)和多次劑量時/後(即穩態)進行後續的 PK 參數測定。

【0289】 **實施例 10：免疫原性(抗藥物抗體)**

【0290】 如果需要，對 ENPP1 劑的免疫原性可以使用抗藥物抗體(ADA)來測量。免疫原性測試可以利用多層次的方法；如果在最初的篩選中檢測到 ADA，則可以進行確認測試以確定特異性。樣品也可用於評估和進一步建立用於特異性確認(即滴度)和中和抗體的試驗。

【0291】 **實施例 11：藥物動力學、藥效學和探索性生物標誌物分析**

【0292】 可對 PK 人群進行藥物動力學分析，ENPP1 劑的 PK 參數可通過描述性統計的處理來總結。也可以評估 PK 和 PD 參數的劑量線性度。可以確定 PK/PD 分析、免疫原性分析；以及探索性生物標誌物分析。

【0293】 **實施例 12：療效的其他決定因素**

【0294】 儘管恢復正常的 PPi 水平是使用 ENPP1 劑治療的療效的主要指標，但如果需要的話，也可以使用其他的物理測量來輔助確定治

療療效。這些物理測量包括以下一項或多項。

【0295】 1. 放射線照相術和成像

a. *骨骼嚴重程度的X*光照片(x-ray)。可以獲得標準的X光照片，以發現佝僂性骨骼畸形。例如，可以獲得手腕和膝蓋的X光照片。

b. *DEXA 掃描*。DEXA 掃描可用於評估骨密度的變化。

c. *正電子發射斷層成像*。計算機斷層成像。基線 $Na^{18}F$-PET/HRpQCT(或 HR-CT)可能是在第一劑量的 ENPP1 劑的 1 個月內進行的全身掃描，以測量基線處動脈和器官的鈣化以及骨骼的異常，並用於未來的干預性評估。$Na^{18}F$-PET 測量骨轉換以及動脈的微鈣化。高分辨率定量計算機斷層成像(HRQCT)或 HR-CT 可以確定非支配性橈骨和脛骨遠端(non-dominant distal radius and tibia)處的骨微結構。計算標準的骨骼幾何參數。

d. *多普勒超聲心動圖*。可在第一劑量的 ENPP1 劑前的 3 天內獲得基線超聲心動圖。多普勒超聲可用於測量心臟功能[LVEF、血流]、心臟和瓣膜的鈣化以及動脈僵化。

e. *光學相干斷層成像*。光學相干斷層成像可用於可視化新內膜增殖。

f. *外周動脈張力測量*。外周動脈張力測量(PAT)可用於評估數字脈搏波幅(PWA)，它與數字容積變化相對應。

g. *腎臟超聲*。腎臟超聲檢查可用於，例如，在開始使用 ENPP1 劑的 1 週內，測量腎臟鈣化。

h. *骨組織形態學和骨活檢*。可進行骨活檢作為基線測量。在進行骨活檢前，較佳四環素負荷 10 天。

【0296】 2. 步行能力

【0297】 步行測試可作為次最大運動測量(submaximal exercise measurement)，以結合心肺、神經肌肉和肌肉骨骼功能測量非臥床患者中的功能能力。6 分鐘步行測試(6MWT)最初由美國胸科協會

(American Thoracic Society)(ATS 2002)開發用於成人，現在普遍用於成人和兒科群體(Mylius 等，2016)，以及患有神經肌肉疾病的兒童，如脊髓性肌萎縮症(Montes 等，2018)、杜氏肌肉營養不良症(McDonald 等，2013)和嬰兒型龐貝病(van der Meijden 等，2018)。2 分鐘步行測試(2MWT)包括在 NIH 工具箱中，並且越來越多地被用來測量相同的性質。

【0298】 6MWT 和 2MWT 可在治療前和治療期間由醫療服務提供者決定施用至患者。如果受試者在基線時不能完成至少 2MWT，則治療期間的另外評估可由醫療服務提供者決定。在測試前和測試後獲得靜息心率。可以記錄 6MWT 的前 2 分鐘和整個 6 分鐘內步行的距離。2 分鐘和 6 分鐘內步行的距離可與年齡和性別匹配的正常數據進行比較(預測值百分比)。

【0299】 **3. 肌力測定法**

【0300】 在治療前及/或治療期間，可由醫療服務提供者決定使用肌力測定法評估力量。手持式肌力測定法是直接測量力量的方法，常用於兒童和成人。可以評估的肌肉群包括：肩部外展、肩部屈曲、肘部屈曲、肘部伸展、髖部外展、髖部屈曲、髖部伸展和膝部伸展。每個肌肉群可以在雙側測量 2 次。

【0301】 a. *握力*。在治療前及/或治療期間，可由醫療服務提供者決定使用握力測力計來測量握力。設備和評估者的說明可以在不同的地點進行標準化。握力可在雙側進行評估，其中每只手進行一次練習和一次最大力量測量，結果可與年齡和性別匹配的正常數據進行比較(如果有的話)。

【0302】 b. *運動範圍*。活動範圍可以用測角器來評估，這是一種測試關節角度和測量關節處移動程度的儀器。測角器的固定臂對準固定體段上的指定骨性標誌，測角器的移動臂對準正在移動的肢體上的指定骨性標誌。為使用運動軸和骨性標誌測量的每一個運動，指定測角器的支點。運動範圍可以評估以下一項或多項：肩部外展、肩部屈曲、肘部屈

曲、肘部伸展、髖部外展、髖部屈曲、髖部伸展和膝部伸展。

【0303】 **4. 聽力測試**

【0304】 中度聽力損失與 ARHR2 有關(Brachet et al., 2014；Steichen-Gersdorf et al., 2015)。基線聽力可以通過以下一種或多種確定：體檢和耳鏡檢查、導抗聽力測驗(通常稱為鼓室測量法)、純音聽力測驗(PTA)(如果可能的話，頻率可達 8 kHz)(如果 PTA 的閾值>15dB，則受試者還應該接受骨傳導測試)、高頻聽力測驗(HFA)，頻率高達 16 kHz。

【0305】 **5. 臨床醫師總體印象量表**

【0306】 臨床總體印象(CGI-S)量表是為用於國家精神衛生研究所贊助的臨床研究而開發的，以提供臨床醫生在開始使用研究藥物之前和之後對患者總體功能看法的簡短、獨立的評估(Guy 1976)。CGI 提供了由臨床醫生決定的考慮了所有可用信息的整體總結性測量，其包括對患者歷史、社會心理環境、症狀、行為以及症狀對患者功能能力的影響的瞭解。可以在治療前及/或治療期間施用 CGI-S，其由醫療服務提供者決定，並且使用範圍從-3 (嚴重惡化)到+3 (顯著改善)的七點量表對變化進行總體評估。

【0307】 **6. 粗大運動功能分類系統-擴展和修訂版**

【0308】 粗大運動功能分類系統-擴展和修訂版(GMFCS-E 和 R)可以在治療前及/或治療期間施用，其由醫療服務提供者決定。GMFCS-E 和 R 對患者發起的運動進行分類，重點是在量表上 1 到 5 的移動。

【0309】 **7. 患者報告結果測量信息系統**

【0310】 患者報告結果測量信息系統(PROMIS)由美國國立衛生研究院(NIH)開發的多種問卷組成，以從患者的角度評估身體、精神和社會福利(www.healthmeasures.net)。這些問卷已被用於患有慢性健康狀況的人的臨床研究中，如 X 連鎖低磷酸鹽血症、關節炎、多發性硬化症和神經纖維瘤病。每份問卷包含 8 到 10 個項目，由參與者以從 1(從不)到 5(總是)的 5 分的李克特量表(Likert scale)進行評分。每份問卷

的分數相加，其中高分表示被測量的領域更多(如更多的疲勞，更多的身體功能)。原始分數基於 50 的平均值和 10 的標準偏差轉換為 T 分數(T-Scores)，以便將研究樣本與一般人群進行比較。PROMIS 量表可包括疼痛干擾(短表 8a)、疼痛強度(版本 3a)、身體功能-上肢(定制簡短表)、身體功能-移動性(短表 13a FACIT 疲勞)、疲勞(短表)和認知影響(短表 8a)，可由醫療服務提供者決定在治療前及/或治療期間施用。這些評估可以由受試者在沒有幫助的情況下完成。

【0311】 **8. 照顧者總體印象量表**

【0312】 在治療前及/或治療期間，可由醫療服務提供者決定對患者的照顧者施用照顧者總體狀態印象。照顧者總體變化印象提供了變化的總體評估，其使用七點量表，範圍從-3 (嚴重惡化)到+3 (顯著改善)。

【0313】 **9. 西安大略和麥克馬斯特大學骨關節炎指數**

【0314】 WOMAC 是患者報告的結果，用於評估髖關節或膝關節疼痛患者的日常生活活動、功能活動、步態、一般健康、疼痛和生活質量(www.sralab.org)。該評估由 24 個項目組成，花費大約需要 12 分鐘施用。WOMAC 可以在治療前及/或治療期間施用，其由醫療服務提供者決定。該評估可以由受試者在沒有幫助的情況下完成。

【0315】 **實施例 13：可溶性(構建體 1118，SEQ ID NO: 118)和骨靶向(構建體 2000，SEQ ID NO: 119)ENPP1-Fc 對頸椎和聽覺表型的比較**

