(19)国家知识产权局

(12)发明专利

(10)授权公告号 CN 113631033 B
(45)授权公告日 2024.10.15

(21)申请号 202080009084.9
(22)申请日 2020.01.20
(65)同一申请的已公布的文献号
申请公布号 CN 113631033 A
(43)申请公布日 2021.11.09
(30)优先权数据
62/794,450 2019.01.18 US
62/821,692 2019.03.21 US
62/877,044 2019.07.22 US
(85)PCT国际申请进入国家阶段日
2021.07.13
(86)PCT国际申请的申请数据
PCT/US2020/014296 2020.01.20
(87)PCT国际申请的公布数据
WO2020/150716 EN 2020.07.23
(73)专利权人 依诺兹梅制药公司
地址 美国马萨诸塞州
专利权人 耶鲁大学
(72)发明人 S·江格斯 D·布拉多克
(74)专利代理机构 北京三友知识产权代理有限公司 11127
专利代理师 李栋修 褚瑶杨
(51)Int.Cl.
A61K 38/00(2006.01)
A01K 67/02(2006.01)
A01K 67/0275(2024.01)
(56)对比文件
US 2018057821 A1,2018.03.01
US 2001020086 A1,2001.09.06
US 8017324 B1,2011.09.13
审查员 刘文豪

权利要求书2页 说明书253页
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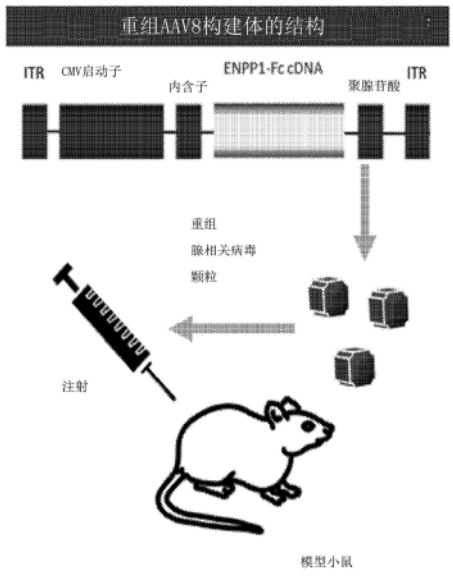
(54)发明名称

与ENPP1或ENPP3缺乏有关的疾病的治疗

(57)摘要

本发明尤其提供了用于体内表达ENPP1或ENPP3的载体(vector)和用于治疗受试对象的钙化和骨化疾病的方法。



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1.一种包含重组多核苷酸的腺相关病毒(AAV)载体,所述重组多核苷酸编码包含外核苷酸焦磷酸酶/磷酸二酯酶-1(ENPP1)的催化结构域的多肽,所述AAV载体包含启动子,并具有选自以下组成的组的血清型:AAV1、AAV2、AAV3、AAV4、AAV5、AAV6、AAV7、AAV8、AAV9和AAV-rh74,其中当所述多核苷酸在哺乳动物细胞中表达时,所述多肽具有减少软组织的异位钙化的活性。

2.根据权利要求1所述的AAV载体,其中所述多肽是融合蛋白,所述融合蛋白包括:(i)ENPP1蛋白和(ii)半衰期延长结构域。

3.根据权利要求2所述的AAV载体,其中半衰期延长结构域是IgG Fc结构域或IgG Fc结构域的功能片段,相对于不存在IgG Fc结构域或其功能片段的多肽的半衰期,其能够延长所述多肽在受试对象中的半衰期。

4.根据权利要求2所述的AAV载体,其中半衰期延长结构域是白蛋白结构域或白蛋白结构域的功能片段,相对于不存在所述白蛋白结构域或其功能片段的多肽的半衰期,其能够延长所述多肽在受试对象中的半衰期。

5.根据权利要求3所述的AAV载体,其中所述多核苷酸编码融合至Fc多肽的所述ENPP1以形成氨基至羧基端顺序的ENPP1-Fc。

6.根据权利要求4所述的AAV载体,其中所述多核苷酸编码融合至人血清白蛋白的所述ENPP1以形成氨基至羧基端顺序的ENPP1-白蛋白。

7.根据权利要求1所述的AAV载体,其中所述启动子是肝特异性启动子。

8.根据权利要求7所述的AAV载体,其中所述肝特异性启动子选自:白蛋白启动子、磷酸烯醇丙酮酸羧激酶(PEPCK)启动子和α-1-抗胰蛋白酶启动子组成的组。

9.根据权利要求7至8中任一项所述的AAV载体,其中所述载体包括编码聚腺苷酸化信号的序列。

10.一种药物组合物,其包括根据权利要求1至9中的任一项所述的AAV载体和生理相容的载体。

11.根据权利要求1至9中的任一项所述的腺相关病毒(AAV)载体,其用于在有需要的受试对象中预防或减轻疾病进展,其中所述疾病选自由以下组成的组:X连锁低磷酸血症(XLH)、慢性肾病(CKD)、矿物质和骨代谢紊乱(MBD)、血管钙化、软组织的病理性钙化、软组织的病理性骨化、婴儿全身性动脉钙化(GACI)、后纵韧带骨化(OPLL)。

12.根据权利要求1至9中的任一项所述的腺相关病毒(AAV)载体,其用于在有需要的受试对象中治疗或预防病理性钙化或病理性骨化的疾病或病症。

13.根据权利要求1至9中的任一项所述的腺相关病毒(AAV)载体,其用于在有需要的受试对象中治疗ENPP1蛋白缺乏,其中所述ENPP1蛋白缺乏与所述受试对象中NPP1基因的功能缺失突变或ABCC6基因的功能缺失突变相关。

14.根据权利要求5所述的AAV载体,其中编码ENPP1-Fc多肽的AAV载体能够在受试对象中产生血浆焦磷酸盐(PPi)的剂量依赖性增加和血浆ENPP1浓度的剂量依赖性增加。

15.根据权利要求1所述的AAV载体,其中多肽序列包括ENPP1蛋白的胞外结构域。

16.根据权利要求1所述的AAV载体,其中所述多肽包括ENPP1蛋白的跨膜结构域。

17.根据权利要求1至4中任一项所述的AAV载体,其中所述多肽包括ENPP1蛋白的核酸酶结构域。

18.根据权利要求1至4中任一项所述的AAV载体,其中所述多肽包括SEQ ID NO:1的残基99-925(Pro Ser Cys至Gln Glu Asp)。

19.根据权利要求1至4中任一项所述的AAV载体,其中所述多肽包括SEQ ID NO:7的残基31-875(Leu Leu Val至Thr Thr Ile)。

20.根据权利要求1至4中任一项所述的AAV载体,其中所述多肽包括SEQ ID NO:1的残基191-591(Val Glu Glu至Gly Ser Leu)。

21.根据权利要求1至4中任一项所述的AAV载体,其中所述多肽包括SEQ ID NO:7的残基140-510(Leu Glu Glu至Glu Val Glu)。

22.根据权利要求1至4中任一项所述的AAV载体,其中所述多肽包括SEQ ID NO:92的残基1-827(Pro Ser Cys至Gln Glu Asp)。

23.根据权利要求1至4中任一项所述的AAV载体,其中所述多肽包括SEQ ID NO:89的残基1-833(Phe Thr Ala至Gln Glu Asp)或SEQ ID NO:91的残基1-830(Gly Leu Lys至Gln Glu Asp)。

24.根据权利要求3所述的AAV载体,其中所述IgG Fc结构域包括SEQ ID NO:34所示的氨基酸序列。

25.根据权利要求4所述的AAV载体,其中所述白蛋白结构域包括如SEQ ID NO:35所示的氨基酸序列。

26.根据权利要求18至25中任一项所述的AAV载体,其中所述多核苷酸编码接头序列。

27.根据权利要求26所述的AAV载体,其中所述接头序列选自SINs:57-88和94组成的组。

28.根据权利要求26至27任一项所述的AAV载体,其中所述接头序列连接所述ENPP1蛋白和融合蛋白的半衰期延长结构域。

与ENPP1或ENPP3缺乏有关的疾病的治疗

[0001] 交叉引用

[0002] 本申请要求2019年1月18日(01/18/2019)提交的美国申请62/794,450号,2019年3月21日(03/21/2019)提交的美国申请62/821,692号,以及2019年7月22日(07/22/2019)提交的美国申请62/877,044号的优先权,其各自的内容通过引用整体并入本文。

技术领域

[0003] 本发明总体涉及通过向哺乳动物提供编码ENPP1或ENPP3的核酸来治疗涉及ENPP1或ENPP3缺乏的疾病。

背景技术

[0004] ENPP1(也称为PC-1)是位于成骨细胞和软骨细胞的矿物质沉积基质囊泡上的2型细胞外膜结合糖蛋白,并且将细胞外核苷酸(主要是ATP)水解成单磷酸腺苷(AMP)和无机焦磷酸盐(PPi)。PPi通过与新生的羟基磷灰石(HA)晶体结合而充当异位组织矿化的有效抑制剂,从而阻止这些晶体未来的生长。ENPP1通过水解三磷酸核苷酸(NTPs)产生PPi,进行性关节强制蛋白(ANK)将胞内PPi转运到细胞外间隙,组织非特异性碱性磷酸酶(TNAP)通过将PPi直接水解成Pi除去PPi。WO 2011/113027-Quinn等人,WO2012/125182-Quinn等人,WO 2016/100803-Quinn等人和WO 2017/218786-Yan等人描述NPP1。

[0005] 与ENPP1类似,ENPP3也属于磷酸二酯酶I/核苷酸焦磷酸酶家族。这些酶是II型跨膜蛋白,其催化多种分子(包括脱氧核苷酸、NAD和核苷酸糖)的磷酸二酯键和磷酸硫酸键的裂解。ENPP1已经显示在治疗异位组织钙化的某些疾病中是有效的,例如在GACI(婴儿全身性动脉钙化)的小鼠模型中减少全身性动脉钙化,GACI为在婴儿中发生的严重疾病并且涉及广泛的动脉钙化(Albright等人,2015,NatureComm.10006)。

发明内容

[0006] 在一个方面,本发明提供了编码包括外核苷酸焦磷酸酶/磷酸二酯酶-1(ENPP1)或外核苷酸焦磷酸酶/磷酸二酯酶-3(ENPP3)的重组多肽的重组多核苷酸。

[0007] 在另一方面,本发明提供了包括本文所述的任何重组多核苷酸的病毒载体(vector)。

[0008] 在一些实施方案中,重组多核苷酸编码人ENPP1或人ENPP3多肽。因此,本发明还提供了包括重组多核苷酸的病毒载体(vector),重组多核苷酸编码包括外核苷酸焦磷酸酶/磷酸二酯酶-1(ENPP1)或外核苷酸焦磷酸酶/磷酸二酯酶-3(ENPP3)的重组多肽。

[0009] 在本文所述的任何多核苷酸或病毒载体(vector)的一些实施方案中,重组多肽是ENPP1融合多肽。

[0010] 在本文所述的任何多核苷酸或病毒载体(vector)的一些实施方案中,重组多肽是ENPP3融合多肽。

[0011] 在本文所述的任何多核苷酸或病毒载体(vector)的一些实施方案中,ENPP1融合

多肽是ENPP1-Fc融合多肽或ENPP1-白蛋白融合多肽。

[0012] 在本文所述的任何多核苷酸或病毒载体(vector)的一些实施方案中,ENPP3融合多肽是ENPP3-Fc融合多肽或ENPP3-白蛋白融合多肽。

[0013] 在本文所述的任何多核苷酸或病毒载体(vector)的一些实施方案中,重组多肽包括融合至ENPP1或ENPP3的信号肽。

[0014] 在本文所述的任何多核苷酸或病毒载体(vector)的一些实施方案中,所述信号肽是天青杀素(Azurocidin)信号肽或NPP2信号肽或NPP7信号肽。

[0015] 在本文所述的任何多核苷酸或病毒载体(vector)的一些实施方案中,病毒载体(vector)是腺相关病毒载体(vector)、或单纯疱疹病毒载体(vector)、或α病毒载体(vector)、或慢病毒载体(vector)。在本发明的一个方面,腺相关病毒载体(vector)(AAV)的血清型是AAV1、或AAV2、或AAV3、或AAV4、或AAV5、或AAV6、或AAV7、或AAV8、或AAV9、或AAV-rh74。

[0016] 在另一方面,本发明提供了包括编码ENPP1-Fc融合多肽的重组多肽的腺相关病毒载体(vector)。

[0017] 在另一个方面,本发明内容提供了腺相关病毒载体(vector),其包括编码包括融合至ENPP1-Fc融合多肽的天青杀素信号肽重组多肽的重组多肽。

[0018] 在一些实施方案中,病毒载体(vector)不是昆虫病毒载体(vector),例如杆状病毒载体(vector)。

[0019] 在一些实施方案中,病毒载体(vector)能够感染哺乳动物细胞如人细胞(例如人肝细胞或HEK细胞、HeLa或A549或肝细胞)。在一些实施方案中,病毒载体(vector)能够感染、进入哺乳动物细胞,和/或与哺乳动物细胞融合,例如人细胞。在一些实施方案中,病毒载体(vector)的多核苷酸的全部或功能部分(例如,能够表达本文所述多肽的部分)整合或整合到与本文所述病毒载体(vector)接触的细胞的基因组中。在一些实施方案中,病毒载体(vector)的多核苷酸的全部或功能部分能够以染色体外状态维持而不整合到与本文所述的病毒载体(vector)接触的哺乳动物细胞的基因组中。

[0020] 在一些实施方案中,重组多核苷酸包括编码病毒蛋白和/或人ENPP1的载体(vector)或质粒。在一些实施方案中,重组多核苷酸包括编码病毒蛋白和/或人ENPP3的载体(vector)或质粒。在一些实施方案中,载体(vector)或质粒能够表达所编码的多肽,该多肽包括融合至外核苷酸焦磷酸酶/磷酸二酯酶-1(ENPP1)或融合至外核苷酸焦磷酸酶/磷酸二酯酶-3(ENPP3)的天青杀素信号肽。

[0021] 在一些实施方案中,所编码的多肽包括融合至外核苷酸焦磷酸酶/磷酸二酯酶-1(ENPP1)的天青杀素信号肽,其包括跨膜结构域、生长调节素结构域、催化结构域和核酸酶结构域。

[0022] 在一些实施方案中,所编码的多肽包括融合至胞外核苷酸焦磷酸酶/磷酸二酯酶-1(ENPP1)的天青杀素信号肽,其分泌至细胞溶质中。

[0023] 在一些实施方案中,编码多肽的重组多核苷酸包括融合至外核苷酸焦磷酸酶/磷酸二酯酶-1(ENPP1)的跨膜结构域,其不被分泌并且是膜结合的。

[0024] 在一些实施方案中,本发明提供了编码包括外核苷酸焦磷酸酶/磷酸二酯酶-1(ENPP1)的多肽的重组多核苷酸。在一些实施方案中,包括外核苷酸焦磷酸酶/磷酸二酯酶-

1(ENPP1)的多肽包括SEQ ID NO:1的氨基酸残基。

[0025] 在一些实施方案中,所编码的多肽包括融合至胞外核苷酸焦磷酸酶/磷酸二酯酶-1(ENPP1)的天青杀素信号肽。

[0026] 在一些实施方案中,所编码的包括融合至外核苷酸焦磷酸酶/磷酸二酯酶-1(ENPP1)的天青杀素信号肽的多肽缺乏聚天冬氨酸结构域或带负电荷的骨靶向结构域。

[0027] 在一些实施方案中,载体(vector)是病毒载体(vector)。在一些实施方案中,病毒载体(vector)是腺相关病毒(AAV)载体(vector)。在一些实施方案中,本文所述的任何多核苷酸编码融合至ENPP1的天青杀素信号肽或融合至ENPP3和ENPP1的天青杀素信号肽或融合至Fc多肽的ENPP3以在氨基至羧基端顺序分别形成天青杀素信号肽-ENPP1-Fc或天青杀素信号肽-ENPP3-Fc。

[0028] 在一些实施方案中,重组多核苷酸编码融合至ENPP1的天青杀素信号肽或融合至ENPP3的天青杀素信号肽以及融合至人血清白蛋白的ENPP1或ENPP3以在氨基至羧基端顺序分别形成的天青杀素信号肽-ENPP1-白蛋白或天青杀素信号肽-ENPP3-白蛋白。

[0029] 在一些实施方案中,Fc或白蛋白序列直接与ENPP1或ENPP3蛋白的C端融合。在一些实施方案中,Fc或白蛋白序列通过接头,例如柔性接头融合至ENPP1或ENPP3蛋白的C端。在一些实施方案中,接头选自SEQ ID NO:57-88。

[0030] 在一些实施方案中,病毒载体(vector)包括并能够表达编码融合至ENPP1或ENPP3的N端的信号肽的核酸序列。在病毒载体(vector)的一些实施方案中,载体(vector)包括启动子。在病毒载体(vector)的一些实施方案中,启动子是肝特异性启动子。

[0031] 在病毒载体(vector)的一些实施方案中,肝特异性启动子选自:白蛋白启动子、磷酸烯醇丙酮酸羧激酶(PEPCK)启动子和α-1-抗胰蛋白酶启动子组成的组。在病毒载体(vector)的一些实施方案中,载体(vector)包括编码聚腺苷酸化信号的序列。

[0032] 在病毒载体(vector)的一些实施方案中,信号肽是天青杀素信号肽。在病毒载体(vector)的一些实施方案中,病毒载体(vector)是腺相关病毒(AAV)载体(vector)。在病毒载体(vector)的一些实施方案中,AAV载体(vector)具有选自以下组成的组的血清型:AAV1、AAV2、AAV3、AAV4、AAV5、AAV6、AAV7、AAV8、AAV9和AAV-rh74。

[0033] 在病毒载体(vector)的一些实施方案中,本发明的多核苷酸编码融合至ENPP1的天青杀素信号肽或融合至ENPP3的天青杀素信号肽,以及融合至Fc多肽的ENPP1或ENPP3以在氨基至羧基端顺序分别形成天青杀素信号肽-ENPP1-Fc或天青杀素信号肽-ENPP3-Fc。

[0034] 在病毒载体(vector)的一些实施方案中,多核苷酸编码融合至ENPP1的天青杀素信号肽或融合至ENPP3的天青杀素信号肽,以及融合至人血清白蛋白的ENPP1或ENPP3以在氨基至羧基端顺序分别形成天青杀素信号肽-ENPP1-白蛋白或天青杀素信号肽-ENPP3-白蛋白。

[0035] 在又一个方面,本发明提供了包括本文描述的任何多核苷酸的细胞(例如,哺乳动物细胞,如啮齿动物细胞、非人灵长类动物细胞、或人类细胞)。

[0036] 在一些实施方案中,本发明还提供一种获得重组病毒载体(vector)的方法,其包括以下步骤:

[0037] i.提供包括本发明的多核苷酸的细胞,

[0038] ii.在足以组装该病毒的条件下维持该细胞,并且

[0039] iii.纯化由细胞产生的病毒载体(vector)。

[0040] 在另一方面,本发明提供了生产重组病毒载体(vector)的方法。该方法,包括:

[0041] i.提供包括本文所述的多核苷酸的细胞或细胞群,其中细胞表达对于将多核苷酸包装或组装到重组病毒载体(vector)中所必需的病毒蛋白;和

[0042] ii.将细胞或细胞群维持在足以组装重组病毒载体(vector)包装的条件下。

[0043] 在一些实施方案中,方法包括从细胞或细胞群,或从维持细胞或细胞群的培养基中纯化病毒载体(vector)。

[0044] 在一些实施方案中,细胞是哺乳动物细胞,如啮齿动物细胞(例如,大鼠细胞、小鼠细胞、仓鼠细胞)、非人灵长类细胞或人类细胞(例如,HEK293、HeLa或A549)。

[0045] 在一些实施方案中,方法还包括将编码一种或多种病毒蛋白(例如包装或组装病毒载体(vector)所必需的那些)的重组核酸,例如通过用含有这种重组核酸的辅助病毒感染细胞,用包括这种重组核酸的辅助质粒转染细胞或细胞群等。

[0046] 在一些实施方案中,病毒载体(vector)在靶细胞中感染后能够表达本文所述的一种或多种多肽。

[0047] 在一些实施方案中,本发明提供包括如本文所述的纯化的病毒载体(vector)的药物组合物。在一些实施方案中,本发明提供了包括如本文所述的无strerile/内毒素的纯化的病毒载体(vector)的无菌药物组合物。