【0316】 圖 13 顯示了在每週用指定的皮下劑量的媒劑或 ENPP1 構建體#1118 和#2000 給藥的 17 週齡的 WT 和 17 週齡的 $Enpp1^{asj}$ 雄性小鼠中的脊柱旁骨贅和關節強直的反應。構建體#1118 從第 3 週開始每週給藥一次，而構建體#2000 從第 5 週開始每週給藥一次。顯微 CT 圖像顯示較佳在構建體#2000 給藥的 $Enpp1^{asj}$ 雄性小鼠中脊柱旁骨贅和關節強直的衰減。

【0317】 圖 14 顯示了在每週用指定的皮下劑量的媒劑或 ENPP1 構建體#1118 和#2000 給藥的 17 週齡的 WT 和 17 週齡的 $Enpp1^{asj}$ 雌

性小鼠中的脊柱旁骨贅和關節強直的反應。構建體#1118 從第 3 週開始每週給藥一次，而構建體#2000 從第 5 週開始每週給藥一次。顯微 CT 圖像顯示，較佳在構建體#2000 給藥的 $Enpp1^{asj}$ 雌性小鼠中脊柱旁骨贅和關節強直的衰減。

【0318】 圖 15A-15B 顯示了在每週用指定的皮下劑量的媒劑或 ENPP1 構建體#1118 和#2000 給藥的 17 週齡的 WT 和 17 週齡的 $Enpp1^{asj}$ 小鼠中的聽覺腦幹反應。構建體#1118 從第 3 週開始每週給藥一次，而構建體 2000 構建體從第 5 週開始每週給藥一次。刺激頻率測量表明，每週 2 mg/Kg 劑量的 ENPP1 構建體#1118，以及每週 0.5 和 1 mg/Kg 劑量的 ENPP1 構建體#2000，可以預防低頻(8 kHz)範圍內的聽力損失。也注意到，較佳在每週 1 mg/Kg 劑量給藥的 ENPP1 構建體#2000 中，在高頻範圍(32 kHz)內 ENPP1 缺陷動物的聽力改善。

【0319】 圖 16 顯示了在每週用指定的皮下劑量的媒劑或 ENPP1 構建體#1118 和#2000 的 WT 和 17 週齡的 $ENPP1^{asj}$ 小鼠中的完整的 FGF23 水平。構建體#1118 從第 3 週開始每週給藥一次，而構建體#2000 構建物從第 5 週開始每週給藥一次。數據顯示，當每週以 1 mg/Kg 和 4 mg/Kg 給藥時，ENPP1 構建體#2000 較佳抑制完整的 FGF23。統計學顯著性是通過方差分析 Kruskal-Wallis 測試，然後通過 Dunn 的事後分析來評估與 WT 水平的差異(單因素方差分析)。統計學顯著性用 p 值表示，並附有以下注釋：*$p<0.05$，**$p<0.01$，***$p<0.001$，****$p<0.0001$。

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【0322】 通過引用併入

【0323】 本文提到的所有出版物和專利通過引用以其整體併入本文，就像每一個單獨的出版物或專利被具體和單獨指明通過引用併入。

【0324】 其他實施方式

【0325】 雖然已經討論了本主題的具體實施方式，但上述說明書是說明性的，而不是限制性的。本領域的技術人員在閱讀本說明書和下面的權利要求書後，許多變化會變得顯而易見。本發明的全部範圍應參照

權利要求書及其等同物，以及說明書和這些變化的全部範圍來確定。

【符號說明】

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【發明申請專利範圍】

【請求項1】 一種治療、改善、預防有需要的患者中的彌漫性特發性骨肥厚症(DISH)及/或脊關節炎的進一步發展及/或進展，及/或預防該患者中的彌漫性特發性骨質增生症(DISH)及/或脊關節炎的方法，該方法包括向該患者施用治療有效量的式(I)的化合物或其鹽或溶劑化物：

蛋白質 -Z- 結構域-X-Y

(I),

其中在(I)中：

蛋白質包括 ENPP1 的催化區；

結構域不存在或為選自人類 IgG Fc 結構域(Fc)、人類血清白蛋白(ALB)和其片段的至少一個；

X 和 Z 獨立地不存在或為包括 1-20 個胺基酸的多肽，並且

Y 是帶負電荷的骨靶向序列；

從而治療、改善、預防該患者中的 DISH 及/或脊關節炎的進一步發展及/或進展及/或預防該患者中的 DISH 及/或脊關節炎。

【請求項2】 如請求項 1 所述的方法，其中該患者具有 ENPP1 單套缺失(haploinsufficiency)。

【請求項3】 如請求項 1 所述的方法，其中該患者沒有 ENPP1 單套缺失。

【請求項4】 如請求項 1 所述的方法，其中該患者不是 ENPP1 缺陷的。

【請求項5】 如請求項 1 所述的方法，其中該患者是 ENPP1 缺陷的。

【請求項6】 如請求項 1 所述的方法，其中該患者藉由至少一種選自以下的途徑施用該化合物：口服、氣溶膠、吸入、直腸、陰道、透皮、皮下、鼻內、頰、舌下、腸胃外、鞘內、胃內、眼科、肺部和局部。

【請求項7】 如請求項 1 所述的方法，其中該化合物被靜脈內或皮下注射施用至該患者。

【請求項8】 如請求項 1 所述的方法，其中向該患者施用該化合物增加該患者的細胞外焦磷酸鹽濃度或預防該患者的細胞外焦磷酸鹽濃度進一步降低。

【請求項9】 如請求項 1 所述的方法，其中向該患者施用該化合物降低該患者的跟腱鈣化、脊柱鈣化、髖關節鈣化和雙側鈣化中的一種或多種或預防該患者的跟腱鈣化、脊柱鈣化、髖關節鈣化和雙側鈣化中的一種或多種的進一步增加。

【請求項10】如請求項 1 所述的方法，其中該結構域包括白蛋白。

【請求項11】如請求項 1 所述的方法，其中該結構域包括 IgG Fc 結構域。

【請求項12】如請求項 1 所述的方法，其中該蛋白質缺乏 ENPP1 跨膜結構域。

【請求項13】如請求項 1 所述的方法，其中該化合物作為醫藥組成物施用至該患者，該醫藥組成物進一步包括至少一種醫藥上可接受的載劑。

【請求項14】如請求項 1 所述的方法，其中該患者是哺乳動物。

【請求項15】如請求項 14 所述的方法，其中該哺乳動物是人類。

【請求項16】如請求項 1 至 15 中任一項所述的方法，其中該蛋白質包括 SEQ ID NO: 1 的胺基酸殘基 99 (PSCAKE)至 925 (QED)。

【請求項17】如請求項 1 至 16 中任一項所述的方法，其中該蛋白質包括 SEQ ID NO: 3 的胺基酸殘基 1 至 833。

【請求項18】如請求項 1 至 16 中任一項所述的方法，其中該蛋白質包括 SEQ ID NO: 2 中描繪的胺基酸序列。

【請求項19】如請求項 1 至 16 中任一項所述的方法，其中該蛋白質包括 SEQ ID NO: 3 或 4 或 5 中描繪的胺基酸序列。

【請求項20】如請求項 1 至 19 中任一項所述的方法，其中相對於缺乏該結構域的該化合物的循環半衰期，該結構域增加了該化合物的循環半衰期。

【請求項21】如請求項 1 所述的方法，其中該患者還被診斷患有選自以下所組成群組的疾病或病症：早發性骨質疏鬆症、骨質減少、與年齡有關的骨質減少、OPLL、遺傳性低血磷酸鹽性佝僂病、X 連鎖低磷酸鹽血症、常染色體隱性低血磷酸鹽性佝僂病 2 型、常染色體顯性低血磷酸鹽性佝僂病和低血磷酸鹽性佝僂病。

【請求項22】如請求項 1 所述的方法，其中該患者沒有被診斷出患有選自以下所組成群組的疾病或病症：早發性骨質疏鬆症、骨質減少、與年齡有關的骨質減少、OPLL、遺傳性低血磷酸鹽性佝僂病、X 連鎖低磷酸鹽血症、常染色體隱性低血磷酸鹽性佝僂病 2 型、常染色體顯性低血磷酸鹽性佝僂病和低血磷酸鹽性佝僂病。