[0048] 在另一方面,本发明提供通过本文所述的任何方法获得和纯化的病毒载体(vector)。

[0049] 在另一方面,本发明提供包括通过本文所述的任何方法获得和纯化的任何病毒载体(vector)的药物组合物。

[0050] 在某些实施方案中,本发明提供了给哺乳动物提供ENPP1或ENPP3的方法,该方法包括给哺乳动物施用本发明的病毒载体(vector)。

[0051] 在某些实施方案中,本发明提供了在哺乳动物(例如人,诸如需要这种表达的人)中表达ENPP1或ENPP3的方法,该方法包括向哺乳动物施用本文所述的任何病毒载体(vector)。在向哺乳动物施用病毒载体(vector)之前,同时和/或之后,该方法可以进一步包括在从哺乳动物获得的生物样本中检测和/或测量以下参数中的一个或多个:ENPP1和/或ENPP3的表达、ENPP1和/或ENPP3的活性水平、和/或焦磷酸盐水平或浓度。在一些实施方案中,在向哺乳动物施用病毒载体(vector)后的1周、1至2周和/或1个月内检测或测量一个或多个参数。在一些实施方案中,哺乳动物(例如,人)是患有ENPP1或ABCC6缺陷的哺乳动物。

[0052] 在另一方面,本发明提供一种药物组合物,其包括如本文所述的病毒载体(vector)中的任一种和生理学上相容的载体(carrier)。

[0053] 在一些实施方案中,本发明提供在有需要的哺乳动物中预防病症或疾病或降低其进展的方法,该方法包括向哺乳动物施用治疗有效量的根据本发明的组合物,其中病症或疾病包括但不限于以下中的一种或多种:NPP1缺乏、低水平的PPi、以动脉和/或结缔组织中的钙和其它矿物质沉积物的积累为特征的进行性疾病、软组织的异位钙化、动脉或静脉钙化、心脏组织(例如主动脉组织和冠状组织)的钙化、弹性纤维假黄瘤(PXE)、X连锁低磷酸血症(X-linked hypophosphatemia、XLH)、慢性肾病(CKD)、矿物质和骨代谢紊乱(MBD)、血管

钙化、软组织的病理性钙化、软组织的病理性骨化、婴儿全身性动脉钙化(GACI)和后纵韧带骨化(OPLL)、由此预防哺乳动物中的疾病或减少其进展。

[0054] 在另一方面,本发明提供一种治疗、预防和/或改善有需要的受试对象中的病理性钙化或病理性骨化的疾病或病症的方法,方法包括施用治疗有效量的本文所述的病毒载体(vector)中的任一种,从而治疗、预防或改善疾病或病症。在一些实施方案中,病毒载体(vector)包括编码人ENPP1或人ENPP3多肽的多核苷酸。

[0055] 在另一方面,本发明提供了治疗患有ENPP1蛋白缺乏的受试对象的方法,该方法包括向受试对象施用治疗有效量的编码重组ENPP1或ENPP3多肽的病毒载体(vector),从而治疗受试对象。在本发明的一个方面,病毒载体(vector)编码人ENPP1或人ENPP3多肽。

[0056] 在另一方面,受试对象患有与受试对象的NPP1基因中的功能缺失突变或受试对象的ABCC6基因中的功能缺失突变相关的疾病或病症或ENPP1蛋白缺乏。

[0057] 在本文所述的任何方法的一些实施方案中,病毒载体(vector)是编码ENPP1-Fc融合多肽的AAV载体(vector),并且载体(vector)以1×10^{12}至1×10^{15}vg/kg,优选1×10^{13}至1×10^{14}vg/kg的剂量施用给受试对象。

[0058] 在本文所述的任何方法的一些实施方案中,病毒载体(vector)是编码ENPP1-Fc融合多肽的AAV载体(vector),并且载体(vector)以5×10^{11}至5×10^{15}vg/kg的剂量施用给受试对象。

[0059] 在本文所述的任何方法的一些实施方案中,病毒载体(vector)是编码ENPP1-Fc融合多肽的AAV载体(vector),并且每名受试对象施用约1×10^{12}至1×10^{15}vg/kg以递送和表达ENPP1-Fc多肽。

[0060] 在本文所述的任何方法的一些实施方案中,病毒载体(vector)是编码ENPP3-Fc融合多肽的AAV载体(vector),并且载体(vector)以1×10^{12}至1×10^{15}vg/kg,优选1×10^{13}至1×10^{14}vg/kg的剂量施用给受试对象。

[0061] 在本文所述的任何方法的一些实施方案中,病毒载体(vector)是编码ENPP3-Fc融合多肽的AAV载体(vector),并且载体(vector)以5×10^{11}至5×10^{15}vg/kg的剂量施用给受试对象。

[0062] 在本文所述的任何方法的一些实施方案中,病毒载体(vector)是编码ENPP3-Fc融合多肽的AAV载体(vector),并且每名受试对象施用约1×10^{12}至1×10^{15}vg/kg以递送和表达ENPP3-Fc多肽。

[0063] 在本文所述的任何方法的一些实施方案中,向受试对象施用编码ENPP1-Fc多肽的AAV载体(vector)在受试对象中产生血浆焦磷酸盐(PPi)的剂量依赖性增加和血浆ENPP1浓度的剂量依赖性增加。

[0064] 在向哺乳动物施用病毒载体(vector)之前、同时和/或之后,本文所述的任何方法可以进一步包括在从哺乳动物获得的生物样本中检测和/或测量以下参数中的一个或多个:ENPP1和/或ENPP3的表达、ENPP1和/或ENPP3的活性水平、和/或焦磷酸盐水平或浓度。在一些实施方案中,在向哺乳动物施用病毒载体(vector)后的1周、1至2周和/或1个月内检测或测量一个或多个参数。

[0065] 在另一方面,本发明提供了在有需要的受试对象中治疗或预防病理性钙化或病理性骨化的疾病或病症的方法,其包括向受试对象施用治疗有效量的编码重组ENPP1或ENPP3

多肽的病毒载体(vector),从而治疗或预防疾病或病症。

[0066] 在另一方面,本发明提供了治疗患有ENPP1蛋白缺乏的受试对象的方法,包括向受试对象施用治疗有效量的编码重组ENPP1或ENPP3多肽的病毒载体(vector),从而治疗受试对象。

[0067] 在本文所述的任何方法的一些实施方案中,疾病或病症或ENPP1蛋白缺乏与受试对象中NPP1基因的功能缺失突变或ABCC6基因的功能缺失突变相关。

[0068] 在本文所述的任何方法的一些实施方案中,病毒载体(vector)编码重组ENPP1多肽。

[0069] 在本文所述的任何方法的一些实施方案中,病毒载体(vector)编码重组ENPP3多肽。

[0070] 在本文所述的任何方法的一些实施方案中,病毒载体(vector)编码重组ENPP1-Fc融合多肽或重组ENPP1-白蛋白融合多肽。

[0071] 在本文所述的任何方法的一些实施方案中,病毒载体(vector)编码重组ENPP3-Fc融合多肽或重组ENPP3-白蛋白融合多肽。

[0072] 在本文所述的任何方法的一些实施方案中,病毒载体(vector)编码包括融合至ENPP1或ENPP3的信号肽的重组多肽。

[0073] 在本文所述的任何方法的一些实施方案中,载体(vector)编码ENPP1-Fc或ENPP1-白蛋白。

[0074] 在本文所述的任何方法的一些实施方案中,信号肽是天青杀素信号肽、NPP2信号肽或NPP7信号肽。

[0075] 在本文所述的任何方法的一些实施方案中,病毒载体(vector)是腺相关病毒载体(vector)、或单纯疱疹病毒载体(vector)、或α病毒载体(vector)、或慢病毒载体(vector)。

[0076] 在本文所述的任何方法的一些实施方案中,腺相关病毒载体(vector)(AAV)的血清型是AAV1、或AAV2、或AAV3、或AAV4、或AAV5、或AAV6、或AAV7、或AAV8、或AAV9、或AAV-rh74。

[0077] 在本文所述的任何方法的一些实施方案中,病毒载体(vector)是编码重组多肽的腺相关病毒(AAV)载体(vector),重组多肽包括融合至ENPP1-Fc融合多肽的天青杀素信号肽。

[0078] 在本文所述的任何方法的一些实施方案中,将编码ENPP1-Fc融合多肽的AAV载体(vector)以1×10^{12}至1×10^{15}vg/kg的剂量施用于受试对象。

[0079] 在本文所述的任何方法的一些实施方案中,剂量为1×10^{13}至1×10^{14}vg/kg。

[0080] 在本文所述的任何方法的一些实施方案中,AAV载体(vector)以5×10^{11}至5×10^{15}vg/kg的剂量施用于受试对象。

[0081] 在本文所述的任何方法的一些实施方案中,载体(vector)是编码ENPP1-Fc的AAV载体(vector),并且以1×10^{12}至1×10^{15}vg/kg的剂量施用于受试对象。在任何上述方法的一些实施方案中,其中向受试对象施用编码ENPP1-Fc多肽的AAV载体(vector)在受试对象中产生血浆焦磷酸盐(PPi)的剂量依赖性增加和血浆ENPP1浓度的剂量依赖性增加。

[0082] 在另一方面,本发明的特征在于包括多核苷酸序列的病毒载体(vector),该多核苷酸序列编码包括ENPP1或ENPP3蛋白的催化结构域的多肽。

[0083] 在本文所述的任何病毒载体(vector)的一些实施方案中,多肽序列包括ENPP1或ENPP3蛋白的胞外结构域。

[0084] 在本文所述的任何病毒载体(vector)的一些实施方案中,多肽包括ENPP1或ENPP3蛋白的跨膜结构域。

[0085] 在本文所述的任何病毒载体(vector)的一些实施方案中,多肽包括ENPP1或ENPP3蛋白的核酸酶结构域。

[0086] 在本文所述的任何病毒载体(vector)的一些实施方案中,多肽包括SEQ ID NO:1的残基99-925(ProSer Cys至Gln Glu Asp)。

[0087] 在本文所述的任何病毒载体(vector)的一些实施方案中,多肽包括SEQ ID NO:7的残基31-875(LeuLeu Val至Thr Thr Ile)。

[0088] 在本文所述的任何病毒载体(vector)的一些实施方案中,多肽包括SEQ ID NO:1的残基191-591(Val Glu Glu至Gly Ser Leu)。

[0089] 在本文所述的任何病毒载体(vector)的一些实施方案中,多肽包括SEQ ID NO:7的残基140-510(Leu Glu Glu至Glu Val Glu)。

[0090] 在本文所述的任何病毒载体(vector)的一些实施方案中,多肽包括SEQ ID NO:92的残基1-827(ProSer Cys至Gln Glu Asp)。

[0091] 在本文所述的任何病毒载体(vector)的一些实施方案中,多肽包括SEQ ID NO:89的残基1-833(PheThr Ala至Gln Glu Asp)或SEQ ID NO:91的残基1-830(Gly Leu Lys至Gln Glu Asp)

[0092] 在本文所述的任何病毒载体(vector)的一些实施方案中,病毒载体(vector)不是昆虫病毒载体(vector)。

[0093] 在本文所述的任何病毒载体(vector)的一些实施方案中,病毒载体(vector)感染或能够感染哺乳动物细胞。

[0094] 在本文所述的任何病毒载体(vector)的一些实施方案中,多核苷酸序列编码启动子序列。

[0095] 在本文所述的任何病毒载体(vector)的一些实施方案中,启动子是肝脏特异性启动子。

[0096] 在本文所述的任何病毒载体(vector)的一些实施方案中,肝特异性启动子选自:白蛋白启动子、磷酸烯醇丙酮酸羧激酶(PEPCK)启动子和α-1-抗胰蛋白酶启动子组成的组。

[0097] 在本文所述的任何病毒载体(vector)的一些实施方案中,多核苷酸序列包括编码聚腺苷酸化信号的核苷酸序列。

[0098] 在本文所述的任何病毒载体(vector)的一些实施方案中,多核苷酸编码在编码ENPP1或ENPP3蛋白的核苷酸序列的氨基端的信号肽。

[0099] 在本文所述的任何病毒载体(vector)的一些实施方案中,信号肽是天青杀素信号肽。

[0100] 在本文所述的任何病毒载体(vector)的一些实施方案中,病毒载体(vector)是腺相关病毒(AAV)载体(vector)。

[0101] 在本文所述的任何病毒载体(vector)的一些实施方案中,AAV载体(vector)具有选自以下组成的组的血清型:AAV1、AAV2、AAV3、AAV4、AAV5、AAV6、AAV7、AAV8、AAV9和AAV-

rh74。

[0102] 在本文所述的任何病毒载体(vector)的一些实施方案中,多核苷酸序列编码融合至ENPP1的天青杀素信号肽或融合至ENPP3的天青杀素信号肽,并且ENPP1或ENPP3融合至Fc多肽以分别形成氨基至羧基端顺序的天青杀素信号肽-ENPP1-Fc或天青杀素信号肽-ENPP3-Fc。

[0103] 在本文所述的任何病毒载体(vector)的一些实施方案中,多核苷酸序列编码融合至ENPP1的天青杀素信号肽或融合至ENPP3的天青杀素信号肽,并且ENPP1或ENPP3融合至人血清白蛋白以分别形成氨基至羧基端顺序的天青杀素信号肽-ENPP1-白蛋白或天青杀素信号肽-ENPP3-白蛋白。

[0104] 在本文所述的任何病毒载体(vector)的一些实施方案中,多肽是融合蛋白,其包括:(i)ENPP1蛋白或ENPP3蛋白和(ii)半衰期延长结构域。

[0105] 在本文所述的任何病毒载体(vector)的一些实施方案中,相对于不存在IgG Fc结构域或其功能片段的多肽的半衰期,半衰期延长结构域是IgG Fc结构域或IgG Fc结构域的功能片段,其能够延长多肽在哺乳动物中的半衰期。

[0106] 在本文所述的任何病毒载体(vector)的一些实施方案中,相对于不存在白蛋白结构域或其功能片段的多肽的半衰期,半衰期延长结构域是白蛋白结构域或白蛋白结构域的功能片段,其能够延长多肽在哺乳动物中的半衰期。

[0107] 在本文所述的任何病毒载体(vector)的一些实施方案中,半衰期延长结构域是融合蛋白中ENPP1或ENPP3蛋白的羧基端。

[0108] 在本文所述的任何病毒载体(vector)的一些实施方案中,IgG Fc结构域包括SEQ ID NO:34所示的氨基酸序列。

[0109] 在本文所述的任何病毒载体(vector)的一些实施方案中,白蛋白结构域包括SEQ ID NO:35所示的氨基酸序列。

[0110] 在本文所述的任何病毒载体(vector)的一些实施方案中,多核苷酸编码接头序列。

[0111] 在本文所述的任何病毒载体(vector)的一些实施方案中,接头序列选自SINs:57-88组成的组。

[0112] 在本文所述的任何病毒载体(vector)的一些实施方案中,接头序列连接ENPP1或ENPP3蛋白和融合蛋白的半衰期延长结构域。

[0113] 在本文所述的任何病毒载体(vector)的一些实施方案中,多肽包括SEQ ID NO:89、91、92和93中描绘的氨基酸序列。

[0114] 在另一方面,本发明提供了用于产生重组病毒载体(vector)的方法,该方法包括:

[0115] i.提供包括编码多肽的多核苷酸的细胞或细胞群,多肽包括ENPP1或ENPP3蛋白的催化结构域,其中细胞表达对于将多核苷酸包装和/或组装到重组病毒载体(vector)中所必需的病毒蛋白;和

[0116] ii.将细胞或细胞群维持在足以组装包括多核苷酸的重组病毒载体(vector)包装的条件下。

[0117] 在本文所述的任何方法的一些实施方案中,哺乳动物细胞是啮齿动物细胞或人类细胞。

[0118] 在本文所述的任何方法的一些实施方案中,病毒载体(vector)是本文所述的任何一种病毒载体(vector)。

[0119] 在一些实施方案中,本文所述的任何方法可进一步包括从细胞或细胞群,或从维持细胞或细胞群的培养基中纯化重组病毒载体(vector)。

[0120] 在另一方面,本发明的特征在于从本文所述的用于产生和/或纯化重组病毒载体(vector)的方法纯化的重组病毒载体(vector)。

[0121] 在另一方面,本发明提供了包括本文所述的病毒载体(vector)或重组病毒载体(vector)中的任一种和药学上可接受的载体(carrier)的药物组合物。

[0122] 在另一方面,本发明提供在有需要的哺乳动物中预防或减少疾病进展的方法,该方法包括:向哺乳动物施用治疗有效量的本文所述的药物组合物中的任一种,从而预防或减少疾病或病症的进展。

[0123] 在本文所述的任何方法的一些实施方案中,哺乳动物是人。

[0124] 在本文所述的任何方法的一些实施方案中,疾病选自由以下组成的组:X连锁低磷酸血症(XLH)、慢性肾病(CKD)、矿物质和骨代谢紊乱(MBD)、血管钙化、软组织的病理性钙化、软组织的病理性骨化、PXE、婴儿全身性动脉钙化(GACI)、后纵韧带骨化(OPLL)。

[0125] 在另一个方面,本发明提供在有需要的受试对象中治疗或预防病理性钙化或病理性骨化的疾病或病症的方法,该方法包括向受试对象施用治疗有效量的本文所述的病毒载体(vector)或药物组合物中的任一种,从而治疗或预防疾病或病症。

[0126] 在另一方面,本发明的特征在于治疗患有ENPP1蛋白缺乏的受试对象的方法,该方法包括向受试对象施用治疗有效量的本文所述的病毒载体(vector)或药物组合物中的任一种,从而治疗受试对象。

[0127] 在本文所述的任何方法的一些实施方案中,疾病或病症或ENPP1蛋白缺乏与受试对象中NPP1基因的功能缺失突变或ABCC6基因的功能缺失突变相关。

[0128] 在本文所述的任何方法的一些实施方案中,病毒载体(vector)或药物组合物以受试对象或哺乳动物1×10^{12}至1×10^{15}vg/kg的剂量施用。

[0129] 在本文所述的任何方法的一些实施方案中,病毒载体(vector)或药物组合物以受试对象或哺乳动物1×10^{13}至1×10^{14}vg/kg的剂量施用。

[0130] 在本文所述的任何方法的一些实施方案中,病毒载体(vector)或药物组合物以受试对象或哺乳动物5×10^{11}至5×10^{15}vg/kg的剂量施用。

[0131] 在本文所述的任何方法的一些实施方案中,病毒载体(vector)或药物组合物以受试对象或哺乳动物1×10^{12}至1×10^{15}的剂量施用。

[0132] 在本文所述的任何方法的一些实施方案中,向受试对象或哺乳动物施用病毒载体(vector)或药物组合物增加受试对象或哺乳动物中的血浆焦磷酸盐(PPi)和/或血浆ENPP1或ENPP3浓度。

[0133] 在一些实施方案中,前述方法中的任一种可以进一步包括在从受试对象或哺乳动物获得的生物样本中检测或测量以下参数中的一个或多个:(i)焦磷酸盐的浓度,(ii)ENPP1或ENPP3的表达水平,和(iii)ENPP1或ENPP3的酶活性。

[0134] 在本文所述的任何方法的一些实施方案中,检测或测量发生在施用病毒载体(vector)或药物组合物之前。

附图说明

[0135] 图1——显示AAV构建体的示意图

[0136] 图2——显示与NPP2和NPP7信号序列相比,使用天青杀素信号序列时ENPP1表达量增加的图。

[0137] 图3——表达ENPP1-Fc融合体的载体(vector)的质粒图谱

[0138] 图4——显示将包括ENPP1构建体的病毒颗粒施用至模型小鼠的示意图。

[0139] 图5——显示在病毒载体(vector)给药后7天、28天和56天从对照组、低剂量和高剂量小鼠队列中收集的血浆样本中的ENPP1活性的剂量依赖性增加的图。

[0140] 图6——显示在病毒载体(vector)给药后7天、28天和56天从对照组、低剂量和高剂量小鼠队列中收集的血浆样本中的ENPP1浓度的剂量依赖性增加的图。

[0141] 图7——显示在病毒载体(vector)给药后7天、28天和56天从对照组、低剂量和高剂量小鼠队列中收集的血浆样本中的血浆PPi浓度的剂量依赖性增加的图。

[0142] 图8——显示Enpp1在病毒载体(vector)给药后持续表达长达112天的图。

[0143] 图9——显示在病毒载体(vector)给药后7天、28天、56天和112天从对照组、低剂量和高剂量小鼠队列中收集的血浆样本中的ENPP1活性的剂量依赖性增加的图。

具体实施方式

[0144] 本发明涉及将编码哺乳动物ENPP1或哺乳动物ENPP3的核酸递送至ENPP1或ENPP3缺乏的哺乳动物。

[0145] 定义

[0146] 除非另外定义,否则本文所使用的所有技术和科学术语均具有与本发明所属领域的普通技术人员通常所理解的相同的含义。尽管在本公开的实践或测试中可使用与本文所述的那些类似或等同的任何方法和材料,但还是描述了示例方法和材料。如本文所用,以下术语中的每一者具有在此部分中与其相关联的含义。

[0147] 冠词“一(a)”和“一(an)”在本文中用于指一个或多于一个(即至少一个)该冠词的语法对象。例如,“一元素”意指一个元素或多于一个元素。

[0148] 为了清楚起见,将以下符号约定应用于本发明。在任何情况下,本文中不遵循此惯例的任何教导仍是本发明内容的一部分,且可鉴于公开教导的上下文而充分理解。蛋白符号以非斜体大写字母公开。作为非限制性实例,’ENPP1’是指蛋白。在某些实施方案中,如果蛋白是人蛋白,则在蛋白符号之前使用’h’。在某些实施方案中,如果蛋白是小鼠蛋白,则在蛋白符号之前使用’m’。人ENPP1被称为‘hENPP1’,以及小鼠ENPP1被称为‘mENPP1’。人基因符号以斜体大写字母公开。作为非限制性实例,对应于蛋白hENPP1的人类基因是ENPP1。小鼠基因符号首字母大写,其余字母小写;此外,小鼠基因符号为斜体。作为非限制性实例,产生蛋白mEnpp1的小鼠基因是Enpp1。关于基因突变的符号显示为大写文本。

[0149] “人ENPP1”:人NPP1(NCBI登录号NP 006199/Uniprot-Swissprot P22413)

[0150] “可溶性人ENPP1”:NCBI登录号NP_006199的96-925位残基

[0151] “人ENPP3”:人NPP3(UniProtKB/Swiss-Prot:O14638.2)

[0152] “可溶性人ENPP3”:UniProtKB/Swiss-Prot:O14638.2的49-875位残基

[0153] “钙化减少”:如本文所用,通过使用非侵入性方法如X射线、显微CT和MRI观察到钙

化减少。还通过使用具有^{99m}Tc-焦磷酸盐(^{99m}PYP)摄取的放射成像推断钙化的减少。通过使用染料例如苏木精(Hematoxylin)和曙红(Eosin,H&E)和茜素红(Alizarin red),根据Braddock等人建立的方案,通过显微计算机断层扫描(CT)扫描和取自心脏、主动脉和肾脏的组织学切片,经由尸检评估小鼠中钙化的存在(《自然通讯》第6卷,文章编号:10006(2015))。

[0154] 对于ENPP1或ENPP3的"酶活性":定义为具有水解成AMP和PPi的ATP水解活性和/或AP3a水解成具有底物结合活性的ATP。

[0155] ATP水解活性可以如下测定。

[0156] NPP1的ATP水解活性

[0157] NPP1容易将ATP水解成AMP和PPi。以ATP为底物测定NPP1的稳态Michaelis-Menten酶常数。可以通过酶促反应的HPLC分析证明NPP1切割ATP,并且通过使用ATP、AMP和ADP标准证实反应的底物和产物的身份。ATP底物在NPP1存在下随时间降解,伴随酶产物AMP的积累。用不同浓度的ATP底物在ATP存在下衍生NPP1的初始速率,并将数据拟合为曲线以获得酶促速率常数。在生理pH下,NPP1的动力学速率常数为Km=144μM和$kcat_t=7.8s^{-1}$。

[0158] NPP3的ATP水解活性

[0159] 以pNP-TMP和ATP为底物测定NPP3的酶活性。将NPP3蛋白在37℃在100mM的Tris-HCl(pH 8.9)和5mM的pNP-TMP或50μM的[γ-32P]ATP存在下孵育。pNP-TMP的水解通过在3%(w/v)三氯乙酸中稀释10倍来终止。随后,用60μl的5N NaOH中和反应混合物,并在405nm下比色定量所形成的对硝基苯酚(pNP)。加入100mM的EDTA抑制ATP的水解。通过薄层色谱法在聚乙烯亚胺纤维素板(Merck)上分析1μl的反应混合物。核苷酸和降解产物通过在pH 3.0的750mM KH_2PO_4中的上行色谱法分离。放射斑点通过放射自显影观察。根据Blytt等人(H.J.Blytt,J.E.Brotherton,L.Butler Anal.Biochem.147(1985),pp.517-520),以轻微修饰(R.Gijsbers,H.Ceulemans,W.Stalmans,M.Bollen J.Biol.Chem.,276(2001),pp.1361-1368),在50μM[α-32P]ATP水解期间形成的核苷酸化中间体被捕获。SDS-PAGE后,通过放射自显影观察捕获的中间体。Bis-pNPP和pNPP也作为NPP3的底物进行了测试。NPP3同工型在pH 8.9的100mM的Tris-HCl和5mM的双-pNPP或pNPP中于37℃孵育2.5小时。随后,在405nm下比色定量所形成的pNP。(Gijsbers Rl,Aoki J,Arai H,Bollen M,FEBS Lett.2003Mar 13;538(1-3):60-4.)在生理pH下,NPP3具有与ENPP1类似的约2.59(±0.04)s^{-1}的kcat值和Km(<8μM)值。(WO 2017/087936)

[0160] HPLC方案

[0161] 用于通过NPP1测量ATP裂解和用于产物鉴定的HPLC方案修改自文献(Stocchi等人,1985,Anal.Biochem.,146:118-124)。在50mM的Tris pH 8.0、140mM的NaCl、5mM的KCl、1mM的$MgCl_2$和1mM的$CaCl_2$缓冲液中含有不同浓度的ATP的反应通过添加0.2至1μM的NPP1开始,并且在不同时间点通过等体积的3M的甲酸或0.5N的KOH淬灭,并且通过冰醋酸再酸化至pH 6。将淬灭的反应溶液系统地稀释,上样到HPLC系统(Waters,Milford Mass.)上,并且通过254或259nm处的UV吸光度监测底物和产物。以0%至10%(或20%)甲醇梯度,使用15mM乙酸铵pH 6.0溶液,将底物和产物在C18,5um 250×4.6mmHPLC柱(Higgins Analytical,Mountain View,Calif.)上分离。根据其相应峰的整合和下式对产物和底物进行定量:

$$面积_{产物/底物} \ / \ \Sigma_{产物/底物}$$

[0162] $$[产物/底物] = \frac{面积_{产物} \ / \ \Sigma_{产物}}{面积_{产物} \ / \ \Sigma_{产物} + 面积_{底物} / \ \Sigma_{底物}} [底物]$$

[0163] 其中[底物]是初始底物浓度。公式中使用的AMP、ADP和ATP的消光系数为15.4mM^{-1}cm'。如果在254nm监测,使用与反应同一天运行的底物和产物标准品,将整合的产物/底物峰面积转化为浓度。

[0164] 病理性钙化:如本文所用,该术语是指钙盐在身体的软组织、分泌和排泄通道中的异常沉积,使其硬化。有两种类型,发生在濒死和死亡组织中的营养不良钙化和转移性钙化,其增加了细胞外钙的水平(高钙血症),超过了细胞和组织的稳态能力。钙化可涉及细胞以及胞外基质组分,例如基底膜中的胶原和动脉壁中的弹性纤维。有钙化倾向的组织的一些实例包括:胃粘膜-胃的内上皮层、肾和肺、角膜、体动脉和肺静脉。

[0165] 病理性骨化:如本文所用,该术语是指一种病理状况,其中骨出现在不在骨系统中的组织和通常不表现成骨特性的结缔组织中。根据受影响的组织或器官的性质将骨化分为三种类型,软骨内骨化是发生在软骨中并代替软骨的骨化。膜内骨化是发生在结缔组织中并代替结缔组织的骨的骨化。化生性骨化:正常软体结构中骨质的发育;也称异位骨化。

[0166] NPP1的"缺乏"是指受试对象血浆中NPP1的水平小于或等于正常水平的5%至10%。健康人类受试对象中NPP1的正常水平大约在10至30ng/ml之间。(Am J Pathol.2001Feb;158(2):543-554.)

[0167] "低"水平的PPi是指这样的状况,其中受试对象血浆焦磷酸盐(PPi高)的水平小于或等于正常水平的2%至5%。健康人类受试对象中血浆PPi的正常水平是大约1.8至2.6μM。(《关节炎和风湿病》(Arthritis and Rheumatism),第22卷第8期(1979年8月))

[0168] "异位性钙化"是指以组织中钙盐的病理性沉积或软组织中骨生长为特征的病症。

[0169] "软组织的异位钙化"是指不适当的生物矿化,通常由磷酸钙、羟基磷灰石、草酸钙和磷酸八钙组成,导致软组织失去硬化。"动脉钙化"是指在动脉和心脏瓣膜中发生的异位钙化,导致动脉硬化和/或狭窄。动脉钙化与动脉粥样硬化斑块负荷和心肌梗死风险增加、外周血管疾病缺血发作增加以及血管成形术后夹层风险增加相关。

[0170] "静脉钙化"是指在静脉中发生的异位钙化,其降低了静脉的弹性并限制了血流,从而导致血压升高和冠状动脉缺陷。

[0171] "血管钙化"是指矿物质在血管系统中的病理性沉积。它有多种形式,包括内膜钙化和中膜钙化,但也可以在心脏瓣膜中发现。血管钙化与动脉粥样硬化、糖尿病、某些遗传病症和肾脏疾病,特别是CKD有关。血管钙化患者发生不良心血管事件的风险较高。血管钙化影响多种患者。特发性婴儿动脉钙化是一种罕见的血管钙化形式,其中新生儿的动脉发生钙化。

[0172] "脑钙化"(BC)是指非特异性神经病理学,其中发生钙和其它矿物质在血管壁和组织实质中的沉积,导致神经元死亡和神经胶质增生。脑钙化通常与各种慢性和急性脑障碍有关,包括唐氏综合征、路易体病、阿尔茨海默病、帕金森病、血管性痴呆、脑肿瘤和各种内分泌病症。

[0173] 心脏组织的钙化是指钙沉积物(可能包括其它矿物质)在心脏组织如主动脉组织

和冠状动脉组织中的积累。

[0174] 如本文所用,“慢性肾脏疾病(CKD)”是指持续三个月以上,影响健康的肾脏结构或功能的异常。在大多数慢性肾脏疾病中,排泄、内分泌和代谢功能普遍下降。心血管疾病是慢性肾病(CKD)患者最常见的死亡原因,并且血管钙化是心血管风险的最强预测因素之一。随着肾功能下降,CKD患者的血管钙化患病率增加,且钙化发生的时间早于一般人群。预防、减少和/或逆转血管钙化可能会增加CKD患者的存活率。

[0175] 慢性肾脏疾病的临床症状包括瘙痒、肌肉痉挛、恶心、食欲不振、脚和脚踝肿胀、失眠和呼吸困难。慢性肾病如果不治疗则倾向于进展为终末期肾病(ESRD)。ESRD的常见症状包括小便无力、疲劳、身体不适、体重减轻、骨痛、皮肤颜色改变、经常形成瘀伤,以及手指、脚趾、手和腿等外肢水肿。钙化防御或钙性尿毒症性小动脉病(CUA)是导致钙在脂肪和皮肤的血管内累积的病症。患有ESRD的患者亚群也可发展成钙化防御。钙化防御的常见症状包括皮肤上大的紫色网状图案,深而痛的肿块溃烂,形成黑褐色结皮无法愈合的开放性疮疡,下肢或脂肪含量较高的区域(如大腿、乳房、臀部和腹部)的皮肤损害。具有钙化防御的人在血液中可能具有高于正常水平的钙(高钙血症)和磷酸盐(高磷血症)。它们也可能具有甲状旁腺功能亢进的症状。当甲状旁腺分泌过多甲状旁腺激素(PTH)时,发生甲状旁腺功能亢进。血浆焦磷酸盐(PPi)水平降低也存在于与终末期肾病(ESRD)相关的血管钙化中。

[0176] 与ESRD相关的血管钙化通过增加脉压、引起或加重高血压,诱发或加剧心肌梗死和中风,从而导致不良预后。大部分ESRD患者并非死于肾衰竭,而是死于ESRD的心血管并发症,值得注意的是,许多非常年轻的ESRD透析患者都有冠状动脉钙化。与CKD相关的血管钙化的组织学亚型被称为Mönckeburg硬化,这是一种血管硬化的形式,在内侧血管壁的肌层中发现钙沉积。这种形式的钙化在组织学上与动脉粥样硬化中通常观察到的内膜或新内膜血管壁钙化不同,但与人CKD患者和本文所述的疾病的啮齿动物模型中观察到的血管钙化相同。

[0177] 如本文所用的“婴儿全身性动脉钙化(GACI)(也称为IACI)”是指在出生前或生命的前几个月内变得明显的影响循环系统的病症。其特征在于,在将血液从心脏运送到身体的其余部分的血管(动脉)的壁中的矿物质钙的异常积聚(钙化)。钙化通常伴随着动脉壁(内膜)衬壁的增厚而发生。这些变化导致动脉的变窄(狭窄)和僵硬,迫使心脏更难工作以泵送血液。因此,受影响的个体可能会出现心力衰竭,症状和体征包括呼吸困难、四肢积液(水肿)、皮肤或嘴唇发青(发绀)、严重高血压(高血压)和心脏增大(心脏扩大)。患有GACI的人还可能在其他器官和组织,特别是关节周围发生钙化。此外,他们可能有听力损失或骨骼软化和弱化,称为佝偻病。

[0178] 全身动脉钙化(GACI)或特发性婴儿动脉钙化(IIAC),其特征是将血液从心脏输送到身体其他部位(动脉)的血管壁中矿物质钙的异常积聚(钙化)。钙化通常伴随着动脉壁(内膜)衬壁的增厚而发生。这些变化导致动脉的变窄(狭窄)和僵硬,迫使心脏更难工作以泵送血液。因此,受影响的个体可能会出现心力衰竭,症状和体征包括呼吸困难、四肢积液(水肿)、皮肤或嘴唇发青(发绀)、严重高血压(高血压)和心脏增大(心脏扩大)。

[0179] 如本文所用“动脉钙化”或“血管钙化”或“动脉硬化”,术语是指以肌肉动脉壁的增厚和弹性丧失为特征的过程。增厚和弹性丧失发生在两个不同的部位,即脉管系统的内膜层和中间层(脉管中间层钙化)。内膜钙化与动脉粥样硬化斑块有关,而中层钙化的特征在

于血管硬化和动脉硬化。这导致动脉弹性降低,并且由于心血管系统的血液动力学受损而增加发病率和死亡率的可能。

[0180] 如本文所用,术语“矿物质和骨代谢紊乱(MBD)”是指以异常激素水平引起人血液中的钙和磷水平失去平衡为特征的病症。矿物质和骨代谢紊乱通常发生在患有CKD的人中,并且影响大部分接受透析的患有肾衰竭的人。

[0181] 骨量减少是一种以骨密度降低为特征的骨疾病,它会导致骨骼变弱,增加骨折的风险。骨软化症是一种以新形成的骨矿化减少为特征的骨病。骨软化症是由严重的维生素D缺乏(这可能是营养性的,也可能是由遗传性综合症引起的)和导致血磷水平非常低的条件引起的。骨软化和骨量减少都增加了骨折的危险。骨软化症的症状包括骨痛和肌肉无力、骨骼压痛、行走困难和肌肉痉挛。

[0182] 如本文所用的“与年龄相关的骨量减少”是指其中骨矿物质密度低于正常的状况。通常,骨量减少患者的骨矿物质密度T值在-1.0和-2.5之间。如果不治疗,骨量减少会发展成骨质疏松,在骨质疏松中骨变脆并极易骨折。

[0183] 如本文所用的术语“后纵韧带骨化(OPLL)”是指导致后纵韧带的异位钙化的骨增生(过度骨生长)状况。后纵韧带连接并稳定脊柱的骨。增厚或钙化的韧带可能压迫脊髓,引起脊髓病变。脊髓病变的症状包括行走困难和大小便控制困难。OPLL也可引起神经根病或神经根受压。颈神经根病的症状包括颈、肩、臂或手的疼痛,麻刺或麻木。

[0184] 由OPLL引起的临床症状和体征分类为:(1)脊髓病,或脊髓损伤,伴有上肢和下肢的运动和感觉障碍、痉挛、排尿功能障碍;(2)神经根型颈椎病,上肢疼痛、感觉障碍;(3)轴向不适,颈部周围疼痛、僵硬。OPLL早期最常见的症状为手部感觉迟钝、麻刺感、笨拙。随着神经功能缺损程度的加重,下肢出现步态障碍等症状。在侧位平片上检测到OPLL,并通过磁共振成像(MRI)和计算机断层扫描(CT)清楚地显示了颈部OPLL的诊断和形态学细节。

[0185] 如本文所用“弹性纤维假黄瘤(PXE)”的术语是指一种进行性疾病,其特征是在弹性纤维中积聚钙和其他矿物质(矿化)。弹性纤维是结缔组织的组分,其为整个身体的结构提供强度和柔性。在PXE中,矿化会影响皮肤、眼睛和血管的弹性纤维,而在其他区域(如消化道)的影响较小。患有PXE的人在颈部、腋下和当关节弯曲时会接触到其他皮肤部位可能会有黄色隆起的丘疹。将血液从心脏输送到身体其他部位的血管(动脉)的矿化可能会导致PXE的其他体征和症状。例如,患有这种病症的人可发展为动脉狭窄(动脉硬化)或称为跛行的病症,其特征在于运动期间由于臂和腿的血流减少而导致的痉挛和疼痛。

[0186] 弹性纤维假黄瘤(PXE,也称为Grönblad-Strandberg综合征)是引起一些组织中弹性纤维断裂和矿化的遗传性疾病。最常见的问题出现在皮肤和眼睛,后来又出现在血管中,表现为过早的动脉粥样硬化。PXE是由16号染色体短臂(16p13.1)上ABCC6基因的常染色体隐性突变引起的。在某些情况下,一部分婴儿在GACI中存活下来,当他们长大后最终发展为弹性纤维假黄瘤(PXE)。PXE的特点是在弹性纤维中钙和其他矿物质的积累(矿化),其是结缔组织的组分。结缔组织为整个身体的结构提供了强度和灵活性。PXE的特征也出现在GACI中,包括腋下和关节弯曲时接触的其他皮肤区域(屈肌区)上称为丘疹的黄色隆起;动脉狭窄,以及在眼睛检查中发现的称为影响眼后组织的血管样条纹症(视网膜出血)。

[0187] 终末期肾病(ESRD):如本文所用是指慢性肾脏疾病的晚期,患者的肾脏不再具有功能。常见症状包括与贫血(低血铁)相关的疲劳、食欲下降、恶心、呕吐、实验室指标异常

(包括钾升高)、与骨骼健康有关的激素异常、磷升高和/或钙降低、高血压(高血压)、手/腿/眼/下背部(骶骨)肿胀以及呼吸急促。

[0188] “钙性尿毒症性小动脉病(CUA)”或“钙化防御”如本文所用是指肾病患者,特别是终末期肾病(ESRD)患者的高发病率和高死亡率的一种疾病。其特征在于位于脂肪组织和皮肤深层的小血管钙化,导致血液凝块,过度钙化导致血液流动减少,导致皮肤细胞死亡。

[0189] 如本文所用“低磷血症性佝偻病”是指由于血液中的磷酸盐水平低,骨骼变得柔软和容易弯曲的一种疾病。症状通常始于儿童早期,严重程度不等,包括腿部弯曲、骨骼畸形;骨痛;关节痛;骨生长不良;和身材矮小。