【發明圖式】

圖 1A

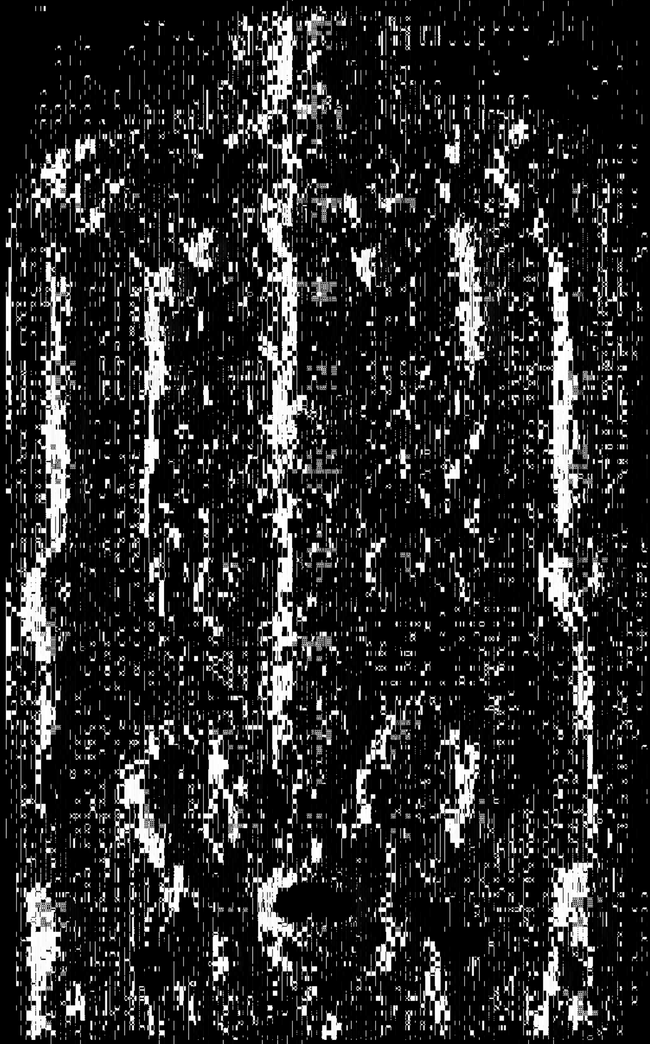

圖 1B

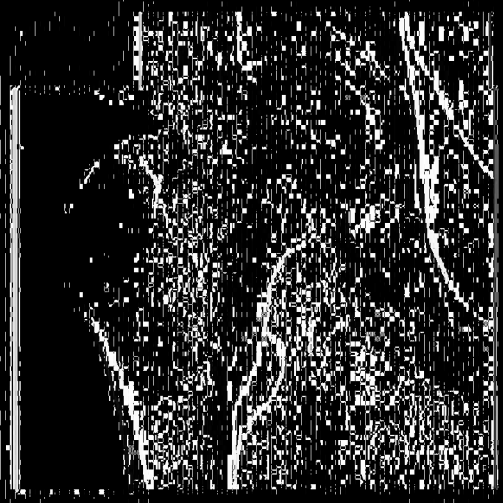

FIG 1C

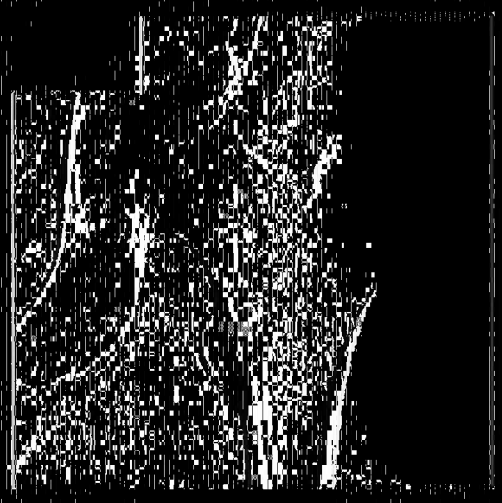

FIG 1D

FIG 1E

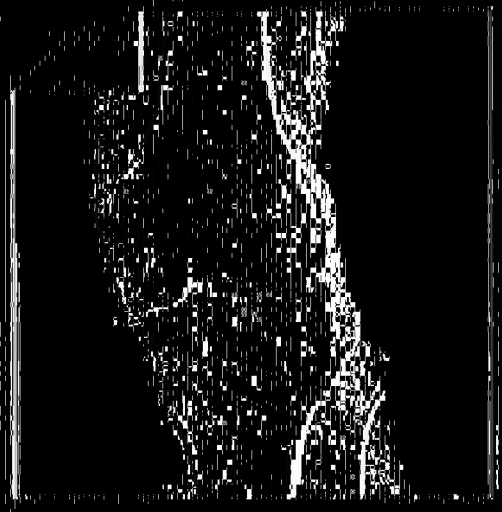

FIG 1F

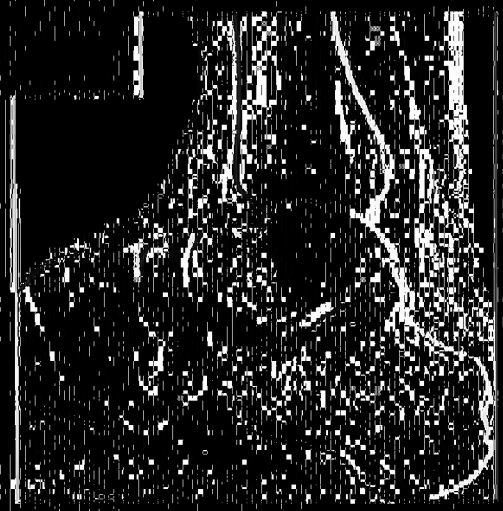

FIG 1G

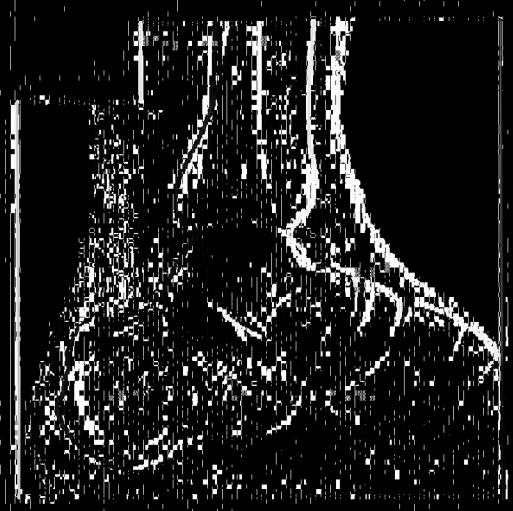

FIG 1H

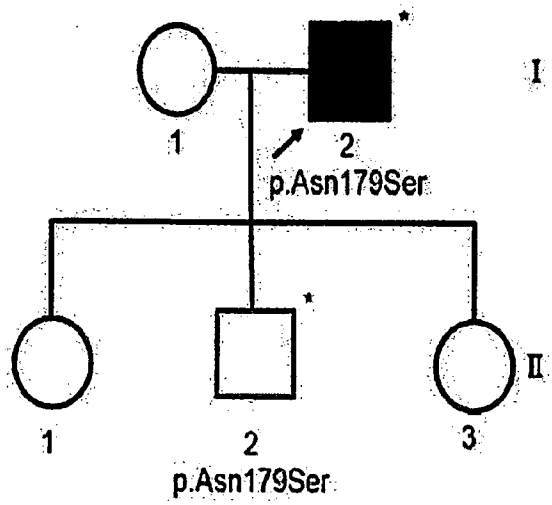
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圖 2A