[0190] 如本文所用的“遗传性低磷血症性佝偻病”指的是一种与血液中低磷酸盐水平有关的疾病(低磷血症)。磷酸盐是骨骼和牙齿正常形成所必需的矿物质。最常见的是由PHEX基因突变引起的。其他可能导致这种情况的基因包括CLCN5、DMP1、ENPP1、FGF23和SLC34A3基因。遗传性低磷血症性佝偻病的其他体征和症状包括颅骨过早融合(颅缝早闭)和牙齿异常。这种疾病还可能导致韧带和肌腱附着在关节上的异常骨骼生长(末端病)。在成年人中,低磷血症的特征是骨骼软化,称为骨软化症。另一种罕见的疾病被称为遗传性低磷血症性佝偻病伴高钙尿症(HHRH),除了低磷血症外,这种疾病的特征是尿液中排出高水平的钙(高钙尿)。

[0191] “X连锁低磷酸血症(XLH)”,如本文所用的术语X连锁低磷酸血症(XLH),也被称为家族性显性低磷血症性佝偻病,或X连锁抗维生素D佝偻病,是一种X连锁显性形式的佝偻病(或骨软化症),不同于大多数佝偻病病例,补充维生素D不能治愈。它会导致骨骼畸形,包括矮小的身材和膝内翻(弓型腿)。它与PHEX基因序列(Xp.22)的突变和随后PHEX蛋白的失活有关。

[0192] “常染色体隐性遗传性低磷血症性佝偻病2型(ARHR2)”,如本文所用的术语是指一种遗传性肾磷酸盐消耗障碍,其特征是低磷血症、佝偻病和/或骨软化和生长缓慢。常染色体隐性遗传性低磷血症性佝偻病2型(ARHR2)是由ENPP1基因纯合子功能缺失突变引起的。

[0193] 如本文所用的“常染色体显性遗传性低磷血症性佝偻病(ADHR)”指的是一种罕见的遗传性疾病,在这种疾病中,尿中磷的过量丢失会导致骨骼形成不良(佝偻病)、骨痛和牙齿脓肿。ADHR是由成纤维细胞生长因子23(FGF23)突变引起的。ADHR的特点是骨骼矿化受损,佝偻病和/或骨软化,骨化三醇(1,25-二羟基维生素D3)水平受抑,肾脏磷酸盐消耗,以及低血清磷酸盐。FGF23的突变使蛋白质更稳定,更不能被蛋白酶切割,从而增强了FGF23的生物活性。FGF23突变体活性的增强降低了近端肾小管细胞顶面钠磷共转运蛋白NPT2a和NPT2c的表达,导致肾脏磷酸盐消耗。

[0194] 低磷血症性佝偻病(以前称为抗维生素D佝偻病)是一种疾病,由于血液中的磷酸盐水平较低,骨骼变得非常柔软,很容易弯曲。症状可包括腿部弯曲和其它骨变形;骨痛;关节痛;骨生长不良;和身材矮小。在一些患病的婴儿中,头骨之间的空间闭合太快,导致颅缝早闭。大多数患者表现为钙磷代谢异常、牙釉质异常、牙萌出延迟、头颅狭长(长头症)。

[0195] 本文可互换使用的术语“腺相关病毒载体(vector)”、“AAV载体(vector)”、“腺相关病毒”、“AAV病毒”、“AAV病毒体”、“AAV病毒颗粒”和“AAV颗粒”是指由至少一种AAV衣壳蛋白(优选由特定AAV血清型的所有衣壳蛋白)和衣壳化的重组病毒基因组组成的病毒颗粒。颗粒包括具有异源多核苷酸和转录调节区的重组病毒基因组,异源多核苷酸包括编码人

ENPP1或人ENPP3或其功能等效变体的序列,)转录调节区至少包括侧接AAV反向端重复序列的启动子。该颗粒通常称为“AAV载体(vector)颗粒”或“AAV载体(vector)”。

[0196] 如本文所用,术语“载体(vector)”意指能够转运与其连接的另一核酸的核酸分子。在一些实施方案中,载体(vector)是质粒,即,其为环状双链DNA环,其中可以连接另外的DNA片段。在一些实施方案中,载体(vector)是病毒载体(vector),其中额外的核苷酸序列可以连接到病毒基因组中。在一些实施方案中,载体(vector)能够在它们所引入的宿主细胞中自主复制(例如,具有细菌复制起点的细菌载体(vector)和游离型哺乳动物载体(vector))。在其它实施方案中,载体(vector)(例如,非游离型哺乳动物载体(vector))在导入宿主细胞后整合到宿主细胞的基因组中,从而与宿主基因组一起复制。此外,某些载体(vector)(表达载体(vector))能够指导与其可操作连接的基因的表达。

[0197] 如本文所用,术语“重组宿主细胞”(或简称“宿主细胞”,如本文所用,是指已经引入外源核酸和/或重组载体(vector)的细胞。应当理解,“重组宿主细胞”和“宿主细胞”不仅指特定的受试对象细胞,而且指这种细胞的后代。因为由于突变或环境影响,在后代中可能发生某些修饰,这样的后代实际上可能不与亲代细胞相同,但仍包括在本文所用的术语“宿主细胞”的范围内。

[0198] 如本文所用,术语“重组病毒基因组”是指AAV基因组,其中至少一个外源表达盒多核苷酸插入天然存在的AAV基因组中。根据本发明的AAV的基因组通常包括顺式作用5′和3′反向端重复序列(ITR)和表达盒。

[0199] 如本文所用,术语“表达盒”是指重组或合成产生的具有一系列特定核酸元件的核酸构建体,其允许特定核酸在靶细胞中转录。根据本发明的AAV载体(vector)的重组病毒基因组的表达盒包括与编码ENPP1或ENPP3或其功能等效变体的核苷酸序列可操作连接的转录调节区。

[0200] 如本文所用,术语“转录调节区”是指能够调节一个或多个基因的表达的核酸片段。根据本发明的转录调节区包括启动子和任选的增强子。

[0201] 如本文所用,术语“启动子”是指核酸片段,其功能是控制位于多核苷酸序列上游的一个或多个多核苷酸的转录,并且通过存在DNA依赖的RNA聚合酶的结合位点、转录起始位点和任何其他DNA序列,包括但不限于转录因子结合位点、抑制子和激活蛋白结合位点,以及本领域中已知的任何其他核苷酸序列直接或间接地作用于调节从启动子转录的量来在结构上识别该核酸片段。在本发明中可以使用任何种类的启动子,包括诱导型启动子、组成型启动子和组织特异性启动子。

[0202] 本文所用的术语“增强子”是指与转录因子结合以增加基因转录的DNA序列元件。增强子的实例可以是但不限于RSV增强子、CMV增强子、HCR增强子等。在另一个实施方案中,增强子是肝特异性增强子,更优选肝控制区增强子(HCR)。

[0203] 如本文所用,术语“可操作地连接”是指启动子序列相对于目的多核苷酸的功能关系和位置(例如,如果启动子或增强子影响序列的转录,则其可操作地连接至编码序列)。通常,可操作连接的启动子与目的序列相邻。然而,增强子不必与目的序列相邻以控制其表达。在另一个实施方案中,启动子和编码ENPP1或ENPP3或其功能等同变体的核苷酸序列。

[0204] 术语“治疗有效量”是指无毒但足以提供所需生物学结果的量的编码ENPP1或ENPP3的病毒载体(vector)。结果是疾病的体征、症状或病因的缓解和/或减轻,或生物系统

的任何其他期望的改变。例如,根据本发明的AAV载体(vector)的治疗有效量是足以产生的量。

[0205] 如本文所用,术语“Cap蛋白”是指具有天然AAV Cap蛋白的至少一种功能活性的多肽(例如,VP1、VP2、VP3)。Cap蛋白的功能活性的实例包括诱导衣壳形成、促进单链DNA累积、促进AAV DNA包装入衣壳(即衣壳化)、结合细胞受体和促进病毒体进入宿主细胞的能力。原则上,在本发明的上下文中可以使用任何Cap蛋白。

[0206] 本文所用的术语“衣壳”是指包装病毒基因组的结构。衣壳由几个由蛋白组成的寡聚结构亚单位组成。例如,AAV具有由三种衣壳蛋白VP1、VP2和VP3的相互作用形成的二十面体衣壳。

[0207] 本文所用的术语“Rep蛋白”是指具有天然AAV Rep蛋白的至少一种功能活性的多肽(例如,Rep 40、52、68、78)。Rep蛋白的“功能活性”是与蛋白质的生理功能相关的任何活性,包括通过识别、结合和切割DNA复制的AAV起始点以及DNA解旋酶活性来促进DNA复制。其它功能包括调节AAV(或其它异源)启动子的转录和AAV DNA到宿主染色体的位点特异性整合。在具体实施方案中,AAV rep基因衍生自血清型AAV1、AAV2、AAV4、AAV5、AAV6、AAV7、AAV8、AAV9、AAV10或AAVrh10;更优选来自AAV血清型,AAV血清型选自AAV2、AAV5、AAV7、AAV8、AAV9、AAV10和AAVrh10组成的组。

[0208] 如本文所用的表达“AAV依赖于其复制的病毒蛋白”是指执行AAV依赖于其复制的功能(即“辅助功能”)的多肽。辅助功能包括AAV复制所需的那些功能,包括但不限于参与AAV基因转录激活、阶段特异性AAV mRNA剪接、AAV DNA复制、cap表达产物合成和AAV衣壳组装。基于病毒的附属功能来源于任何已知的辅助病毒,例如腺病毒、疱疹病毒(除单纯疱疹病毒1型之外)和痘苗病毒。辅助功能包括但不限于腺病毒E1、E2a、VA和E4或疱疹病毒UL5、ULB、UL52和UL29以及疱疹病毒聚合酶。在另一个实施方案中,AAV依赖于其复制的蛋白衍生自腺病毒。

[0209] 如本文所用的术语“腺相关病毒ITR”或“AAV ITR”是指腺相关病毒基因组DNA链两端存在的反向端重复序列。ITR序列是AAV基因组高效增殖所必需的。这些序列的另一个特性是它们形成发夹的能力。该特征有助于其自身引发(self-priming),其允许第二DNA链的引发酶非依赖性合成。修饰这些ITR序列的方法是本领域已知的(Brown T,“《基因克隆》(Gene Cloning)”,Chapman&Hall,London,GB,1995;Watson R等人,“《重组DNA》(Recombinant DNA)”,第二版.Scientific American Books,New York,N.Y.,US,1992;Alberts B等人,“《细胞的分子生物学》(Molecular Biology of the Cell”,GarlandPublishing Inc.),New York,N.Y.,US,2008;Innis M等人,Eds.,“《PCR方案,方法和应用指南》(PCRProtocols.A Guide to Methods and Applications)”,Academic Press Inc.,San Diego,Calif.,US,1990;和Schleef M,Ed.,“《用于治疗和疫苗接种的质粒》(Plasmid for Therapy and Vaccination)”,Wiley-VCH Verlag GmbH,Weinheim,Del.,2001)。

[0210] 术语“组织特异性”启动子仅在特定类型的分化细胞或组织中有活性。通常,组织特异性启动子中的下游基因在其特异性的组织中的活性程度远远高于其他任何组织。在这种情况下,在除启动子特异性的组织之外的任何组织中,启动子可能几乎没有或基本上没有活性。

[0211] 如本文所用,术语“骨骼肌特异性启动子”是指用作启动子的核酸序列(即调节与启动子可操作连接的选定核酸序列的表达),并且其促进选定核酸序列在骨骼肌的特定组织细胞中的表达。骨骼肌特异性启动子的实例包括但不限于肌球蛋白轻链启动子(MLC)和肌肉肌酸激酶启动子(MCK)。

[0212] 如本文所用,术语“肝脏特异性启动子”是指用作启动子的核酸序列(即调节与启动子可操作连接的选定核酸序列的表达),并且其促进选定核酸序列在肝细胞中的表达。通常,肝脏特异性启动子在肝脏中的活性高于其在体内任何其他组织中的活性。肝特异性启动子可以是组成型的或诱导型的。合适的肝脏特异性启动子包括但不限于[α]1-抗胰蛋白酶(AAT)启动子、甲状腺激素结合球蛋白启动子、甲胎蛋白启动子、乙醇脱氢酶启动子、第VIII因子(FVIII)启动子、HBV基本核心启动子(BCP)和前S2启动子、白蛋白启动子、-460-73bp磷酸烯醇丙酮酸羧激酶(PEPCK)启动子、甲状腺素结合球蛋白(TBG)启动子、肝控制区域(HCR)-ApoCII融合启动子、HCR-hAAT融合启动子、与小鼠白蛋白基因增强子(Ealb)元件结合的AAT启动子、载脂蛋白E启动子、低密度脂蛋白启动子、丙酮酸激酶启动子、卵磷脂胆固醇酰基转移酶(LCAT)启动子、载脂蛋白H(ApoH)启动子、转铁蛋白启动子、转甲状腺蛋白启动子、α-纤维蛋白原和β-纤维蛋白原启动子、α1-抗胰凝乳蛋白酶启动子、α2-HS糖蛋白启动子、结合珠蛋白启动子、铜蓝蛋白启动子、纤溶酶原启动子、补体蛋白启动子(CIq、CIr、C2、C3、C4、C5、C6、C8、C9、补体因子I和因子H)、C3补体活化剂和[α]-酸性糖蛋白启动子。另外的组织特异性启动子可以在组织特异性启动子数据库TiProD(核酸研究,J4:D104-D107(2006))。在另一个实施方案中,肝特异性启动子选自:白蛋白启动子、磷酸烯醇丙酮酸羧激酶(PEPCK)启动子和α1-抗胰蛋白酶启动子组成的组;更优选α1-抗胰蛋白酶启动子;甚至更优选人α1-抗胰蛋白酶启动子。

[0213] 如本文所用,术语“诱导型启动子”是指例如通过施用化学诱导物而受到生理或发育调控的启动子。例如,其可以是四环素诱导型启动子,米非司酮(RU-486)非诱导型启动子等。

[0214] 如本文所用,术语“组成型启动子”是指在几乎或不考虑细胞环境条件的情况下,其活性在生物体的所有细胞中或在大多数发育阶段期间维持在相对恒定水平的启动子。在另一个实施方案中,转录调节区允许ENPP1的组成型表达。组成型启动子的实例包括但不限于逆转录病毒劳斯氏肉瘤病毒(RSV)LTR启动子(任选地具有RSV增强子)、巨细胞病毒(CMV)启动子(任选地具有CMV增强子)、SV40启动子、二氢叶酸还原酶启动子、β-肌动蛋白启动子、磷酸甘油激酶(PGK)启动子和EF1a启动子(Boshart M等人,《细胞》(Cell)1985;41;521-530)。优选地,组成型启动子适用于ENPP1在肝脏中的表达,并且包括但不限于次黄嘌呤磷酸核糖基转移酶(HPTR)启动子、腺苷脱氨酶启动子、丙酮酸激酶启动子、β-肌动蛋白启动子、延伸因子1α(EF1)启动子、磷酸甘油酸激酶(PGK)启动子、泛素(Ubc)启动子、白蛋白启动子、和其它组成型启动子。在细胞中组成型发挥功能的示例性病毒启动子包括,例如,SV40早期启动子区(Bernoist和Chambon,1981,《自然》(Nature)290:304-310),包含在劳斯氏肉瘤病毒的3′长端重复序列中的启动子(Yamamoto等人,1980,《细胞》(Cell)22:787-797),或疱疹胸苷激酶启动子(Wagner等人,1981,《美国科学院院报》(Proc.Natl.Acad.Sci.U.S.A.)78:1441-1445)。

[0215] 本文所用的术语“聚腺苷酸化信号”涉及介导多聚腺嘌呤片段与mRNA的3′端连接

的核酸序列。合适的聚腺苷酸化信号包括但不限于SV40早期聚腺苷酸化信号、SV40晚期聚腺苷酸化信号、HSV胸苷激酶聚腺苷酸化信号、鱼精蛋白基因聚腺苷酸化信号、腺病毒5EIb聚腺苷酸化信号、牛生长激素聚腺苷酸化信号、人变体生长激素聚腺苷酸化信号等。

[0216] 术语“核苷酸或核酸序列”在本文中可与“多核苷酸”互换使用,并且涉及任何长度的核苷酸的任何聚合形式。核苷酸序列编码信号肽和ENPP1蛋白或其功能等效变体。

[0217] 如本文所用,术语“信号肽”是指在蛋白翻译期间结合在目的新生蛋白的氨基端的氨基酸残基序列(长度范围为10至30个残基)。信号肽被信号识别颗粒(SRP)识别并在内质网转运后被信号肽酶裂解。(Lodish等人,2000,《分子细胞生物学》(Molecular Cell Biology),第4版)。

[0218] 本文所用的术语“受试对象”是指个体哺乳动物,例如人、非人灵长类动物(例如黑猩猩和其它猿和猴物种)、农场动物(例如鸟、鱼、牛、绵羊、猪、山羊、和马)、家养哺乳动物(例如狗和猫)或实验动物(例如啮齿动物、如小鼠、大鼠和豚鼠)。该术语包括任何年龄或性别的受试对象。在另一个实施方案中受试对象为哺乳动物,优选为人。

[0219] 如果疾病或病症的症状的严重程度,患者经历这种症状的频率或这两者降低,则疾病或病症“减轻”。

[0220] 如本文所用的术语“改变”、“缺陷”、“变化”或“突变”是指细胞中影响其编码的多肽的功能、活性、表达(转录或翻译)或构象的基因突变,包括错义和无义突变、插入、缺失、移码和提前终止。

[0221] “疾病”是动物的健康状态,其中动物不能维持体内平衡,并且其中如果疾病没有改善,则动物的健康继续变差。

[0222] 动物中的“病症”是其中动物能够维持体内平衡的健康状态,但其中动物的健康状态不如不存在该病症时有利。在不治疗的情况下,病症不一定引起动物健康状态的进一步降低。

[0223] 如本文所用,术语“免疫应答”或“免疫反应”是指宿主对侵入(感染)病原生物中的抗原的免疫系统,或外源蛋白的引入或表达。免疫应答一般是体液免疫和局部免疫;B细胞产生的抗体在抗原-抗体复合物中与抗原结合以灭活或中和抗原。当人蛋白被注射到小鼠模型系统中时,通常观察到免疫应答。通常,通过在导入外源抗原之前注射免疫抑制剂来使小鼠模型系统具有免疫耐受,以确保更好的活力。

[0224] 如本文所用,术语“免疫抑制”是使用免疫抑制药物故意降低宿主免疫系统的活化或功效以促进针对外源抗原(例如外源蛋白、器官移植物、骨髓和组织移植)的免疫耐受。免疫抑制剂药物的非限制性实例包括抗CD4(GK1.5)抗体、环磷酰胺、硫唑嘌呤(Imuran)、霉酚酸酯(Cellcept)、环孢菌素(Neoral、Sandimmune、Gengraf)、甲氨蝶呤(Rheumatrex)、来氟米特(Arabinomide)、环磷酰胺(Cytoxan)和苯丁酸氮芥(Leukeran)。

[0225] 如本文所用,术语“ENPP”或“NPP”是指外核苷酸焦磷酸酶/磷酸二酯酶。

[0226] 如本文所用,术语“ENPP1蛋白”或“ENPP1多肽”是指由ENPP1基因编码的外核苷酸焦磷酸酶/磷酸二酯酶-1蛋白。编码的蛋白是一种II型跨膜糖蛋白,切割多种底物,包括核苷酸和核苷酸糖的磷酸二酯键和核苷酸和核苷酸糖的焦磷酸盐键。ENPP1蛋白具有跨膜结构域和可溶性胞外结构域。胞外结构域进一步细分为生长调节素B结构域、催化结构域和核酸酶结构域。野生型ENPP1的序列和结构在授予Braddock等人的PCT申请公开WO 2014/

126965号中详细描述,其全文以引用的方式并入本文中。

[0227] 哺乳动物ENPP1和ENPP3多肽、其突变体或突变片段已经在国际PCT申请公开WO/2014/126965-Braddock等人、WO/2016/187408-Braddock等人、WO/2017/087936-Braddock等人、和WO2018/027024-Braddock等人中公开,其全文通过引用的方式整体并入本文。

[0228] 如本文所用,术语“ENPP3蛋白”或“ENPP3多肽”是指由ENPP3基因编码的外核苷酸焦磷酸酶/磷酸二酯酶-3蛋白。编码的蛋白是一种II型跨膜糖蛋白,切割多种底物,包括核苷酸和核苷酸糖的磷酸二酯键和核苷酸和核苷酸糖的焦磷酸盐键。ENPP3蛋白具有跨膜结构域和可溶性胞外结构域。野生型ENPP3的序列和结构在授予Braddock等人的PCT申请公开WO/2017/087936号中详细描述,其全文以引用的方式并入本文中。

[0229] 如本文所用,术语“ENPP1前体蛋白”是指在ENPP1 N端具有其信号肽序列的ENPP1。在蛋白水解时,信号序列从ENPP1切割以提供ENPP1蛋白。在本发明中有用的信号肽序列包括但不限于白蛋白信号序列、天青杀素信号序列、ENPP1信号肽序列、ENPP2信号肽序列、ENPP7信号肽序列和/或ENPP5信号肽序列。

[0230] 如本文所用,术语“ENPP3前体蛋白”是指在ENPP3 N端具有其信号肽序列的ENPP3。在蛋白水解时,信号序列从ENPP3切割以提供ENPP3蛋白。在本发明中有用的信号肽序列包括但不限于白蛋白信号肽序列、天青杀素信号肽序列、ENPP1信号肽序列、ENPP2信号肽序列、ENPP7信号肽序列和/或ENPP5信号肽序列。

[0231] 如本文所用,术语“天青杀素信号肽序列”是指衍生自人天青杀素的信号肽。天青杀素,也称为阳离子抗微生物蛋白CAP37或肝素结合蛋白(HBP),是在人中由AZU1基因编码的蛋白。编码天青杀素信号肽(MTRLTVLALLAGLLASSRA)的核苷酸序列与NPP1或NPP3基因的核苷酸序列融合,其在编码时产生ENPP1前体蛋白或ENPP3前体蛋白。(《用于开发高表达CHO细胞系的优化的信号肽》(Optimized signal peptidesfor the development of high expressing CHO cell lines),Kober等人,Biotechnol Bioeng.2013Apr;110(4):1164-73)。

[0232] 如本文所用,术语“ENPP1-Fc构建体”是指与IgG分子(优选人IgG)的FcR结合结构域重组融合和/或化学缀合(包括共价和非共价缀合)的ENPP1。在某些实施方案中,ENPP1的C端与FcR结合结构域的N端融合或缀合。

[0233] 如本文所用,术语“ENPP3-Fc构建体”是指与IgG分子(优选人IgG)的FcR结合结构域重组融合和/或化学缀合(包括共价和非共价缀合)的ENPP3。在某些实施方案中,ENPP1的C端与FcR结合结构域的N端融合或缀合。

[0234] 如本文所用,术语“Fc”是指人IgG(免疫球蛋白)Fc结构域。IgG亚型如IgG1、IgG2、IgG3和IgG4预期用作Fc结构域。

[0235] 如本文所用,“Fc区或Fc多肽”是IgG分子的与通过木瓜蛋白酶酶切IgG分子获得的可结晶片段相关的部分。Fc区包括通过二硫键连接的IgG分子的两条重链的C端一半。它没有抗原结合活性,但含有碳水化合物部分和补体和Fc受体(包括FcRn受体)的结合位点。Fc片段包括整个第二恒定结构域CH2(人IgG1的残基231-340,根据Kabat编号系统)和第三恒定结构域CH3(残基341-447,根据Kabat编号系统)。术语“IgG铰链-Fc区”或“铰链-Fc片段”是指由Fc区(残基231-447)和从Fc区的N端延伸的铰链区(残基216-230)组成的IgG分子的区域。术语“恒定结构域”是指相对于免疫球蛋白的其它部分(可变结构域)具有更保守的氨

基酸序列的免疫球蛋白分子的部分,其含有抗原结合位点。恒定区包括重链的CH1、CH2和CH3结构域和轻链的CHL结构域。

[0236] 如本文所用,当应用于核酸时,术语“片段”是指较大核酸的亚序列。核酸的“片段”可以是至少约15、50至100、100至500、500至1000、1000至1500个核苷酸、1500至2500或2500个核苷酸(以及在之间的任何整数值)。如本文所用,当应用于蛋白或肽时,术语“片段”是指较大蛋白或肽的亚序列,并且长度可以是至少约20、50、100、200、300或400个氨基酸(以及在之间的任何整数值)。

[0237] “分离的”意指从天然状态改变或除去。例如,天然存在于活体动物中的核酸或多肽不是“分离的”,而是与天然状态的共存物质部分或完全分离的相同核酸或多肽是“分离的”。分离的核酸或蛋白可以以基本上纯化的形式存在,或者可以存在于非天然环境例如宿主细胞中。

[0238] “寡核苷酸”或“多核苷酸”是长度范围为至少2个,在某些实施方案中至少8、15或25个核苷酸,但可以长达50、100、1000或5000个核苷酸的核酸或与多核苷酸特异性杂交的化合物。

[0239] 如本文所用,术语“患者”、“个体”或“受试对象”是指人。

[0240] 如本文所用,术语“药物组合物”或“组合物”是指在本发明中有用的至少一种化合物与药学上可接受的载体(carrier)的混合物。药物组合物有助于将化合物给患者施用。本领域存在多种给药技术,包括但不限于皮下、静脉、口服、气雾剂、吸入、直肠、阴道、经皮、鼻腔、口含、舌下、胃肠外、鞘内、胃内、眼部、肺部和局部给药。

[0241] 如本文所用,术语“药学上可接受的”是指材料,诸如载体(carrier)或稀释剂,其不消除化合物的生物活性或特性,并且相对无毒,即,可将材料施用至个体,而不会引起不合需要的生物效应或以有害方式与包括其的组合物的任何组分相互作用;例如,磷酸盐缓冲盐水(PBS)。

[0242] 如本文所用,术语“血浆焦磷酸盐(PPi)水平”是指存在于动物血浆中的焦磷酸盐的量。在某些实施方案中,动物包括大鼠、小鼠、猫、狗、人、母牛和马。由于从血小板释放,需要测定血浆而不是血清中的PPi。存在几种测量PPi的方法,其中一种是通过使用尿苷-二磷酸葡萄糖(UDPG)焦磷酸化酶修饰的酶测定(Lust&Seegmiller,1976,《临床化学学报》(Clin.Chim.Acta)66:241-249;Cheung&Suhadolnik,1977,《分析生物化学》(Anal.Biochem.)83:61-63)。典型地,健康受试对象中的正常PPi水平的范围从约1μm至约3μM,在一些情况下在1-2μm之间。具有缺陷的ENPP1表达的受试对象倾向于表现出低ppi水平,其范围为低于正常水平至少10%、低于正常水平至少20%、低于正常水平至少30%、低于正常水平至少40%、低于正常水平至少50%、低于正常水平至少60%、低于正常水平至少70%、低于正常水平至少80%及其组合。在患有GACI的患者中,发现ppi水平小于1μm,并且在一些情况下低于检测水平。在患有PXE的患者中,ppi水平低于0.5μm。(《动脉粥样硬化、血栓和血管生物学(Arterioscler Thromb Vasc Biol.)2014年9月;34(9):1985-9;Braddock等人,《自然通讯》(Nat Commun.)2015;6:10006.)

[0243] 如本文所用,术语“多肽”是指由通过肽键连接的氨基酸残基、相关的天然存在的结构变体及其合成的非天然存在的类似物组成的聚合物。

[0244] 如本文所用,术语“PPi”是指焦磷酸盐。

[0245] 如本文所用,术语“预防”意指如果没有病症或疾病发生,则没有病症或疾病,或如果已经发生病症或疾病,则没有进一步的病症或疾病发生。还考虑的是预防与病症或疾病相关的一些或所有症状的能力。

[0246] 如本文所用的“样本”或“生物样本”是指从受试对象分离的生物材料。生物样本可以含有适合于检测受试对象中的生理学或病理学过程的mRNA、多肽或其他标志物的任何生物材料,并且可以包括从该个体获得的流体、组织、细胞和/或非细胞材料。

[0247] 如本文所用,“基本上纯化的”是指基本上不含其它组分。例如,基本上纯化的多肽是已经与在其天然存在状态下通常与其相关的其它组分分离的多肽。非限制性实施方案包括95%纯度、99%纯度、99.5%纯度、99.9%纯度和100%纯度。

[0248] 如本文所用,术语“治疗(treatment)”或“治疗(treating)”定义为向患者应用或施用治疗剂,即本发明中有用的化合物(单独或与另一种药剂组合),或向来自患者的分离的组织或细胞系应用或施用治疗剂(例如用于诊断或体外应用),其具有疾病或病症,疾病或病症的症状或发展疾病或病症的潜能,目的是治好、治愈、减轻、缓解、改变、治疗、改善、提高或影响疾病或病症、疾病或病症的症状或发展疾病或病症的潜能。基于从药物基因组学领域获得的知识,可以特别定制或修饰这样的治疗。

[0249] 如本文所用,术语“预防(prevent)”、“预防(preventing)”和“预防(prevention)”是指抑制受试对象疾病的开始或减少受试对象疾病的发生。预防可以是完全的(例如受试对象中完全不存在病理性细胞)或部分的。预防还指降低对临床病症的易感性。

[0250] 如本文所用,术语“野生型”是指从天然存在的来源分离的基因或基因产物。在群体中最频繁观察到野生型基因,因此任意设计人NPP1或NPP3基因的“正常”或“野生型”形式。相反,术语“功能等同物”是指NPP1或NPP3基因或基因产物,当与野生型基因或基因产物相比时,其在序列和/或功能特性(即,改变的特性)上显示出修饰。可以分离天然存在的突变体;这些通过当与野生型基因或基因产物比较时它们具有改变的特性(包括改变的核酸序列)的事实来鉴定。

[0251] 如本文所用,术语“功能等同物变体”涉及与ENPP1或ENPP3(上文定义)的序列基本上同源并且分别保持ENPP1或ENPP3的酶促和生物学活性的多肽。用于确定变体是否保持天然ENPP1或ENPP3的生物活性的方法是本领域技术人员广泛已知的,并且包括说明书的实验部分中使用的任何测定。特别地,本发明包括由病毒载体(vector)递送的ENPP1或ENPP3的功能等同物变体。

[0252] ENPP1或ENPP3的功能等同物变体分别是与天然ENPP1或ENPP3基本同源的多肽。表述“基本上同源的”涉及当蛋白序列与上述ENPP1或ENPP3序列具有分别至少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%的同一性程度的蛋白序列。

[0253] 使用本领域技术人员广泛已知的计算机算法和方法确定两种多肽之间的同一性程度。两个氨基酸序列之间的同一性优选通过使用BLASTP算法(BLAST Manual,Altschul,S.,等人,NCBI NLM NIH Bethesda,Md.20894,Altschul,S.,等人,《分子生物学杂志》(J.Mol.Biol.)215:403-410(1990))确定,虽然也可以使用其它类似的算法。使用具有本文所述的参数的BLAST和BLAST 2.0来确定序列同一性百分比。用于进行BLAST分析的软件可通过国家生物技术信息中心(National Center for BiotechnologyInformation)公开获

得。

[0254] ENPP1或ENPP3的“功能等同物变体”可以通过替换多核苷酸内的核苷酸而获得,核苷酸是考虑了分别用于产生ENPP1或ENPP3的宿主细胞中的密码子偏好性。这种“密码子优化”可通过结合密码子频率表的计算机算法确定,密码子频率表如威斯康星大学程序包9.0版,遗传学计算机组,Madison,Wis(University of Wisconsin Package Version 9.0,Genetics Computer Group,Madison,Wis)提供的密码子偏好“Human high.cod”。

[0255] 如本文所用的“约”当涉及诸如量、持续时间等的可测量值时,意指涵盖与指定值的±20%或±10%的变化,在某些实施方案中±5%,在某些实施方案中±1%,在某些实施方案中±0.1%,因为这样的变化适合于执行所公开的方法。

[0256] 本发明提供了本发明的蛋白序列和核酸序列的代表性实例。通过反向翻译和密码子优化可以将蛋白序列转化为核酸序列。本领域有几种支持这种转换的可用工具,例如Expasy(https://www.expasy.org/)和生物信息学服务器(http://www.bioinformatics.org)。

[0257] 范围:贯穿本发明,根据本发明的各个方面可以范围形式呈现。应当理解,范围形式的描述仅仅是为了方便和简洁,并且不应当被解释为对根据本发明的范围的刚性限制。因此,范围的描述应当被认为已经具体公开了所有可能的子范围以及该范围内的单个数值。例如,诸如从1至6的范围的描述应被认为已经具体公开了子范围,诸如从1至3、从1至4、从1至5、从2至4、从2至6、从3至6等,以及该范围内的个别数字,例如,1、2、2.7、3、4、5、5.3和6。这与范围的宽度无关。

[0258] 用于体内表达ENPP1和ENPP3的病毒载体(vector)

[0259] 可以将遗传物质如包括NPP1或NPP3序列的多核苷酸引入哺乳动物以补偿ENPP1或ENPP3多肽的缺陷。

[0260] 某些修饰的病毒通常用作携带编码序列的载体(vector),因为在哺乳动物给药后,病毒感染细胞并表达编码的蛋白。根据本发明有用的修饰病毒衍生自病毒,其包括例如:细小病毒、小核糖核酸病毒、伪狂犬病病毒、肝炎病毒A、B或C、乳头瘤病毒、乳多空病毒(例如多瘤病毒和SV40)或疱疹病毒(例如EB病毒、水痘带状疱疹病毒、巨细胞病毒、带状疱疹和单纯疱疹病毒1型和2型)、RNA病毒或逆转录病毒、例如莫洛尼鼠白血病病毒或慢病毒(即衍生自人免疫缺陷病毒、猫免疫缺陷病毒、马感染性贫血病毒等)。根据本发明有用的DNA病毒有:腺相关病毒腺病毒、甲病毒和慢病毒。

[0261] 病毒载体(vector)通常通过注射施用,最通常通过静脉内(IV)直接施用到体内,或直接施用到特定组织,在那里它被单个细胞吸收。或者,可通过使病毒载体(vector)离体与患者细胞样本接触来施用病毒载体(vector),从而使病毒载体(vector)感染细胞,然后将含有载体(vector)的细胞送回患者。一旦病毒载体(vector)被递送,编码序列表达并产生功能蛋白。通常,病毒载体(vector)对细胞的感染和转导是通过一系列顺序事件发生的:病毒衣壳与靶细胞表面上的受体相互作用,通过内吞作用内化,通过内吞/蛋白酶体区室的细胞内转运、内体逃逸、核输入、病毒体脱壳和病毒DNA双链转化,其导致目的重组编码序列的转录和表达。(Colella等人,《分子治疗方法与临床发展》(Mol Ther Methods Clin Dev.)2017年12月1日;8:87-104.)。

[0262] 根据本发明的腺相关病毒载体(vector)

[0263] AAV指属于细小病毒科的依赖病毒属的病毒。AAV基因组大约4.7千碱基长,由线性单链脱氧核糖核酸(ssDNA)构成,可以是正义或负义的。基因组包括位于DNA链两端的反向端重复序列(ITRs)和两个开放阅读框(ORF):rep和cap。rep框架由编码AAV生命周期所需的非结构复制(Rep)蛋白的四个重叠基因组成。cap架含有结构VP衣壳蛋白VP1、VP2和VP3的重叠核苷酸序列,它们相互作用形成二十面体对称的衣壳。

[0264] 端145个核苷酸是自身互补的并且被组织成使得形成T形发夹的能量上稳定的分子内双链体可以形成。这些发夹结构用作病毒DNA复制的起点,用作细胞DNA聚合酶复合物的引物。在哺乳动物细胞中野生型AAV感染后,rep基因(即Rep78和Rep52)分别从P5启动子和P19启动子表达,并且这两种Rep蛋白在病毒基因组的复制中具有功能。Rep ORF中的剪接事件导致实际上4种Rep蛋白的表达(即Rep78、Rep68、Rep52和Rep40)。然而,已经显示编码Rep78和Rep52蛋白的未剪接的mRNA在哺乳动物细胞中足以产生AAV载体(vector)。在昆虫细胞中,Rep78和Rep52蛋白也足以产生AAV载体(vector)。

[0265] AAV载体(vector)通常缺乏rep和cap框架。当存在于已经用编码和表达rep和cap基因产物的载体(vector)(即,AAV Rep和Cap蛋白)转染的宿主细胞中时,这样的AAV载体(vector)可以被复制并包装成感染性病毒颗粒,并且其中宿主细胞已经用编码和表达来自腺病毒开放阅读框E4orf6的蛋白的载体(vector)转染。

[0266] 在一个实施方案中,本发明涉及包括编码哺乳动物ENPP1或哺乳动物ENPP3的序列的腺相关病毒(AAV)表达载体(vector),并且在哺乳动物给药后,该载体(vector)在细胞中表达ENPP1或ENPP3前体,该前体包括在其羧基端与ENPP1或ENPP3的氨基端融合的天青杀素信号肽。ENPP1或ENPP3前体可以包括稳定结构域,例如IgG Fc区或人白蛋白。在前体从细胞分泌时,信号肽被切割并且在细胞外提供酶活性可溶的哺乳动物ENPP1或ENPP3。

[0267] AAV表达载体(vector)可以包括表达盒,该表达盒包括与核苷酸序列可操作连接的转录调节区,核苷酸序列包括与编码多肽的重组核酸序列可操作连接的转录调节区,多肽包括天青杀素信号肽序列和外核苷酸焦磷酸酶/磷酸二酯酶(ENPP1)多肽序列。

[0268] 在一些实施方案中,表达盒包括启动子和增强子、Kozak序列GCCACCATGG、编码哺乳动物NPP1蛋白的核苷酸序列或编码哺乳动物NPP3蛋白的核苷酸序列、其它合适的调节元件和聚腺苷酸化信号。

[0269] 在一些实施方案中,根据本发明的AAV载体(vector)的AAV重组基因组缺少rep开放阅读框和/或cap开放阅读框。

[0270] 根据本发明的AAV载体(vector)包括来自任何血清型的衣壳。通常,AAV血清型在氨基酸和核酸水平上具有显著同源性的基因组序列,提供一组相同的遗传功能,并通过几乎相同的机制复制和装配。特别地,本发明的AAV可属于AAV(AAV1)、AAV2、AAV3(包括3A和3B型)、AAV4、AAV5、AAV6、AAV7、AAV8、AAV9、AAV10、AAVrh10、AAV11、禽AAV、牛AAV、犬AAV、马AAV或绵羊AAV的血清型1型。

[0271] 不同AAV血清型的基因组序列的实例可以在文献或公共数据库如GenBank中找到。例如,GenBank登录号NC_001401.2(AAV2)、NC_001829.1(AAV4)、NC_006152.1(AAV5)、AF028704.1(AAV6)、NC_006260.1(AAV7)、NC_006261.1(AAV8)、AX753250.1(AAV9)和AX753362.1(AAV10)。

[0272] 在一些实施方案中,根据本发明的腺相关病毒载体(vector)包括衍生自选自由

AAV2、AAV5、AAV7、AAV8、AAV9、AAV10和AAVrh10血清型组成的组的血清型的衣壳。在另一个实施方案中,AAV的血清型是AAV8。如果病毒载体(vector)包括编码衣壳蛋白的序列,这些可以被修饰以包括外源序列以将AAV引导至一种或多种特定细胞类型,或增加靶向载体(vector)递送至细胞的效率,或促进AAV的纯化或检测,或降低宿主应答。

[0273] 公开的申请US2017/0290926-Smith等人,其内容通过引用整体并入本文,详细描述了AAV载体(vector)产生、递送和施用的过程。

[0274] 根据本发明有用的腺病毒载体(vector)