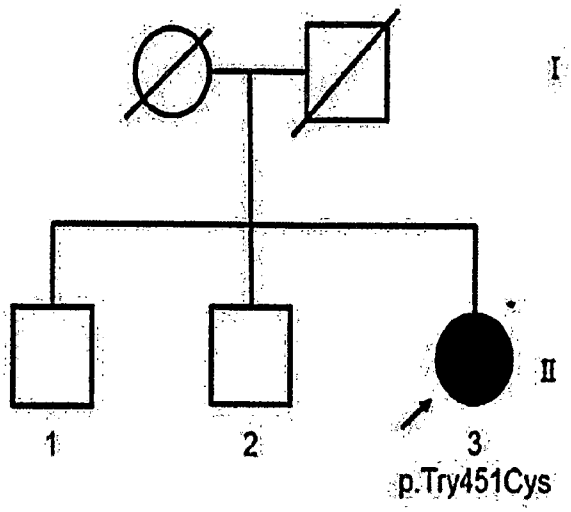

I
II
1
2
3
p.Try451Cys

圖 2B

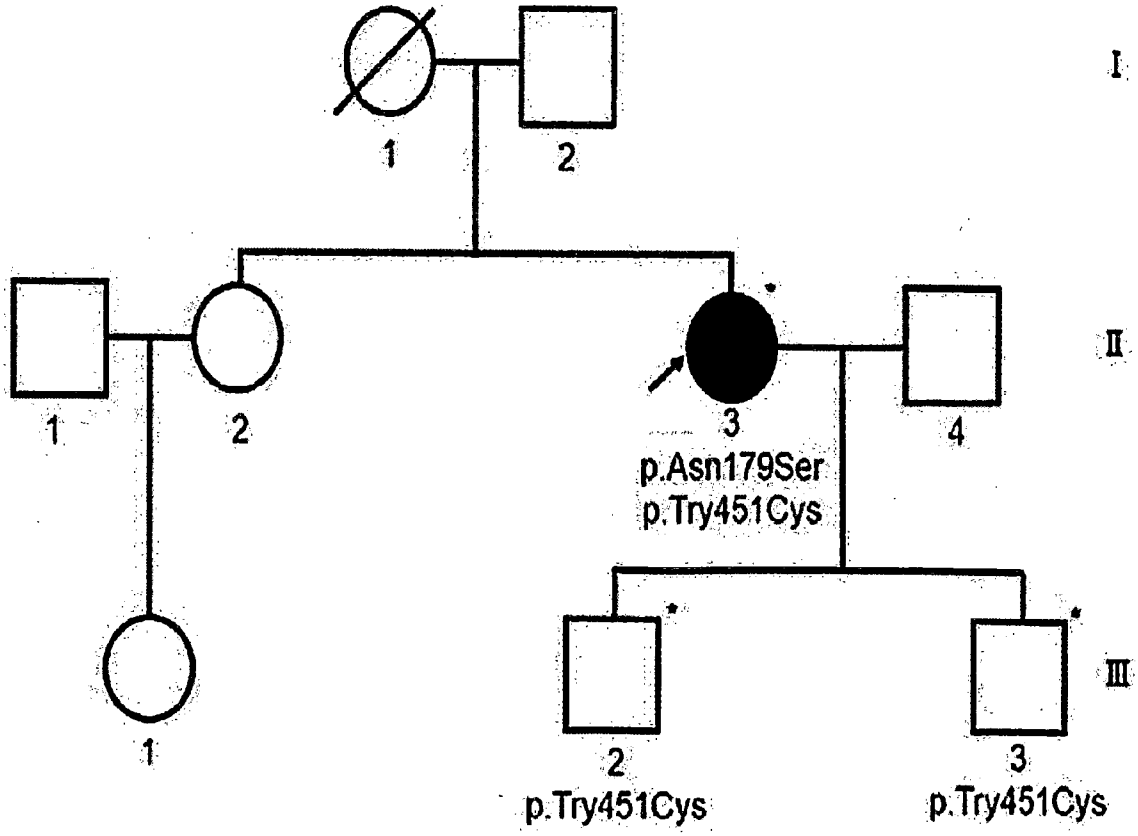

I
1
2
II
1
2
3
p.Asn179Ser
p.Try451Cys
4
III
1
2
p.Try451Cys
3
p.Try451Cys

圖 2C

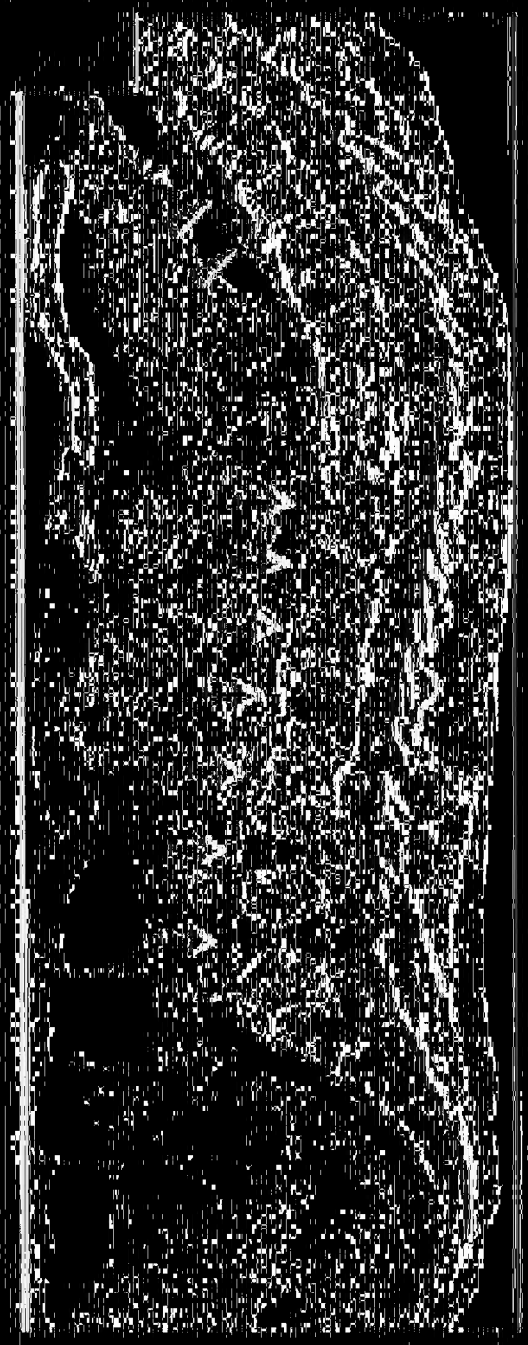


Fig. 3A

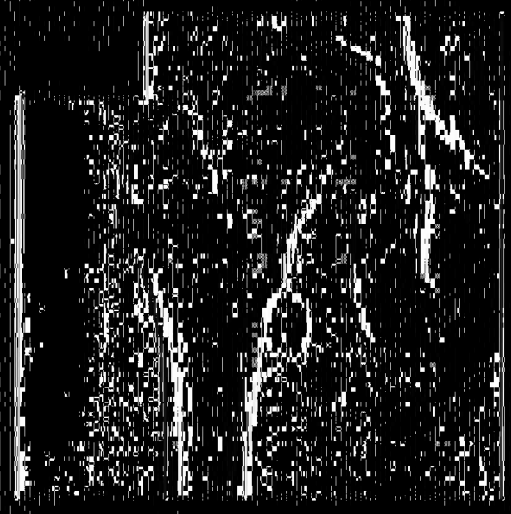


图 3B

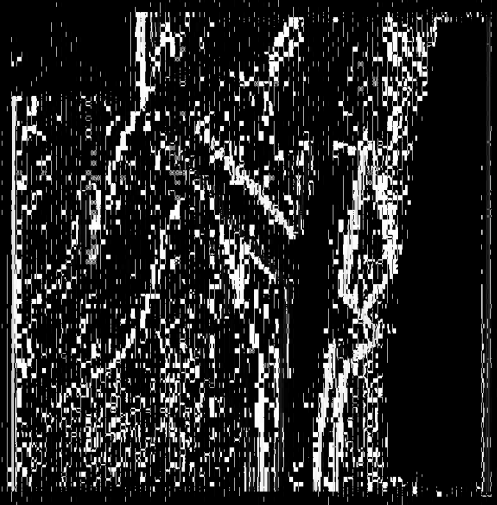


图 3C

图 3D

图 3E

图 3F

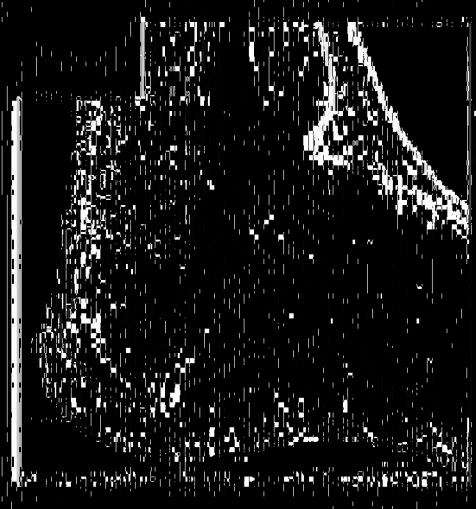


图 3G

Fig. 6

Fig. 5

Fig. 4

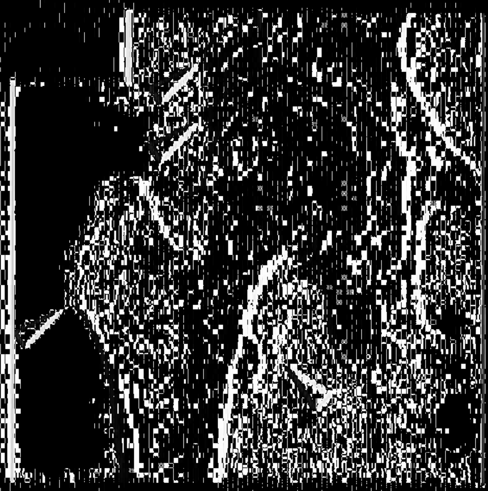


图 4D

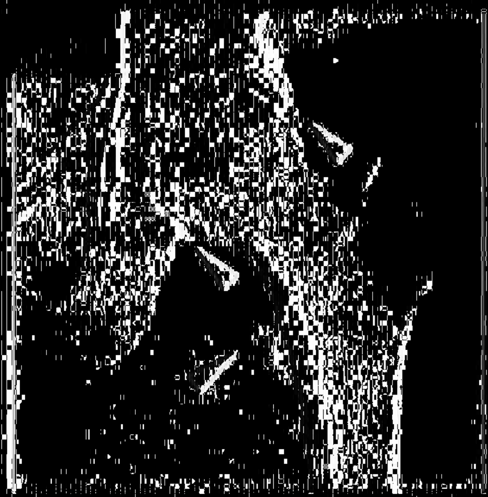


图 4E

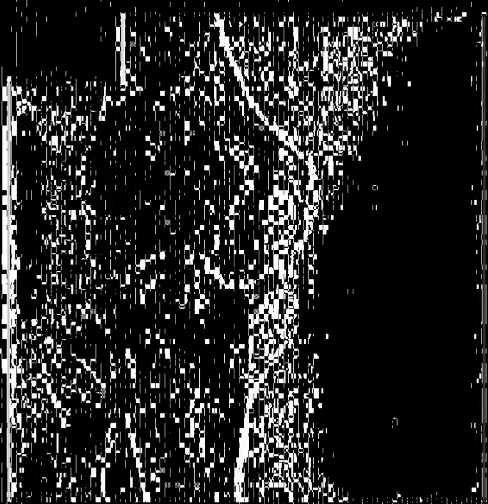


图 4F

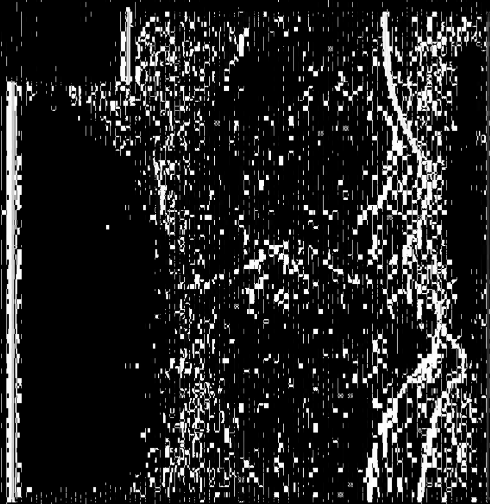


图 4G

图 4H

图 4I

图 5A

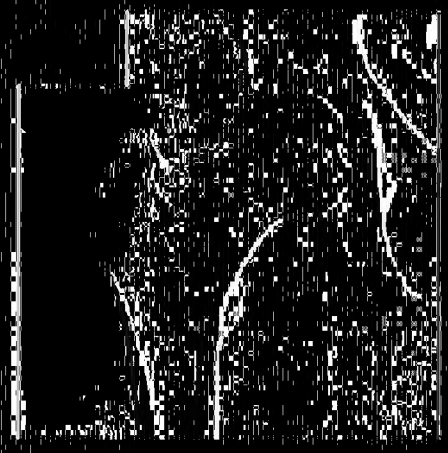


图 5B

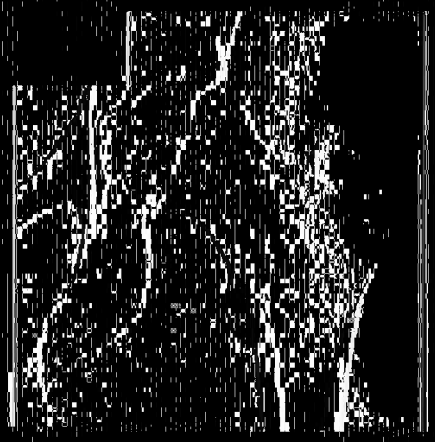


图 5C

图 5D

图 5E

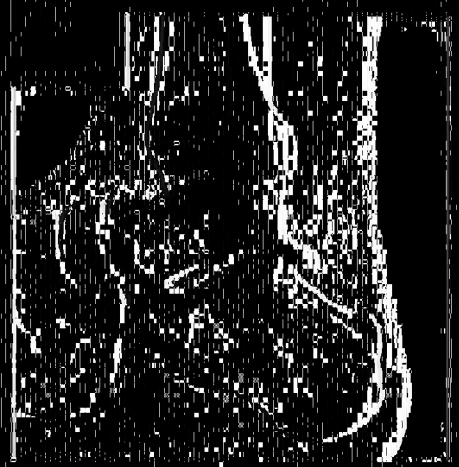


图 5F

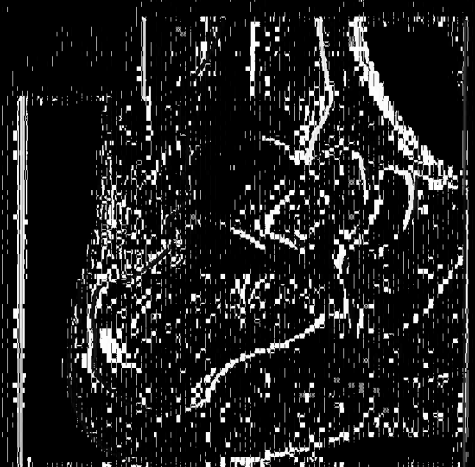


图 5G

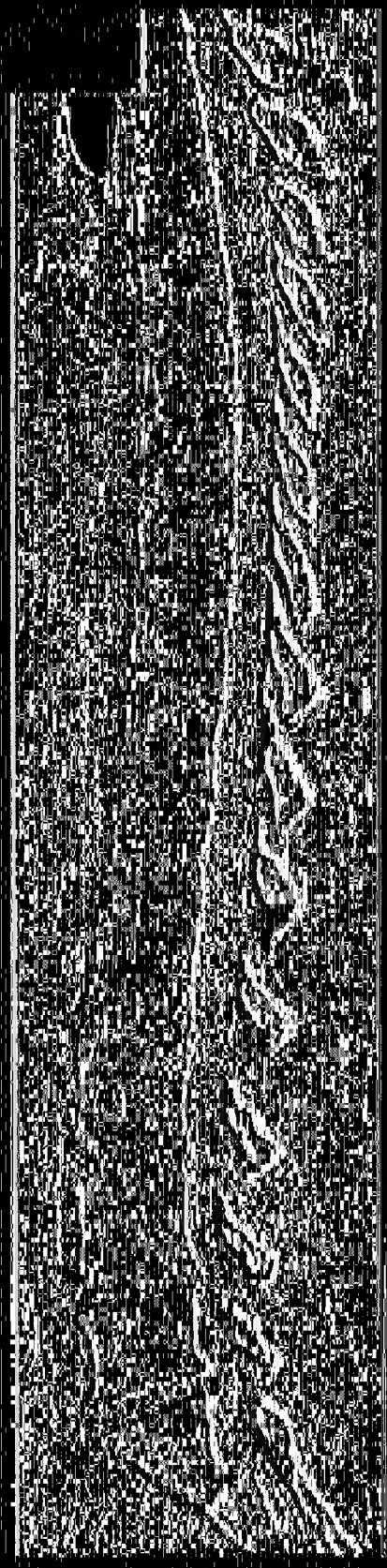


图 6A

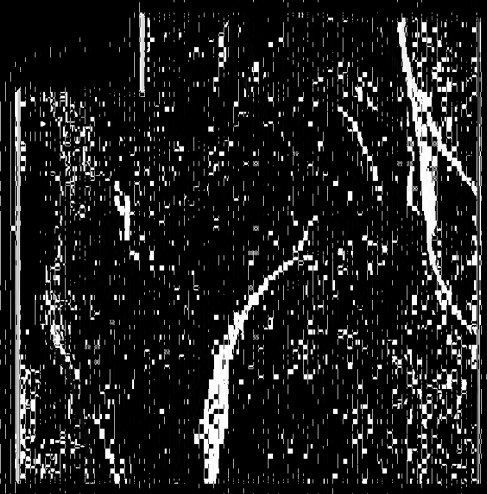


FIG 6B

FIG 6C

FIG 6D

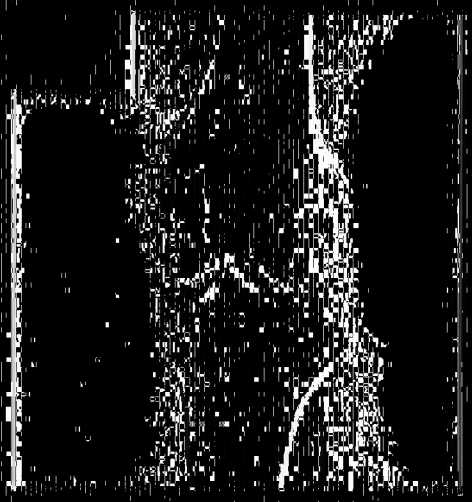


FIG 6E

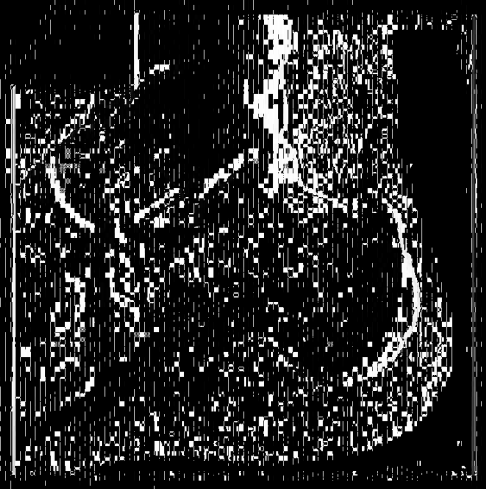


FIG 6F

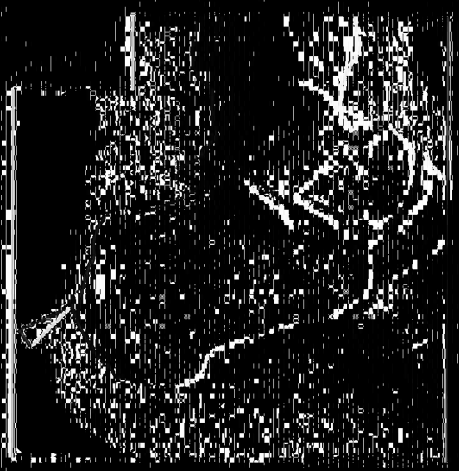


FIG 6G

FIG. 7A

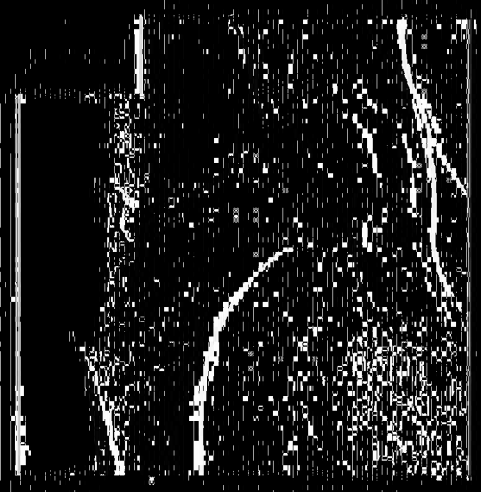


图 7B

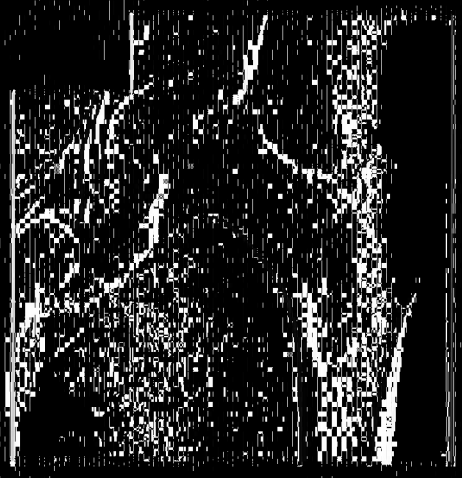


图 7C

图 7D