[0275] 可以对腺病毒进行操作,使其编码并表达所需的基因产物(例如,ENPP1或ENPP3),同时使其在正常裂解病毒生命周期中复制的能力失活。此外,腺病毒对气道上皮具有天然靶向性。病毒能够感染呼吸道中发现的休眠细胞,提供优于逆转录病毒的主要优点。实现腺病毒表达而不将病毒DNA整合到宿主细胞染色体中,从而减轻了对插入突变的担忧。此外,腺病毒作为肠道活疫苗已经使用了多年,其具有优异的安全性(Schwartz,A.R.等人(1974)《美国呼吸系统疾病综论》(Am.Rev.Respir.Dis.)109:233-238)。最后,已经在许多实例中证明了腺病毒介导的基因转移,包括将α-1-抗胰蛋白酶和CFTR转移至棉鼠的肺部(Rosenfeld,M.A.等人(1991)《科学》(Science)252:431-434;Rosenfeld等人,(1992)《细胞》(Cell)68:143-155)。此外,试图建立腺病毒作为人类癌症病原体的广泛研究是一致阴性的(Green,M.等人(1979)《美国科学院院报》(Proc.Natl.Acad.Sci.USA)76:6606)。

[0276] 假性腺病毒载体(vector)(PAV)——PAV含有腺病毒反向端重复序列和辅助病毒依赖性复制和包装载体(vector)所需的最小腺病毒5′序列。这些载体(vector)不含有潜在的有害病毒基因,对大约36kb的外源物质具有理论能力,可以以合理的高滴度产生并维持亲本病毒对分裂和非分裂的人靶细胞类型的靶向性。PAV载体(vector)可以作为质粒携带的构建体或感染性病毒颗粒被维持。作为质粒构建体,PAV通过野生型或缺陷型辅助病毒,由来自高效复制和包装这些序列所必需的野生型2型腺病毒的最小序列和任何所需的额外的外源遗传物质组成。

[0277] 美国专利公开US 7,318,919-Gregory等人详细描述了产生、递送腺病毒载体(vector)的方法及其用于治疗疾病的相应用途,其内容通过引用整体并入本文。本发明涵盖使用腺病毒载体(vector)将编码ENPP1或ENPP3的核苷酸递送至需要其的受试对象,以及使用其的治疗方法。

[0278] 根据本发明有用的单纯疱疹载体(vector)

[0279] 单纯疱疹载体(vector)(基于HSV的病毒载体(vector))适合用作将核酸序列导入多种细胞类型的载体(vector)。成熟的HSV病毒体由包膜二十面体衣壳组成,病毒基因组由152kb的线性双链DNA分子组成。在另一个实施方案中,基于HSV的病毒载体(vector)缺乏至少一种必需HSV基因。在一些实施方案中,缺乏至少一种必需HSV基因的基于HSV的病毒载体(vector)是复制缺陷型的。大多数复制缺陷型HSV载体(vector)含有缺失以除去一个或多个即刻早期、早期或晚期的HSV基因,以防止复制。例如,HSV载体(vector)可能缺乏即刻早期基因,即刻早期基因选自ICP4、ICP22、ICP27、ICP47及其组合组成的组。HSV载体(vector)的优点是其能够进入可导致长期DNA表达的潜伏阶段,以及其能够容纳高达25kb的外源DNA插入物的大病毒DNA基因组。

[0280] 基于HSV的载体(vector)描述于例如美国专利5,837,532-Preston等人、5,846,

782-Wickham等人、和5,804,413-Deluca等人、以及国际专利申请WO 91/02788-Preston等人、WO 96/04394-Preston等人、WO 98/15637-Deluca等人、和WO 99/06583-Glorioso等人。HSV载体(vector)可仅在HSV基因组的早期区,仅HSV基因组的即刻早期区,仅HSV基因组的晚期区,或HSV基因组的早期和晚期区二者中缺乏复制必需基因功能。HSV载体(vector)的生产涉及使用本领域熟知的标准分子生物学技术。

[0281] 复制缺陷型HSV载体(vector)通常在互补细胞系中产生,互补细胞系以合适的水平提供复制缺陷型HSV载体(vector)中不存在但病毒增殖所需的基因功能,以产生高滴度的病毒载体(vector)原种。编码该蛋白的核酸序列的表达受与该核酸序列可操作地连接的合适的表达控制序列控制。“表达控制序列”是促进、增强或控制另一核酸序列的表达(通常且优选转录)的任何核酸序列。

[0282] 合适的表达控制序列包括组成型启动子、诱导型启动子、阻抑型启动子和增强子。载体(vector)中编码蛋白的核酸序列可以通过其内源启动子或优选通过非天然启动子序列调节。合适的非天然启动子的实例包括人巨细胞病毒(HCMV)启动子,例如HCMV即刻早期启动子(HCMV IEp)、衍生自人免疫缺陷病毒(HIV)的启动子,例如HIV长端重复序列启动子、磷酸甘油酸激酶(PGK)启动子、劳斯氏肉瘤病毒(RSV)启动子,例如RSV长端重复序列、小鼠乳腺肿瘤病毒(MMTV)启动子、Lap2启动子或疱疹胸苷激酶启动子(Wagner等人,《美国科学院院报》(Proc.Natl.Acad.Sci.),78,1444-1445(1981))、衍生自SV40或EB病毒的启动子等。在另一个实施方案中,启动子是HCMV IEp。

[0283] 启动子也可以是诱导型启动子,即,根据合适的信号上调和/或下调的启动子。例如,由药剂上调的表达控制序列在疼痛管理应用中特别有用。例如,启动子可以是药学上可诱导的启动子(例如,对四环素敏感的同源启动子)。启动子可以通过本领域已知的方法导入载体(vector)的基因组中,例如,通过在基因组的给定区域导入独特的限制性位点。

[0284] 美国专利公开US 7,531,167-Glorioso等人详细描述了产生、递送单纯疱疹载体(vector)的过程及其用于治疗疾病的相应用途,其内容通过引用整体并入本文。本发明涵盖使用单纯疱疹病毒载体(vector)将编码ENPP1或ENPP3的核苷酸递送至需要其的受试对象,以及使用其的治疗方法。

[0285] 根据本发明有用的甲病毒属载体(vector)

[0286] 已经从不同类型的甲病毒属开发了甲病毒属表达载体(vector),包括辛德毕斯病毒(SIN)、塞姆利基森林病毒(SFV)和委内瑞拉马脑炎(VEE)病毒。甲病毒复制子在其5′端含有编码病毒复制酶(Rep)的开放阅读框,当病毒RNA转染到细胞中时,Rep被翻译。Rep被表达为多蛋白,该多蛋白随后被加工成四个亚单位(nsps 1至nsps 4)。未加工的Rep可以将RNA载体(vector)复制到负链RNA中,这个过程只发生在转染或感染后的前3至4小时。Rep加工后将以负链RNA为模板合成更多的复制子分子。经加工的Rep还可以识别负链RNA或亚基因组启动子中的内部序列,由此它将合成对应于复制子3′端的亚基因组正链RNA。该亚基因组RNA将被翻译以大量产生异源蛋白。

[0287] 从在nsp2(nsp2中的SIN P726L载体(vector))的726位含有单一氨基酸变化(L的P)的SIN分离的非致细胞病变突变体显示Rep过度加工(Frolov等人,1999,《病毒学杂志》(J.Virol.)73:3854-65)。该突变体能够在BHK细胞中有效地建立连续复制。这种非致细胞病变的SIN载体(vector)已经在体外广泛使用,因为它能够提供长期持续的转基因表达,具

有良好的稳定性水平和大约4％的原始SIN载体(vector)获得的表达水平(Agapov等人,1998,《美国科学院院报》(Proc.Natl.Acad.Sci.USA.)95:12989-94)。同样地,专利申请WO2008065225-Smerdou等人描述了一种在复制酶nsp2亚单位中具有突变R649H/P718T的非致细胞病变的SFV载体(vector)。上述载体(vector)允许通过在抗生素存在下培养的方式获得能够组成型和稳定表达目的基因的细胞系,其抗性基因被整合到甲病毒载体(vector)中(Casales等人,2008,《病毒学》(Virology),376:242-51)。

[0288] 本发明考虑设计包括与甲病毒属复制子互补的DNA序列的载体(vector),其中已经掺入了如NPP1或NPP3的目的基因的序列以及用于位点特异性重组的识别序列。通过载体(vector),可以获得和选择其中已经将包括目的基因的序列的甲病毒属复制子整合到细胞基因组中的细胞,使得细胞稳定表达ENPP1或ENPP3多肽。本发明还考虑产生其中α病毒复制子受诱导型启动子控制的表达载体(vector)。当载体(vector)被掺入通过掺入编码转录激活因子的表达盒而额外修饰的细胞中时,转录激活因子在给定配体存在的情况下能够正向调节调节甲型病毒复制子转录的启动子的活性。

[0289] 美国专利公开US10,011,847-Aranda等人详细描述了产生、递送甲病毒载体(vector)的方法及其用于治疗疾病的相应用途,其内容通过引用整体并入本文。本发明涵盖使用甲病毒载体(vector)将编码ENPP1或ENPP3的核苷酸递送至需要其的受试对象,以及使用其的治疗方法。

[0290] 根据本发明有用的慢病毒载体(vector)

[0291] 慢病毒属于逆转录病毒科(Retroviridae)的病毒属,其特征在于孵育期长。慢病毒可以将显著量的病毒RNA递送到宿主细胞的DNA中,并且在逆转录病毒中具有能够感染非分裂细胞的独特能力。慢病毒载体(vector),特别是来源于HIV-1的慢病毒载体(vector)是广泛研究和经常使用的载体(vector)。慢病毒载体(vector)骨架的进化和病毒将重组DNA分子(转基因)递送到靶细胞中的能力已经时期在基因治疗和体外重组蛋白生产中的功能基因的恢复中得以应用。

[0292] 本发明考虑了慢病毒载体(vector),其包括合适的启动子和转基因以表达目的蛋白如ENPP1或ENPP3。典型地,载体(vector)的骨架来自猿猴免疫缺陷病毒(SIV),例如SIV1或非洲绿猴SIV(SIV-AGM)。在一个实施方案中,启动子优选是杂合人CMV增强子/EF1a(hCEF)启动子。本发明包括制备慢病毒载体(vector)的方法,包括表达目的基因的慢病毒载体(vector)的组合物,和在基因治疗中表达ENPP1或ENPP3蛋白以治疗钙化或骨化疾病的用途。根据本发明的慢病毒载体(vector)也可用于基因治疗的方法中以促进治疗性蛋白的分泌。作为进一步的实例,本发明提供治疗性蛋白分泌到呼吸道或循环系统的管腔中。因此,根据本发明的载体(vector)的给药及其通过气道细胞的摄取可以使得能够使用肺(或鼻或气道)作为“工厂”以产生治疗性蛋白,治疗性蛋白然后被分泌并以治疗水平进入体循环,在体循环中它可以行进至目的细胞/组织以引起治疗效果。与胞内或膜蛋白相反,此类分泌蛋白的产生不依赖于被转导的特定疾病靶细胞,这是显著的优点并且实现高水平的蛋白表达。因此,慢病毒载体(vector)还可以治疗其他非呼吸道疾病,如心血管疾病和血液病。慢病毒载体(vector),例如根据本发明的那些,可以整合到转导细胞的基因组中并导致长期表达,使得它们适于转导干/祖细胞。

[0293] 美国专利申请公开US2017/0096684-Alton等人详细描述了产生、递送慢病毒载体

(vector)的方法及其用于治疗疾病的相应用途,其内容通过引用整体并入本文。本发明涵盖使用慢病毒载体(vector)将编码ENPP1或ENPP3的核苷酸递送至需要其的受试对象,以及使用其的治疗方法。

[0294] 序列

[0295] SEQ ID NO:1-ENPP1氨基酸序列-野生型

Met Glu Arg Asp Gly Cys Ala Gly Gly Gly Ser Arg Gly Gly Glu Gly

1 5 10 15

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

20 25 30

Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala Ser

35 40 45

Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala

[0296]

50 55 60

Arg Ala Arg Thr Ala Lys Asp Pro Asn Thr Tyr Lys Val Leu Ser Leu

65 70 75 80

Val Leu Ser Val Cys Val Leu Thr Thr Ile Leu Gly Cys Ile Phe Gly

85 90 95

Leu Lys Pro Ser Cys Ala Lys Glu Val Lys Ser Cys Lys Gly Arg Cys

100 105 110

Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala Ala Cys Val Glu
115 120 125
Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys Ile Glu Pro Glu
130 135 140
His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu Lys Arg Leu Thr
145 150 155 160
Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp Lys Gly Asp Cys
165 170 175
Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp Val Glu
180 185 190
Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro Ala Gly Phe Glu
195 200 205
Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe Arg Ala Glu Tyr
210 215 220

[0297] Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser Lys Leu Lys Lys
225 230 235 240
Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr Lys Thr
245 250 255
Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu Ser His
260 265 270
Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala Ser Phe
275 280 285
Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys Gly Glu
290 295 300
Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly Thr Phe
305 310 315 320
Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro Asp Ile
325 330 335
Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Leu Ala

340 345 350

Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His Phe Tyr

355 360 365

Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr Gly Pro

370 375 380

Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly Met Val

385 390 395 400

Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg Cys Leu

405 410 415

Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser Cys Lys

420 425 430

Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn Ile Lys

435 440 445

Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val Pro Asp

[0298] 450 455 460

Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu Ser Cys

465 470 475 480

Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe Leu Pro

485 490 495

Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu Thr Phe

500 505 510

Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu Arg Lys

515 520 525

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

530 535 540

Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys His Gly Ile Glu

545 550 555 560

Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu

565 570 575

Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn
580 585 590
His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His Pro Lys Glu Val
595 600 605
His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp Asn Leu
610 615 620
Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe Gln Thr
625 630 635 640
Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His Glu Thr
645 650 655
Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr Ile Cys
660 665 670
Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp Ile Leu
675 680 685

[0299] Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser Phe Ser
690 695 700
Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile Pro Leu
705 710 715 720
Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val Ser
725 730 735
Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser Gly Ile
740 745 750
Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln Ser
755 760 765
Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys Tyr
770 775 780
Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val Phe Asp
785 790 795 800
Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln Lys

805 810 815

Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe Phe

820 825 830

Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His Cys

835 840 845

Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp Asn

850 855 860

[0300] Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu Glu

865 870 875 880

Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile Thr

885 890 895

Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile Leu

900 905 910

Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp

915 920 925

[0301] 上述NPP1氨基酸序列包括细胞质结构域、跨膜结构域、SMB1结构域、SMB2结构域、磷酸二酯酶/催化结构域、接头结构域和核酸酶结构域。SMB1结构域、SMB2结构域、催化结构域、接头结构域和核酸酶结构域统称为胞外结构域。残基1-76(Met Glu Arg至Thr Tyr Lys)对应于细胞质结构域。残基77-97(Val Leu Ser至Phe Gly Leu)对应于跨膜结构域。残基99-925(Pro Ser Cys至Gln Glu Asp)对应于胞外结构域。残基104-144(Glu Val Lys至Glu Pro Glu)对应于SMB1结构域,而残基145-189(His Ile Trp至Glu Lys Ser)对应于SMB2结构域。残基597-647对应于连接催化结构域和核酸酶结构域的接头结构域。残基191-591(Val Glu Glu至Gly Ser Leu)对应于催化/磷酸二酯酶结构域。残基654-925(His Glu Thr至Gln Glu Asp)对应于核酸酶结构域。基于人NPP1序列(NCBI登录号NP_006199/Uniprot-Swissprot P22413)对残基编号并对结构域分类

[0302] SEQ ID No:2-天青杀素-ENPP1-FC

MTRLTVLALLAGLLASSRA**APSCAKEVKSCKGRCFERTFGNCRCDAACVELGNCCLDYQETCIEPEHIWTCNKFRCGEKRLTRSL

[0303] CACSDDCKDKGDCCINYSSVCQGEKSWVEEPCESINEPQCPAGFETPPTLLFSLDGFRAEYLHTWGGLLPVISKLKKCGTYTKNMRPVYPT

KTFPNHYSIVTGLYPESHGIIDNKMYDPKMNASFSLKSKEKFNPEWYKGEPIWVTAKYQGLKSGTFFWPGSDVEINGIFPDIYKMYNGSVP

FEERILAVLQWLQLPKDERPHFYTLYLEEPDSSGHSYGPVSSEVIKALQRVDGMVGMLMDGLKELNLHRCLNLILISDHGMEQGSCKKYIY
LNKYLGDVKNIKVIYGPAARLRPSDVPDKYYSFNYEGIARNLSCREPNQHFKPYLKHFLPKRLHFAKSDRIEPLTFYLDPQWQLALNPSER
KYCGSGFHGSDNVFSNMQALFVGYGPGFKHGIEADTFENIEVYNLMCDLLNLTPAPNNGTHGSLNHLLKNPVYTPKHPKEVHPLVQCPFTR
NPRDNLGCSCNPSILPIEDFQTQFNLTVAEEKIIKHETLPYGRPRVLQKENTICLLSQHQFMSGYSQDILMPLWTSYTVDRNDSFSTEDFS
[0304] NCLYQDFRIPLSPVHKCSFYKNNTKVSYGFLSPPQLNKNSSGIYSEALLTTNIVPMYQSFQVIWRYFHDTLLRKYAEERNGVNVVSGPVFD
FDYDGRCDSLENLRQKRRVIRNQEILIPTHFFIVLTSCKDTSQTPLHCENLDTLAFILPHRTDNSESCVHGKHDSSWVEELLMLHRARITD
VEHITGLSFYQQRKEPVSDILKLKTHLPTFSQEDLINDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[0305] 单下划线-天青杀素信号序列,双下划线-ENPP1序列的起始和结束,粗体残基-Fc序列,**表示信号序列的切割点。

[0306] SEQ ID No:3-天青杀素-ENPP1-Alb

MTRLTVLALLAGLLASSRA**APSCAKEVKSCKGRCFERTFGNCRCDAACVELGNCCLDYQETCIEPEHIWTCNKFRCGEKRLTRSL
CACSDDCKDKGDCCINYSSVCQGEKSWVEEPCESINEPQCPAGFETPPTLLFSLDGFRAEYLHTWGGLLPVISKLKKCGTYTKNMRPVYPT
KTFPNHYSIVTGLYPESHGIIDNKMYDPKMNASFSLKSKEKFNPEWYKGEPIWVTAKYQGLKSGTFFWPGSDVEINGIFPDIYKMYNGSVP
FEERILAVLQWLQLPKDERPHFYTLYLEEPDSSGHSYGPVSSEVIKALQRVDGMVGMLMDGLKELNLHRCLNLILISDHGMEQGSCKKYIY
LNKYLGDVKNIKVIYGPAARLRPSDVPDKYYSFNYEGIARNLSCREPNQHFKPYLKHFLPKRLHFAKSDRIEPLTFYLDPQWQLALNPSER
KYCGSGFHGSDNVFSNMQALFVGYGPGFKHGIEADTFENIEVYNLMCDLLNLTPAPNNGTHGSLNHLLKNPVYTPKHPKEVHPLVQCPFTR
NPRDNLGCSCNPSILPIEDFQTQFNLTVAEEKIIKHETLPYGRPRVLQKENTICLLSQHQFMSGYSQDILMPLWTSYTVDRNDSFSTEDFS
NCLYQDFRIPLSPVHKCSFYKNNTKVSYGFLSPPQLNKNSSGIYSEALLTTNIVPMYQSFQVIWRYFHDTLLRKYAEERNGVNVVSGPVFD
[0307] FDYDGRCDSLENLRQKRRVIRNQEILIPTHFFIVLTSCKDTSQTPLHCENLDTLAFILPHRTDNSESCVHGKHDSSWVEELLMLHRARITD
VEHITGLSFYQQRKEPVSDILKLKTHLPTFSQEDLINMKWVTFLLLLFVSGSAFSRGVFRREAHKSEIAHRYNDLGEQHFKGLVLIAFSQY
LQKCSYDEHAKLVQEVTDFAKTCVADESAANCDKSLHTLFGDKLCAIPNLRENYGELADCCTKQEPERNECFLQHKDDNPSLPPFERPEAE
AMCTSFKENPTTFMGHYLHEVARRHPYFYAPELLYYAEQYNEILTQCCAEADKESCLTPKLDGVKEKALVSSVRQRMKCSSMQKFGERAFK
AWAVARLSQTFPNADFAEITKLATDLTKVNKECCHGDLLECADDRAELAKYMCENQATISSKLQTCCDKPLLKKAHCLSEVEHDTMPADLP
AIAADFVEDQEVCKNYAEAKDVFLGTFLYEYSRRHPDYSVSLLLRLAKKYEATLEKCCAEANPPACYGTVLAEFQPLVEEPKNLVKTNCDL
YEKLGEYGFQNAILVRYTQKAPQVSTPTLVEAARNLGRVGTKCCTLPEDQRLPCVEDYLSAILNRVCLLHEKTPVSEHVTKCCSGSLVERR
PCFSALTVDETYVPKEFKAETFTFHSDICTLPEKEKQIKKQTALAELVKHKPKATAEQLKTVMDDFAQFLDTCCKAADKDTCFSTEGPNLV
TRCKDALARSWSHPQFEK