图 7E

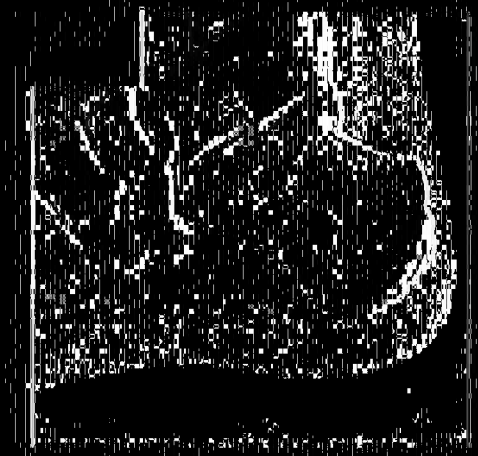
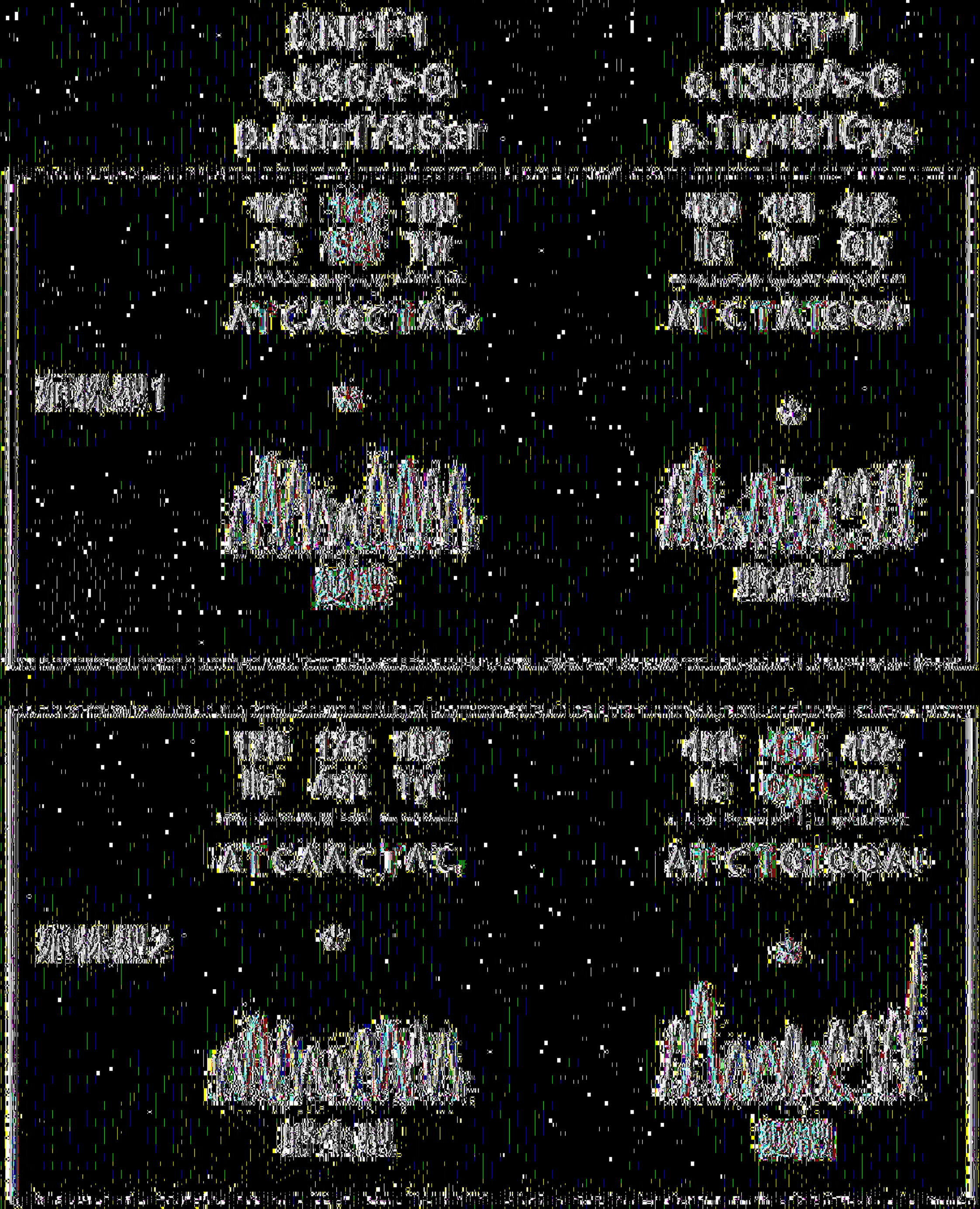


图 7F

图 7G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ENPP1
c.1352A>G
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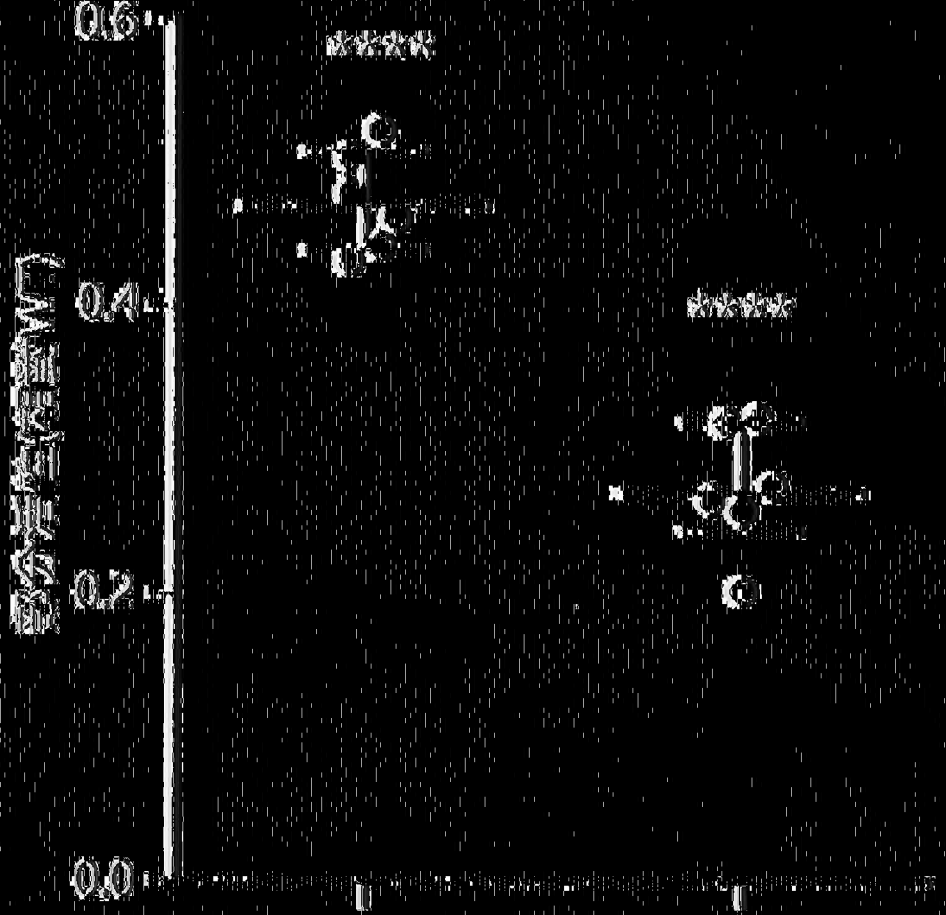
Ile Ser Tyr
ATCAGCTAC
450 451 452
Ile Tyr Gly
ATCTATGGA
178 179 180
Ile Asn Tyr
ATCAACTAC
450 451 452
Ile Cys Gly
ATCTGTGGA

圖 8


1
108
144
189
191
591
661
926
CD
TM
SM1
SM2
N1793
Y1513C

図9


0.6
0.4
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0.0
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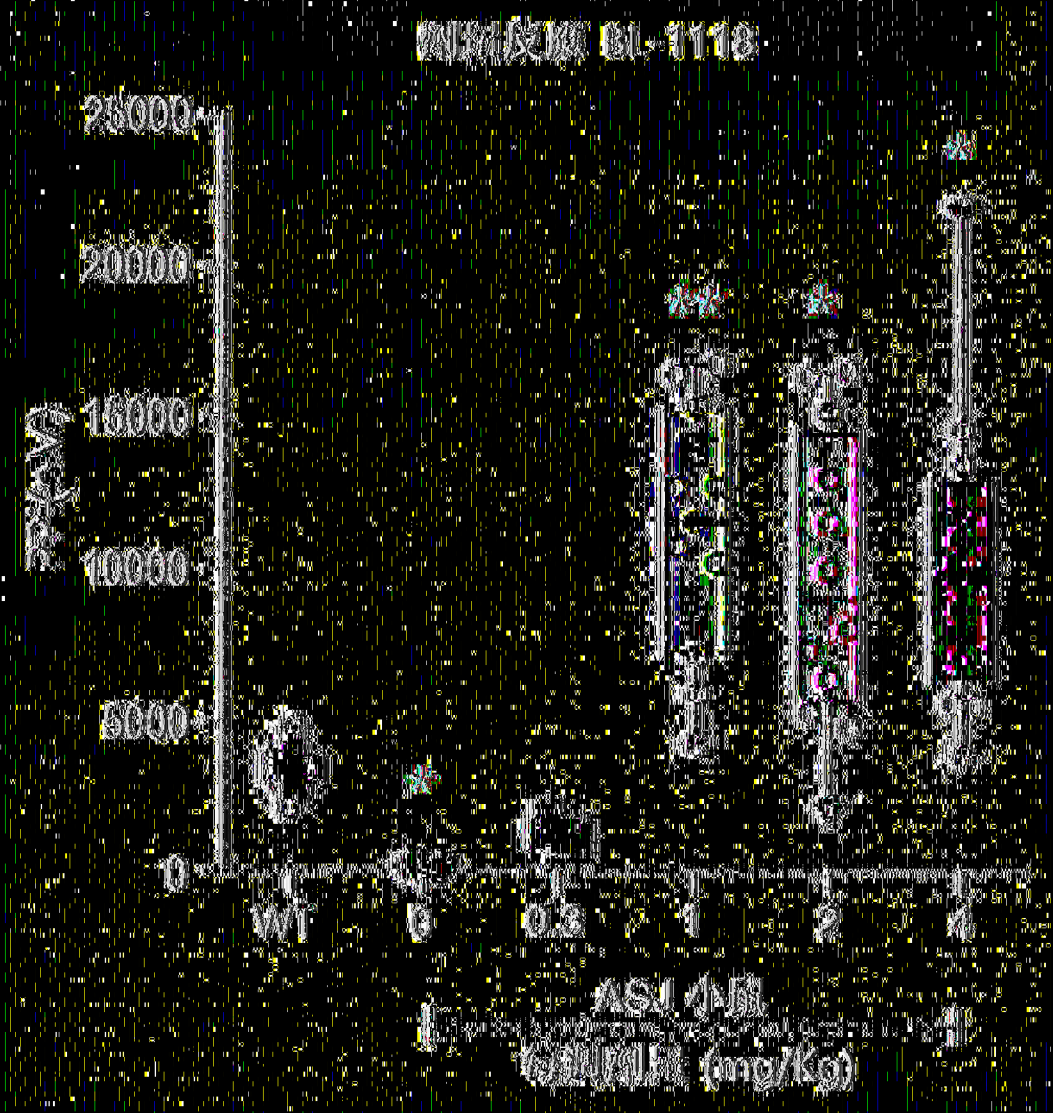
Y1513C

図10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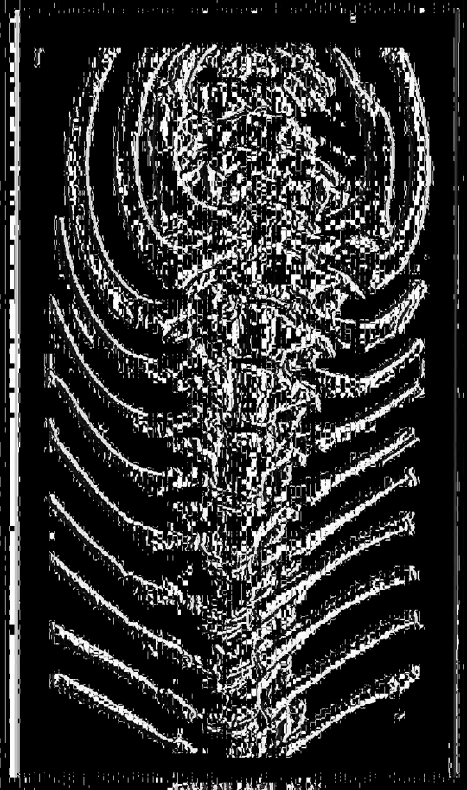
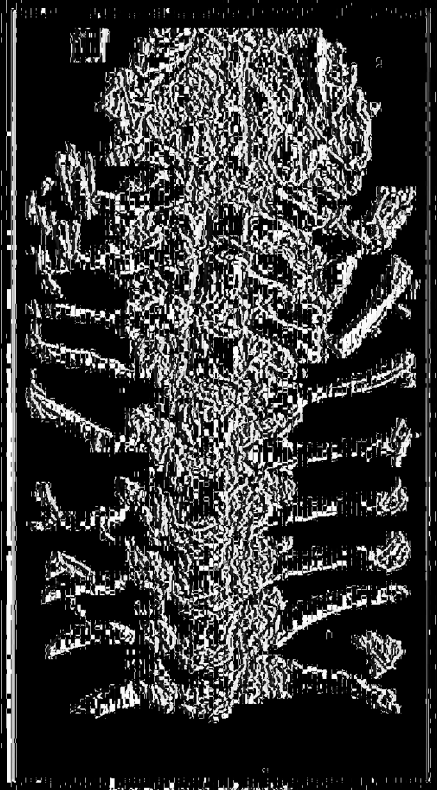
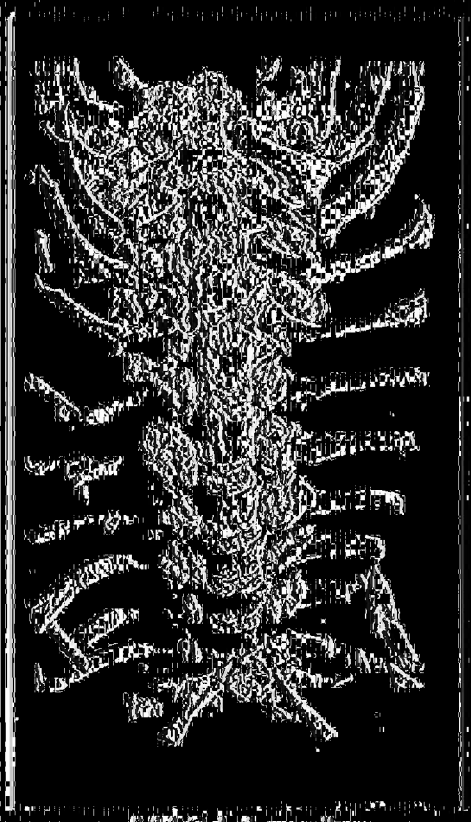
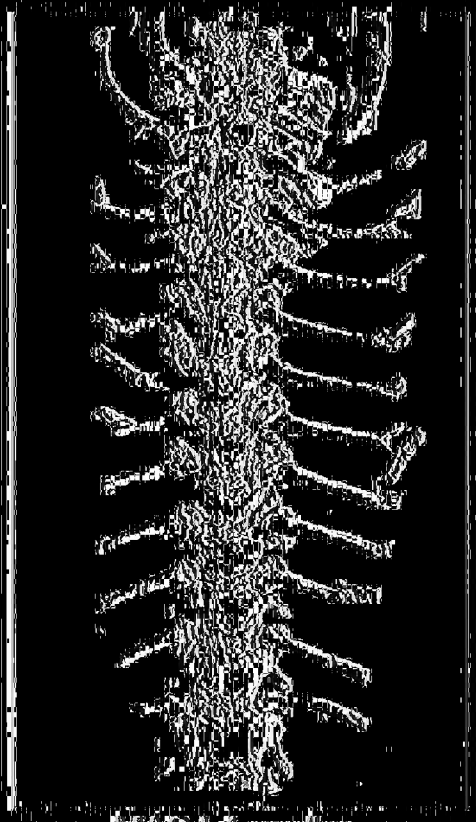
25000
20000
15000
10000
5000
0
Viable cell (cells/mL)
WT
0
0.5
1
2
4
ASJ 小用量
(mg/Kg)