[0308] 单下划线-天青杀素信号序列,双下划线-ENPP1序列的起始和结束,粗体残基-白蛋白序列,**表示信号序列的切割点。

[0309] SEQ ID No:4-天青杀素-ENPP1

MTRLTVLALLAGLLASSRA**APSCAKEVKSCKGRCFERTFGNCRCDAACVELGNCCLDYQETCIEPEHIWTCNKFRCGEKRLTRSL
[0310] CACSDDCKDKGDCCINYSSVCQGEKSWVEEPCESINEPQCPAGFETPPTLLFSLDGFRAEYLHTWGGLLPVISKLKKCGTYTKNMRPVYPT
KTFPNHYSIVTGLYPESHGIIDNKMYDPKMNASFSLKSKEKFNPEWYKGEPIWVTAKYQGLKSGTFFWPGSDVEINGIFPDIYKMYNGSVP

FEERILAVLQWLQLPKDERPHFYTLYLEEPDSSGHSYGPVSSEVIKALQRVDGMVGMLMDGLKELNLHRCLNLILISDHGMEQGSCKKYIY
LNKYLGDVKNIKVIYGPAARLRPSDVPDKYYSFNYEGIARNLSCREPNQHFKPYLKHFLPKRLHFAKSDRIEPLTFYLDPQWQLALNPSER
KYCGSGFHGSDNVFSNMQALFVGYGPGFKHGIEADTFENIEVYNLMCDLLNLTPAPNNGTHGSLNHLLKNPVYTPKHPKEVHPLVQCPFTR
NPRDNLGCSCNPSILPIEDFQTQFNLTVAEEKIIKHETLPYGRPRVLQKENTICLLSQHQFMSGYSQDILMPLWTSYTVDRNDSFSTEDFS
NCLYQDFRIPLSPVHKCSFYKNNTKVSYGFLSPPQLNKNSSGIYSEALLTTNIVPMYQSFQVIWRYFHDTLLRKYAEERNGVNVVSGPVFD
FDYDGRCDSLENLRQKRRVIRNQEILIPTHFFIVLTSCKDTSQTAPSCAKEVKSCKGRCFERTFGNCRCDAACVELGNCCLDYQETCIEPE
HIWTCNKFRCGEKRLTRSLCACSDDCKDKGDCCINYSSVCQGEKSWVEEPCESINEPQCPAGFETPPTLLFSLDGFRAEYLHTWGGLLPVI
[0311] SKLKKCGTYTKNMRPVYPTKTFPNHYSIVTGLYPESHGIIDNKMYDPKMNASFSLKSKEKFNPEWYKGEPIWVTAKYQGLKSGTFFWPGSD
VEINGIFPDIYKMYNGSVPFEERILAVLQWLQLPKDERPHFYTLYLEEPDSSGHSYGPVSSEVIKALQRVDGMVGMLMDGLKELNLHRCLN
LILISDHGMEQGSCKKYIYLNKYLGDVKNIKVIYGPAARLRPSDVPDKYYSFNYEGIARNLSCREPNQHFKPYLKHFLPKRLHFAKSDRIE
PLTFYLDPQWQLALNPSERKYCGSGFHGSDNVFSNMQALFVGYGPGFKHGIEADTFENIEVYNLMCDLLNLTPAPNNGTHGSLNHLLKNPV
YTPKHPKEVHPLVQCPFTRNPRDNLGCSCNPSILPIEDFQTQFNLTVAEEKIIKHETLPYGRPRVLQKENTICLLSQHQFMSGYSQDILMP
LWTSYTVDRNDSFSTEDFSNCLYQDFRIPLSPVHKCSFYKNNTKVSYGFLSPPQLNKNSSGIYSEALLTTNIVPMYQSFQVIWRYFHDTLL
RKYAEERNGVNVVSGPVFDFDYDGRCDSLENLRQKRRVIRNQEILIPTHFFIVLTSCKDTSQTPLHCENLDTLAFILPHRTDNSESCVHGK
HDSSWVEELLMLHRARITDVEHITGLSFYQQRKEPVSDILKLKTHLPTFSQED

[0312] 单下划线-天青杀素信号序列,双下划线-ENPP1序列的起始和结束,**表示信号序列的切割点。

[0313] SEQ ID NO:5-ENPP2氨基酸序列-野生型

Met Ala Arg Arg Ser Ser Phe Gln Ser Cys Gln Ile Ile Ser Leu Phe
1 5 10 15
Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly Phe Thr Ala His Arg
20 25 30
Ile Lys Arg Ala Glu Gly Trp Glu Glu Gly Pro Pro Thr Val Leu Ser
35 40 45
Asp Ser Pro Trp Thr Asn Ile Ser Gly Ser Cys Lys Gly Arg Cys Phe
[0314] 50 55 60
Glu Leu Gln Glu Ala Gly Pro Pro Asp Cys Arg Cys Asp Asn Leu Cys
65 70 75 80
Lys Ser Tyr Thr Ser Cys Cys His Asp Phe Asp Glu Leu Cys Leu Lys
85 90 95
Thr Ala Arg Gly Trp Glu Cys Thr Lys Asp Arg Cys Gly Glu Val Arg
100 105 110
Asn Glu Glu Asn Ala Cys His Cys Ser Glu Asp Cys Leu Ala Arg Gly

115 120 125

Asp Cys Cys Thr Asn Tyr Gln Val Val Cys Lys Gly Glu Ser His Trp

130 135 140

Val Asp Asp Asp Cys Glu Glu Ile Lys Ala Ala Glu Cys Pro Ala Gly

145 150 155 160

Phe Val Arg Pro Pro Leu Ile Ile Phe Ser Val Asp Gly Phe Arg Ala

165 170 175

Ser Tyr Met Lys Lys Gly Ser Lys Val Met Pro Asn Ile Glu Lys Leu

180 185 190

Arg Ser Cys Gly Thr His Ser Pro Tyr Met Arg Pro Val Tyr Pro Thr

195 200 205

Lys Thr Phe Pro Asn Leu Tyr Thr Leu Ala Thr Gly Leu Tyr Pro Glu

210 215 220

Ser His Gly Ile Val Gly Asn Ser Met Tyr Asp Pro Val Phe Asp Ala

[0315] 225 230 235 240

Thr Phe His Leu Arg Gly Arg Glu Lys Phe Asn His Arg Trp Trp Gly

245 250 255

Gly Gln Pro Leu Trp Ile Thr Ala Thr Lys Gln Gly Val Lys Ala Gly

260 265 270

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

275 280 285

Ile Leu Gln Trp Leu Thr Leu Pro Asp His Glu Arg Pro Ser Val Tyr

290 295 300

Ala Phe Tyr Ser Glu Gln Pro Asp Phe Ser Gly His Lys Tyr Gly Pro

305 310 315 320

Phe Gly Pro Glu Met Thr Asn Pro Leu Arg Glu Ile Asp Lys Ile Val

325 330 335

Gly Gln Leu Met Asp Gly Leu Lys Gln Leu Lys Leu His Arg Cys Val

340 345 350

Asn Val Ile Phe Val Gly Asp His Gly Met Glu Asp Val Thr Cys Asp
355 360 365
Arg Thr Glu Phe Leu Ser Asn Tyr Leu Thr Asn Val Asp Asp Ile Thr
370 375 380
Leu Val Pro Gly Thr Leu Gly Arg Ile Arg Ser Lys Phe Ser Asn Asn
385 390 395 400
Ala Lys Tyr Asp Pro Lys Ala Ile Ile Ala Asn Leu Thr Cys Lys Lys
405 410 415
Pro Asp Gln His Phe Lys Pro Tyr Leu Lys Gln His Leu Pro Lys Arg
420 425 430
Leu His Tyr Ala Asn Asn Arg Arg Ile Glu Asp Ile His Leu Leu Val
435 440 445
Glu Arg Arg Trp His Val Ala Arg Lys Pro Leu Asp Val Tyr Lys Lys
450 455 460

[0316] Pro Ser Gly Lys Cys Phe Phe Gln Gly Asp His Gly Phe Asp Asn Lys
465 470 475 480
Val Asn Ser Met Gln Thr Val Phe Val Gly Tyr Gly Ser Thr Phe Lys
485 490 495
Tyr Lys Thr Lys Val Pro Pro Phe Glu Asn Ile Glu Leu Tyr Asn Val
500 505 510
Met Cys Asp Leu Leu Gly Leu Lys Pro Ala Pro Asn Asn Gly Thr His
515 520 525
Gly Ser Leu Asn His Leu Leu Arg Thr Asn Thr Phe Arg Pro Thr Met
530 535 540
Pro Glu Glu Val Thr Arg Pro Asn Tyr Pro Gly Ile Met Tyr Leu Gln
545 550 555 560
Ser Asp Phe Asp Leu Gly Cys Thr Cys Asp Asp Lys Val Glu Pro Lys
565 570 575
Asn Lys Leu Asp Glu Leu Asn Lys Arg Leu His Thr Lys Gly Ser Thr

580 585 590

Glu Ala Glu Thr Arg Lys Phe Arg Gly Ser Arg Asn Glu Asn Lys Glu

595 600 605

Asn Ile Asn Gly Asn Phe Glu Pro Arg Lys Glu Arg His Leu Leu Tyr

610 615 620

Gly Arg Pro Ala Val Leu Tyr Arg Thr Arg Tyr Asp Ile Leu Tyr His

625 630 635 640

Thr Asp Phe Glu Ser Gly Tyr Ser Glu Ile Phe Leu Met Pro Leu Trp

645 650 655

Thr Ser Tyr Thr Val Ser Lys Gln Ala Glu Val Ser Ser Val Pro Asp

660 665 670

His Leu Thr Ser Cys Val Arg Pro Asp Val Arg Val Ser Pro Ser Phe

675 680 685

Ser Gln Asn Cys Leu Ala Tyr Lys Asn Asp Lys Gln Met Ser Tyr Gly

[0317] 690 695 700

Phe Leu Phe Pro Pro Tyr Leu Ser Ser Ser Pro Glu Ala Lys Tyr Asp

705 710 715 720

Ala Phe Leu Val Thr Asn Met Val Pro Met Tyr Pro Ala Phe Lys Arg

725 730 735

Val Trp Asn Tyr Phe Gln Arg Val Leu Val Lys Lys Tyr Ala Ser Glu

740 745 750

Arg Asn Gly Val Asn Val Ile Ser Gly Pro Ile Phe Asp Tyr Asp Tyr

755 760 765

Asp Gly Leu His Asp Thr Glu Asp Lys Ile Lys Gln Tyr Val Glu Gly

770 775 780

Ser Ser Ile Pro Val Pro Thr His Tyr Tyr Ser Ile Ile Thr Ser Cys

785 790 795 800

Leu Asp Phe Thr Gln Pro Ala Asp Lys Cys Asp Gly Pro Leu Ser Val

805 810 815

Ser Ser Phe Ile Leu Pro His Arg Pro Asp Asn Glu Glu Ser Cys Asn
820 825 830
Ser Ser Glu Asp Glu Ser Lys Trp Val Glu Glu Leu Met Lys Met His
835 840 845
Thr Ala Arg Val Arg Asp Ile Glu His Leu Thr Ser Leu Asp Phe Phe
[0318] 850 855 860
Arg Lys Thr Ser Arg Ser Tyr Pro Glu Ile Leu Thr Leu Lys Thr Tyr
865 870 875 880

Leu His Thr Tyr Glu Ser Glu Ile
885

[0319] SEQ.ID NO:6-ENPP3的胞外结构域:

Glu Lys Gln Gly Ser Cys Arg Lys Lys Cys Phe Asp Ala Ser Phe Arg
1 5 10 15
Gly Leu Glu Asn Cys Arg Cys Asp Val Ala Cys Lys Asp Arg Gly Asp
20 25 30
Cys Cys Trp Asp Phe Glu Asp Thr Cys Val Glu Ser Thr Arg Ile Trp
35 40 45
Met Cys Asn Lys Phe Arg Cys Gly Glu Thr Arg Leu Glu Ala Ser Leu
50 55 60
[0320]
Cys Ser Cys Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys Cys Ala Asp
65 70 75 80
Tyr Lys Ser Val Cys Gln Gly Glu Thr Ser Trp Leu Glu Glu Asn Cys
85 90 95
Asp Thr Ala Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp Leu Pro Pro
100 105 110
Val Ile Leu Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr Leu Tyr Thr
115 120 125

Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys Thr Cys Gly Ile
130 135 140
His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr Phe Pro Asn
145 150 155 160
His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly Ile Ile
165 170 175
Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser Leu Ser
180 185 190
Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro Met Trp
195 200 205
Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe Trp Pro
210 215 220
Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr Met Pro
225 230 235 240

[0321] Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu Leu Lys
245 250 255
Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr Met Tyr
260 265 270
Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val Ser Ala
275 280 285
Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala Phe Gly Met Leu
290 295 300
Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn Ile Ile
305 310 315 320
Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys Met Glu
325 330 335
Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr Met Tyr Glu
340 345 350
Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro His Asp Phe Phe

355 360 365

Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg Lys Pro

370 375 380

Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys Arg Leu

385 390 395 400

His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His Leu Phe Val Asp

405 410 415

Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys Gly Gly

420 425 430

Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala Ile Phe

435 440 445

Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu Pro Phe

450 455 460

Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg Ile Gln

[0322] 465 470 475 480

Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His Leu Leu Lys

485 490 495

Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys Phe Ser

500 505 510

Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu Asp Cys Phe

515 520 525

Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn Gln Met

530 535 540

Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val Asn Leu

545 550 555 560

Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val Asp His Cys Leu

565 570 575

Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala Met Arg Met

580 585 590

Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp Thr Ser Pro
595 600 605
Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp Val Arg Val Pro
610 615 620
Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys Asn Ile
625 630 635 640
Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser Asp Ser
645 650 655
Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro Met Tyr Glu Glu
660 665 670
Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu Leu Ile Lys His
675 680 685
Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile Phe Asp
690 695 700

[0323]
Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr Lys His
705 710 715 720
Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val Val Leu
725 730 735
Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro Gly Trp
740 745 750
Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn Val Glu
755 760 765
Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu Arg Phe
770 775 780
Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr Gly Leu
785 790 795 800
Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu Gln Leu
805 810 815
Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile

[0324]
820 825

[0325] SEQ.ID NO:7-NPP3氨基酸序列:

[0326]

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

[0327] Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val Ser Ala
325 330 335
Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala Phe Gly Met Leu
340 345 350
Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn Ile Ile
355 360 365
Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys Met Glu
370 375 380
Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr Met Tyr Glu
385 390 395 400
Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro His Asp Phe Phe
405 410 415
Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg Lys Pro
420 425 430
Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys Arg Leu

435 440 445

His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His Leu Phe Val Asp

450 455 460

Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys Gly Gly

465 470 475 480

Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala Ile Phe

485 490 495

Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu Pro Phe

500 505 510

Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg Ile Gln

515 520 525

Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His Leu Leu Lys

530 535 540

Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys Phe Ser

[0328] 545 550 555 560

Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu Asp Cys Phe

565 570 575

Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn Gln Met

580 585 590

Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val Asn Leu

595 600 605

Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val Asp His Cys Leu

610 615 620

Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala Met Arg Met

625 630 635 640

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

645 650 655

Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp Val Arg Val Pro

660 665 670

Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys Asn Ile
675 680 685
Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser Asp Ser
690 695 700
Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro Met Tyr Glu Glu
705 710 715 720
Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu Leu Ile Lys His
725 730 735
Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile Phe Asp
740 745 750
Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr Lys His
755 760 765
Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val Val Leu
[0329]
770 775 780
Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro Gly Trp
785 790 795 800
Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn Val Glu
805 810 815
Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu Arg Phe
820 825 830
Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr Gly Leu
835 840 845
Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu Gln Leu
850 855 860
Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile
865 870 875

[0330] 上文所示的NPP3氨基酸序列包括细胞质结构域、跨膜结构域、磷酸二酯酶/催化结构域和核酸酶结构域。催化结构域和核酸酶结构域共同称作胞外结构域。残基1-11(Met Glu Ser至Ala Thr Glu)对应于细胞质结构域。残基12-30(Gln Pro Val至Leu Leu Ala)对应于跨膜结构域。残基31-875(Leu Leu Val至Thr Thr Ile)对应于胞外结构域。残基140-

510(Leu Glu Glu至Glu Val Glu)对应于催化/磷酸二酯酶结构域。残基605至875(Lys Val Asn至Thr Thr Ile)对应于核酸酶结构域。基于人NPP3序列(UniProtKB/Swiss-Prot:014638.2)对残基编号并对结构域分类

[0331] SEQ ID No:8-天青杀素-ENPP3-FC

MTRLTVLALLAGLLASSRA**AKQGSCRKKCFDASFRGLENCRCDVACKDRGDCCWDFEDTCVESTRIWMCNKFRCGETRLEASLCS
CSDDCLQRKDCCADYKSVCQGETSWLEENCDTAQQSQCPEGFDLPPVILFSMDGFRAEYLYTWDTLMPNINKLKTCGIHSKYMRAMYPTKT
FPNHYTIVTGLYPESHGIIDNNMYDVNLNKNFSLSSKEQNNPAWWHGQPMNLTAMYQGLKAATYFWPGSEVAINGSFPSIYMPYNGSVPFE
ERISTLLKWLDLPKAERPRFYTMYFEEPDSSGHAGGPVSARVIKALQVVDHAFGMLMEGLKQRNLHNCVNIILLADHGMDQTYCNKMEYMT
DYFPRINFFYMYEGPAPRIRAHNIPHDFFSFNSEEIVRNLSCRKPDQHFKPYLTPDLPKRLHYAKNVRIDKVHLFVDQQWLAVRSKSNTNC
GGGNHGYNNEFRSMEAIFLAHGPSFKEKTEVEPFENIEVYNLMCDLLRIQPAPNNGTHGSLNHLLKVPFYEPSHAEEVSKFSVCGFANPLP
TESLDCFCPHLQNSTQLEQVNQMLNLTQEEITATVKVNLPFGRPRVLQKNVDHCLLYHREYVSGFGKAMRMPMWSSYTVPQLGDTSPLPPT
VPDCLRADVRVPPSESQKCSFYLADKNITHGFLYPPASNRTSDSQYDALITSNLVPMYEEFRKMWDYFHSVLLIKHATERNGVNVVSGPIF
DYNYDGHFDAPDEITKHLANTDVPIPTHYFVVLTSCKNKSHTPENCPGWLDVLPFIIPHRPTNVESCPEGKPEALWVEERFTAHIARVRDV
ELLTGLDFYQDKVQPVSEILQLKTYLPTFETTI**DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY**
VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[0332]