圖 12

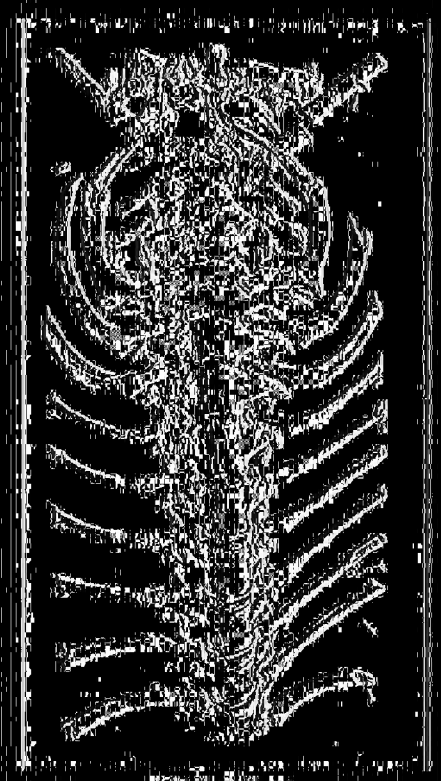


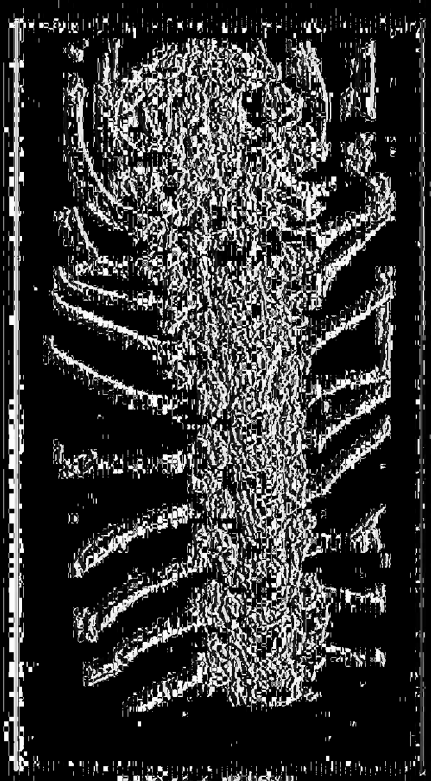


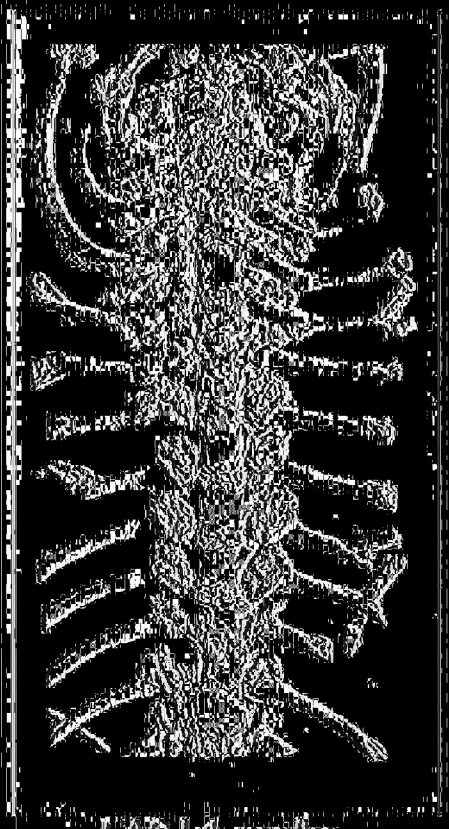


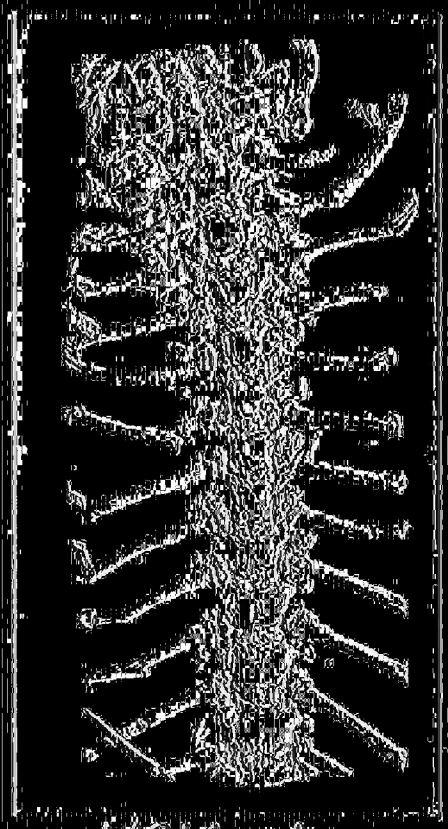


[Fig. 13]









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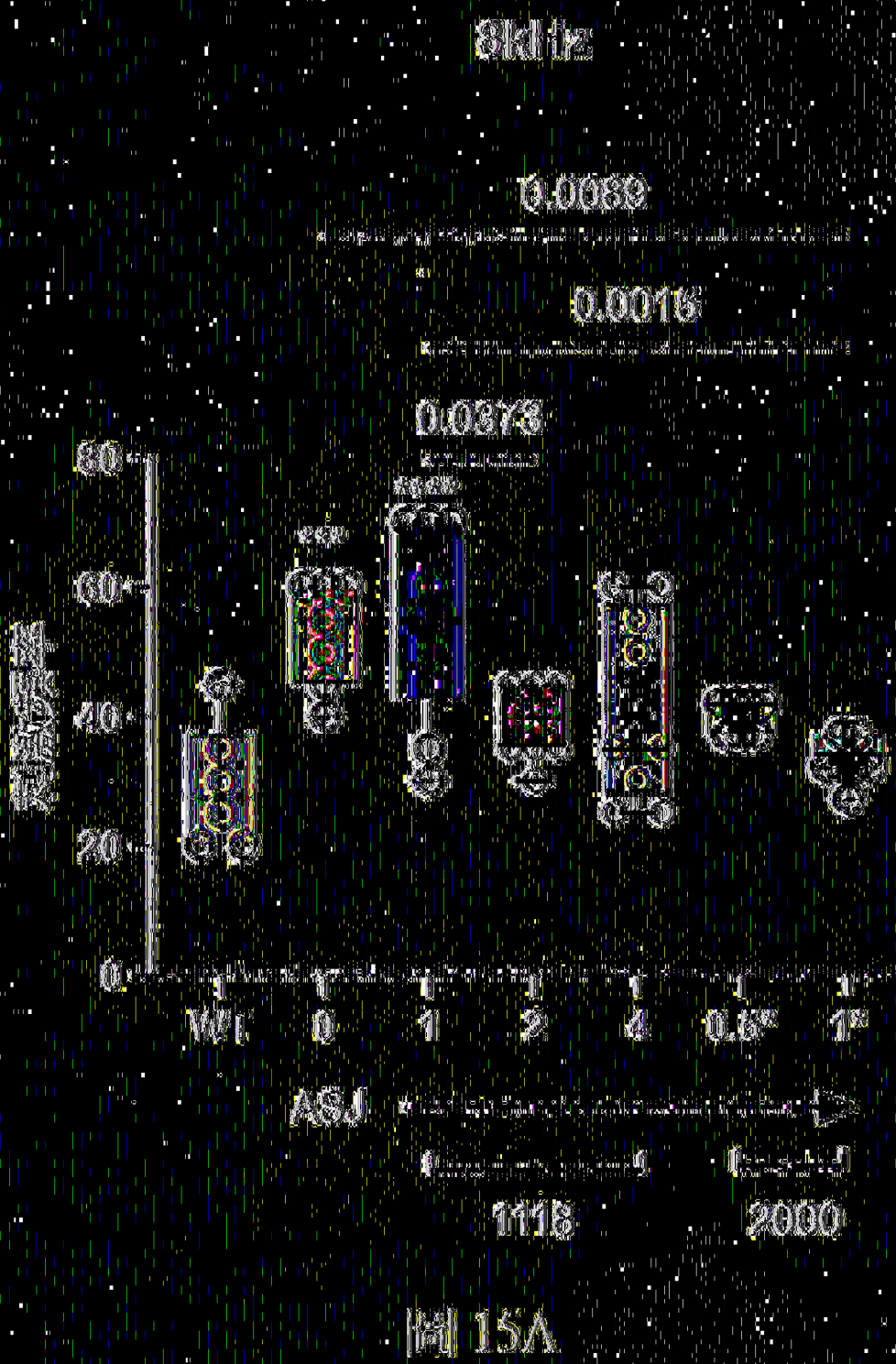

표 15A

1116

2006

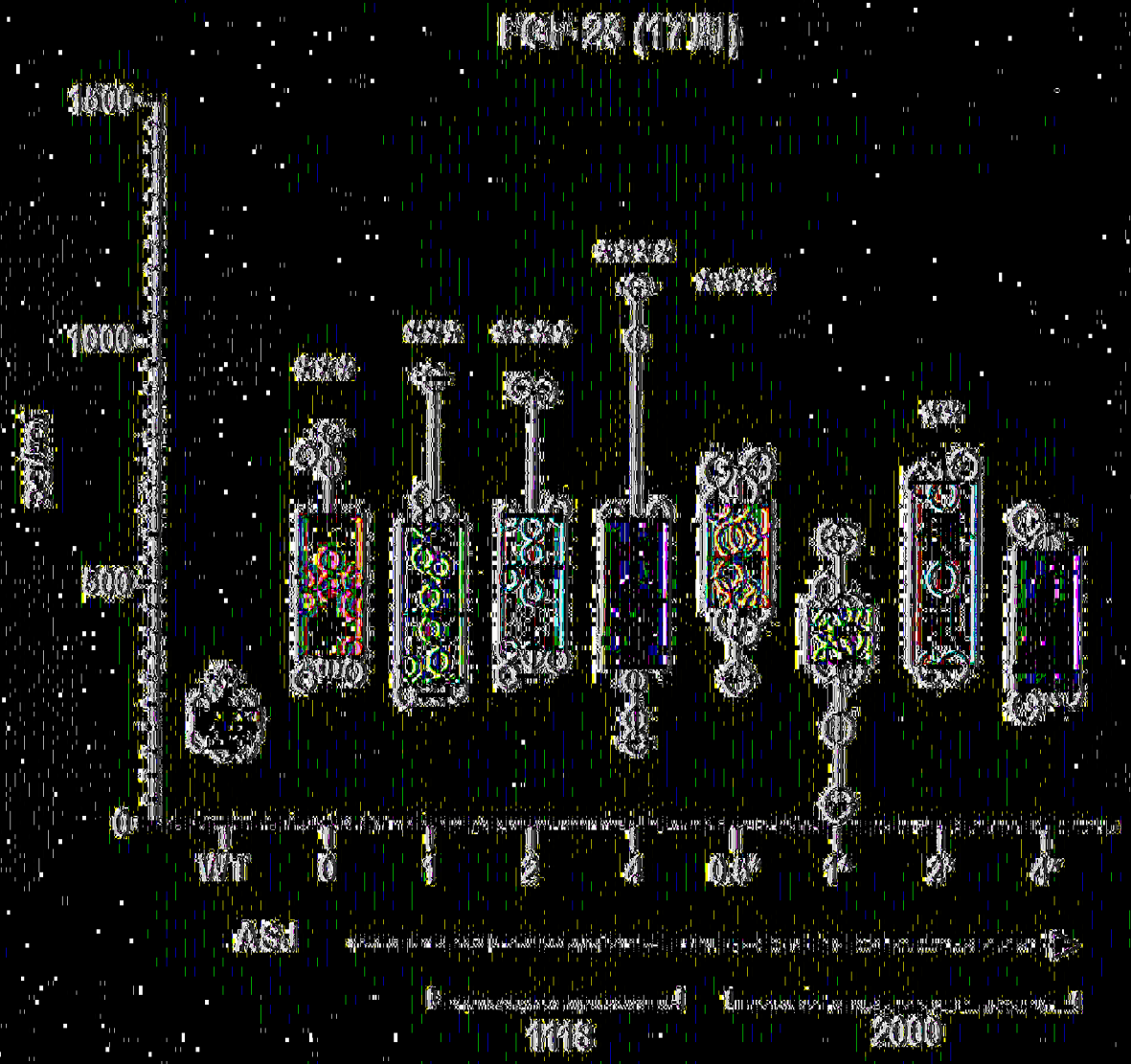

图 16

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