[0333] 单下划线-天青杀素信号序列,双下划线-ENPP3序列的起始和结束,粗体残基-Fc序列,**表示信号序列的切割点。

[0334] SEQ ID No:9-天青杀素-ENPP3-白蛋白

MTRLTVLALLAGLLASSRA**AKQGSCRKKCFDASFRGLENCRCDVACKDRGDCCWDFEDTCVESTRIWMCNKFRCGETRLEASLCS
CSDDCLQRKDCCADYKSVCQGETSWLEENCDTAQQSQCPEGFDLPPVILFSMDGFRAEYLYTWDTLMPNINKLKTCGIHSKYMRAMYPTKT
FPNHYTIVTGLYPESHGIIDNNMYDVNLNKNFSLSSKEQNNPAWWHGQPMNLTAMYQGLKAATYFWPGSEVAINGSFPSIYMPYNGSVPFE
ERISTLLKWLDLPKAERPRFYTMYFEEPDSSGHAGGPVSARVIKALQVVDHAFGMLMEGLKQRNLHNCVNIILLADHGMDQTYCNKMEYMT
DYFPRINFFYMYEGPAPRIRAHNIPHDFFSFNSEEIVRNLSCRKPDQHFKPYLTPDLPKRLHYAKNVRIDKVHLFVDQQWLAVRSKSNTNC
GGGNHGYNNEFRSMEAIFLAHGPSFKEKTEVEPFENIEVYNLMCDLLRIQPAPNNGTHGSLNHLLKVPFYEPSHAEEVSKFSVCGFANPLP
TESLDCFCPHLQNSTQLEQVNQMLNLTQEEITATVKVNLPFGRPRVLQKNVDHCLLYHREYVSGFGKAMRMPMWSSYTVPQLGDTSPLPPT
VPDCLRADVRVPPSESQKCSFYLADKNITHGFLYPPASNRTSDSQYDALITSNLVPMYEEFRKMWDYFHSVLLIKHATERNGVNVVSGPIF
DYNYDGHFDAPDEITKHLANTDVPIPTHYFVVLTSCKNKSHTPENCPGWLDVLPFIIPHRPTNVESCPEGKPEALWVEERFTAHIARVRDV
ELLTGLDFYQDKVQPVSEILQLKTYLPTFETTI**MKWVTFLLLLFVSGSAFSRGVFRREAHKSEIAHRYNDLGEQHFKGLVLIAFSQYLQKC**
SYDEHAKLVQEVTDFAKTCVADESAANCDKSLHTLFGDKLCAIPNLRENYGELADCCTKQEPERNECFLQHKDDNPSLPPFERPEAEAMCT
SFKENPTTFMGHYLHEVARRHPYFYAPELLYYAEQYNEILTQCCAEADKESCLTPKLDGVKEKALVSSVRQRMKCSSMQKFGERAFKAWAV
ARLSQTFPNADFAEITKLATDLTKVNKECCHGDLLECADDRAELAKYMCENQATISSKLQTCCDKPLLKKAHCLSEVEHDTMPADLPAIAA
DFVEDQEVCKNYAEAKDVFLGTFLYEYSRRHPDYSVSLLLRLAKKYEATLEKCCAEANPPACYGTVLAEFQPLVEEPKNLVKTNCDLYEKL
GEYGFQNAILVRYTQKAPQVSTPTLVEAARNLGRVGTKCCTLPEDQRLPCVEDYLSAILNRVCLLHEKTPVSEHVTKCCSGSLVERRPCFS
ALTVDETYVPKEFKAETFTFHSDICTLPEKEKQIKKQTALAELVKHKPKATAEQLKTVMDDFAQFLDTCCKAADKDTCFSTEGPNLVTRCK
DALARSWSHPQFEK

[0335]

[0336]

[0337] 单下划线-天青杀素信号序列,双下划线-ENPP3序列的起始和结束,粗体残基-白蛋白序列,**表示信号序列的切割点。

[0338] SEQ ID No:10-天青杀素-ENPP3

[0339] MTRLTVLALLAGLLASSRA**AKQGSCRKKCFDASFRGLENCRCDVACKDRGDCCWDFEDTCVESTRIWMCNKFRCGETRLEASLCS
CSDDCLQRKDCCADYKSVCQGETSWLEENCDTAQQSQCPEGFDLPPVILFSMDGFRAEYLYTWDTLMPNINKLKTCGIHSKYMRAMYPTKT
FPNHYTIVTGLYPESHGIIDNNMYDVNLNKNFSLSSKEQNNPAWWHGQPMNLTAMYQGLKAATYFWPGSEVAINGSFPSIYMPYNGSVPFE
ERISTLLKWLDLPKAERPRFYTMYFEEPDSSGHAGGPVSARVIKALQVVDHAFGMLMEGLKQRNLHNCVNIILLADHGMDQTYCNKMEYMT
DYFPRINFFYMYEGPAPRIRAHNIPHDFFSFNSEEIVRNLSCRKPDQHFKPYLTPDLPKRLHYAKNVRIDKVHLFVDQQWLAVRSKSNTNC
GGGNHGYNNEFRSMEAIFLAHGPSFKEKTEVEPFENIEVYNLMCDLLRIQPAPNNGTHGSLNHLLKVPFYEPSHAEEVSKFSVCGFANPLP
TESLDCFCPHLQNSTQLEQVNQMLNLTQEEITATVKVNLPFGRPRVLQKNVDHCLLYHREYVSGFGKAMRMPMWSSYTVPQLGDTSPLPPT
VPDCLRADVRVPPSESQKCSFYLADKNITHGFLYPPASNRTSDSQYDALITSNLVPMYEEFRKMWDYFHSVLLIKHATERNGVNVVSGPIF
DYNYDGHFDAPDEITKHLANTDVPIPTHYFVVLTSCKNKSHTPENCPGWLDVLPFIIPHRPTNVESCPEGKPEALWVEERFTAHIARVRDV
ELLTGLDFYQDKVQPVSEILQLKTYLPTFETTI

[0340] 单下划线-天青杀素信号序列,双下划线-ENPP3序列的起始和结束,**表示信号序列的切割点。

[0341] SEQ.ID NO:11-ENPP4氨基酸序列-野生型

[0342]

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

Val Thr Lys Lys His Phe Ser Asp Ser Asn Asp Lys Asp Pro Phe Trp
100 105 110
Trp Asn Glu Ala Val Pro Ile Trp Val Thr Asn Gln Leu Gln Glu Asn
115 120 125
Arg Ser Ser Ala Ala Ala Met Trp Pro Gly Thr Asp Val Pro Ile His
130 135 140
Asp Thr Ile Ser Ser Tyr Phe Met Asn Tyr Asn Ser Ser Val Ser Phe
145 150 155 160
Glu Glu Arg Leu Asn Asn Ile Thr Met Trp Leu Asn Asn Ser Asn Pro
165 170 175
Pro Val Thr Phe Ala Thr Leu Tyr Trp Glu Glu Pro Asp Ala Ser Gly
180 185 190
His Lys Tyr Gly Pro Glu Asp Lys Glu Asn Met Ser Arg Val Leu Lys
195 200 205

[0343]

Lys Ile Asp Asp Leu Ile Gly Asp Leu Val Gln Arg Leu Lys Met Leu
210 215 220
Gly Leu Trp Glu Asn Leu Asn Val Ile Ile Thr Ser Asp His Gly Met
225 230 235 240
Thr Gln Cys Ser Gln Asp Arg Leu Ile Asn Leu Asp Ser Cys Ile Asp
245 250 255
His Ser Tyr Tyr Thr Leu Ile Asp Leu Ser Pro Val Ala Ala Ile Leu
260 265 270
Pro Lys Ile Asn Arg Thr Glu Val Tyr Asn Lys Leu Lys Asn Cys Ser
275 280 285
Pro His Met Asn Val Tyr Leu Lys Glu Asp Ile Pro Asn Arg Phe Tyr
290 295 300
Tyr Gln His Asn Asp Arg Ile Gln Pro Ile Ile Leu Val Ala Asp Glu
305 310 315 320
Gly Trp Thr Ile Val Leu Asn Glu Ser Ser Gln Lys Leu Gly Asp His

325 330 335

Gly Tyr Asp Asn Ser Leu Pro Ser Met His Pro Phe Leu Ala Ala His

340 345 350

Gly Pro Ala Phe His Lys Gly Tyr Lys His Ser Thr Ile Asn Ile Val

355 360 365

Asp Ile Tyr Pro Met Met Cys His Ile Leu Gly Leu Lys Pro His Pro

370 375 380

Asn Asn Gly Thr Phe Gly His Thr Lys Cys Leu Leu Val Asp Gln Trp

385 390 395 400

[0344]

Cys Ile Asn Leu Pro Glu Ala Ile Ala Ile Val Ile Gly Ser Leu Leu

405 410 415

Val Leu Thr Met Leu Thr Cys Leu Ile Ile Ile Met Gln Asn Arg Leu

420 425 430

Ser Val Pro Arg Pro Phe Ser Arg Leu Gln Leu Gln Glu Asp Asp Asp

435 440 445

Asp Pro Leu Ile Gly

450

[0345] SEQ.ID NO:12-ENPP51氨基酸序列

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

1 5 10 15

Leu Ser Thr Thr Phe Ser Leu Gln**Pro Ser Cys Ala Lys Glu Val Lys

20 25 30

Ser Cys Lys Gly Arg Cys Phe Glu Arg Thr Phe Ser Asn Cys Arg Cys

35 40 45

Asp Ala Ala Cys Val Ser Leu Gly Asn Cys Cys Leu Asp Phe Gln Glu

50 55 60

Thr Cys Val Glu Pro Thr His Ile Trp Thr Cys Asn Lys Phe Arg Cys
65 70 75 80
Gly Glu Lys Arg Leu Ser Arg Phe Val Cys Ser Cys Ala Asp Asp Cys
85 90 95
Lys Thr His Asn Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln Asp
100 105 110
Lys Lys Ser Trp Val Glu Glu Thr Cys Glu Ser Ile Asp Thr Pro Glu
115 120 125
Cys Pro Ala Glu Phe Glu Ser Pro Pro Thr Leu Leu Phe Ser Leu Asp
130 135 140
Gly Phe Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro Val
145 150 155 160
Ile Ser Lys Leu Lys Asn Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro
165 170 175

[0346] Met Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly
180 185 190
Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro
195 200 205
Lys Met Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro
210 215 220
Leu Trp Tyr Lys Gly Gln Pro Ile Trp Val Thr Ala Asn His Gln Glu
225 230 235 240
Val Lys Ser Gly Thr Tyr Phe Trp Pro Gly Ser Asp Val Glu Ile Asp
245 250 255
Gly Ile Leu Pro Asp Ile Tyr Lys Val Tyr Asn Gly Ser Val Pro Phe
260 265 270
Glu Glu Arg Ile Leu Ala Val Leu Glu Trp Leu Gln Leu Pro Ser His
275 280 285
Glu Arg Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser

290 295 300

Gly His Ser His Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln

305 310 315 320

Lys Val Asp Arg Leu Val Gly Met Leu Met Asp Gly Leu Lys Asp Leu

325 330 335

Gly Leu Asp Lys Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met

340 345 350

Glu Gln Gly Ser Cys Lys Lys Tyr Val Tyr Leu Asn Lys Tyr Leu Gly

355 360 365

Asp Val Asn Asn Val Lys Val Val Tyr Gly Pro Ala Ala Arg Leu Arg

370 375 380

Pro Thr Asp Val Pro Glu Thr Tyr Tyr Ser Phe Asn Tyr Glu Ala Leu

385 390 395 400

Ala Lys Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Arg Pro Tyr

[0347] 405 410 415

Leu Lys Pro Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg

420 425 430

Ile Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu

435 440 445

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

450 455 460

Asn Leu Phe Ser Asn Met Gln Ala Leu Phe Ile Gly Tyr Gly Pro Ala

465 470 475 480

Phe Lys His Gly Ala Glu Val Asp Ser Phe Glu Asn Ile Glu Val Tyr

485 490 495

Asn Leu Met Cys Asp Leu Leu Gly Leu Ile Pro Ala Pro Asn Asn Gly

500 505 510

Ser His Gly Ser Leu Asn His Leu Leu Lys Lys Pro Ile Tyr Asn Pro

515 520 525

Ser His Pro Lys Glu Glu Gly Phe Leu Ser Gln Cys Pro Ile Lys Ser
530 535 540
Thr Ser Asn Asp Leu Gly Cys Thr Cys Asp Pro Trp Ile Val Pro Ile
545 550 555 560
Lys Asp Phe Glu Lys Gln Leu Asn Leu Thr Thr Glu Asp Val Asp Asp
565 570 575
Ile Tyr His Met Thr Val Pro Tyr Gly Arg Pro Arg Ile Leu Leu Lys
580 585 590
Gln His Arg Val Cys Leu Leu Gln Gln Gln Gln Phe Leu Thr Gly Tyr
595 600 605
Ser Leu Asp Leu Leu Met Pro Leu Trp Ala Ser Tyr Thr Phe Leu Ser
610 615 620
Asn Asp Gln Phe Ser Arg Asp Asp Phe Ser Asn Cys Leu Tyr Gln Asp
625 630 635 640

[0348]
Leu Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Tyr Tyr Lys Ser
645 650 655
Asn Ser Lys Leu Ser Tyr Gly Phe Leu Thr Pro Pro Arg Leu Asn Arg
660 665 670
Val Ser Asn His Ile Tyr Ser Glu Ala Leu Leu Thr Ser Asn Ile Val
675 680 685
Pro Met Tyr Gln Ser Phe Gln Val Ile Trp His Tyr Leu His Asp Thr
690 695 700
Leu Leu Gln Arg Tyr Ala His Glu Arg Asn Gly Ile Asn Val Val Ser
705 710 715 720
Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Tyr Asp Ser Leu Glu
725 730 735
Ile Leu Lys Gln Asn Ser Arg Val Ile Arg Ser Gln Glu Ile Leu Ile
740 745 750
Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Gln Leu Ser Glu

755 760 765

Thr Pro Leu Glu Cys Ser Ala Leu Glu Ser Ser Ala Tyr Ile Leu Pro

770 775 780

His Arg Pro Asp Asn Ile Glu Ser Cys Thr His Gly Lys Arg Glu Ser

785 790 795 800

Ser Trp Val Glu Glu Leu Leu Thr Leu His Arg Ala Arg Val Thr Asp

[0349]

805 810 815

Val Glu Leu Ile Thr Gly Leu Ser Phe Tyr Gln Asp Arg Gln Glu Ser

820 825 830

Val Ser Glu Leu Leu Arg Leu Lys Thr His Leu Pro Ile Phe Ser Gln

835 840 845

Glu Asp

850

[0350] 单下划线:信号肽序列;双下划线:NPP1的开始和结束;**=在信号肽序列上的切割位置

[0351] SEQ.ID NO:13-ENPP51-ALB氨基酸序列:

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

1 5 10 15

Leu Ser Thr Thr Phe Ser Leu Gln**Pro Ser Cys Ala Lys Glu Val Lys

20 25 30

Ser Cys Lys Gly Arg Cys Phe Glu Arg Thr Phe Ser Asn Cys Arg Cys

35 40 45

[0352]

Asp Ala Ala Cys Val Ser Leu Gly Asn Cys Cys Leu Asp Phe Gln Glu

50 55 60

Thr Cys Val Glu Pro Thr His Ile Trp Thr Cys Asn Lys Phe Arg Cys

65 70 75 80

Gly Glu Lys Arg Leu Ser Arg Phe Val Cys Ser Cys Ala Asp Asp Cys

85 90 95

Lys Thr His Asn Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln Asp
100 105 110
Lys Lys Ser Trp Val Glu Glu Thr Cys Glu Ser Ile Asp Thr Pro Glu
115 120 125
Cys Pro Ala Glu Phe Glu Ser Pro Pro Thr Leu Leu Phe Ser Leu Asp
130 135 140
Gly Phe Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro Val
145 150 155 160
Ile Ser Lys Leu Lys Asn Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro
165 170 175
Met Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly
180 185 190
Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro
195 200 205

[0353]
Lys Met Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro
210 215 220
Leu Trp Tyr Lys Gly Gln Pro Ile Trp Val Thr Ala Asn His Gln Glu
225 230 235 240
Val Lys Ser Gly Thr Tyr Phe Trp Pro Gly Ser Asp Val Glu Ile Asp
245 250 255
Gly Ile Leu Pro Asp Ile Tyr Lys Val Tyr Asn Gly Ser Val Pro Phe
260 265 270
Glu Glu Arg Ile Leu Ala Val Leu Glu Trp Leu Gln Leu Pro Ser His
275 280 285
Glu Arg Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser
290 295 300
Gly His Ser His Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln
305 310 315 320
Lys Val Asp Arg Leu Val Gly Met Leu Met Asp Gly Leu Lys Asp Leu

325 330 335

Gly Leu Asp Lys Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met

340 345 350

Glu Gln Gly Ser Cys Lys Lys Tyr Val Tyr Leu Asn Lys Tyr Leu Gly

355 360 365

Asp Val Asn Asn Val Lys Val Val Tyr Gly Pro Ala Ala Arg Leu Arg

370 375 380

Pro Thr Asp Val Pro Glu Thr Tyr Tyr Ser Phe Asn Tyr Glu Ala Leu

385 390 395 400

Ala Lys Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Arg Pro Tyr

405 410 415

Leu Lys Pro Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg

420 425 430

Ile Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu

[0354] 435 440 445

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

450 455 460

Asn Leu Phe Ser Asn Met Gln Ala Leu Phe Ile Gly Tyr Gly Pro Ala

465 470 475 480

Phe Lys His Gly Ala Glu Val Asp Ser Phe Glu Asn Ile Glu Val Tyr

485 490 495

Asn Leu Met Cys Asp Leu Leu Gly Leu Ile Pro Ala Pro Asn Asn Gly

500 505 510

Ser His Gly Ser Leu Asn His Leu Leu Lys Lys Pro Ile Tyr Asn Pro

515 520 525

Ser His Pro Lys Glu Glu Gly Phe Leu Ser Gln Cys Pro Ile Lys Ser

530 535 540

Thr Ser Asn Asp Leu Gly Cys Thr Cys Asp Pro Trp Ile Val Pro Ile

545 550 555 560

Lys Asp Phe Glu Lys Gln Leu Asn Leu Thr Thr Glu Asp Val Asp Asp
565 570 575
Ile Tyr His Met Thr Val Pro Tyr Gly Arg Pro Arg Ile Leu Leu Lys
580 585 590
Gln His Arg Val Cys Leu Leu Gln Gln Gln Gln Phe Leu Thr Gly Tyr
595 600 605
Ser Leu Asp Leu Leu Met Pro Leu Trp Ala Ser Tyr Thr Phe Leu Ser
610 615 620
Asn Asp Gln Phe Ser Arg Asp Asp Phe Ser Asn Cys Leu Tyr Gln Asp
625 630 635 640
Leu Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Tyr Tyr Lys Ser
645 650 655
Asn Ser Lys Leu Ser Tyr Gly Phe Leu Thr Pro Pro Arg Leu Asn Arg
660 665 670

[0355] Val Ser Asn His Ile Tyr Ser Glu Ala Leu Leu Thr Ser Asn Ile Val
675 680 685
Pro Met Tyr Gln Ser Phe Gln Val Ile Trp His Tyr Leu His Asp Thr
690 695 700
Leu Leu Gln Arg Tyr Ala His Glu Arg Asn Gly Ile Asn Val Val Ser
705 710 715 720
Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Tyr Asp Ser Leu Glu
725 730 735
Ile Leu Lys Gln Asn Ser Arg Val Ile Arg Ser Gln Glu Ile Leu Ile
740 745 750
Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Gln Leu Ser Glu
755 760 765
Thr Pro Leu Glu Cys Ser Ala Leu Glu Ser Ser Ala Tyr Ile Leu Pro
770 775 780
His Arg Pro Asp Asn Ile Glu Ser Cys Thr His Gly Lys Arg Glu Ser

785 790 795 800

Ser Trp Val Glu Glu Leu Leu Thr Leu His Arg Ala Arg Val Thr Asp

805 810 815

Val Glu Leu Ile Thr Gly Leu Ser Phe Tyr Gln Asp Arg Gln Glu Ser

820 825 830

Val Ser Glu Leu Leu Arg Leu Lys Thr His Leu Pro Ile Phe Ser Gln

835 840 845

Glu Asp Gly Gly Ser Gly Gly Ser Met Lys Trp Val Thr Phe Leu Leu

850 855 860

Leu Leu Phe Val Ser Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg

865 870 875 880

Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu

885 890 895

Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln

[0356] 900 905 910

Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu Val Thr Asp

915 920 925

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys

930 935 940

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu

945 950 955 960

Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro

965 970 975

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Ser Leu

980 985 990

Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met Cys Thr Ser Phe Lys

995 1000 1005

Glu Asn Pro Thr Thr Phe Met Gly His Tyr Leu His Glu Val Ala

1010 1015 1020

Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Tyr Tyr Ala
1025 1030 1035

Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys Ala Glu Ala Asp
1040 1045 1050

Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val Lys Glu Lys
1055 1060 1065

Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys Ser Ser Met
1070 1075 1080

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
1085 1090 1095

Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr Lys
1100 1105 1110

Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly
1115 1120 1125

[0357] Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr
1130 1135 1140

Met Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys
1145 1150 1155

Cys Asp Lys Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val
1160 1165 1170

Glu His Asp Thr Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp
1175 1180 1185

Phe Val Glu Asp Gln Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys
1190 1195 1200

Asp Val Phe Leu Gly Thr Phe Leu Tyr Glu Tyr Ser Arg Arg His
1205 1210 1215

Pro Asp Tyr Ser Val Ser Leu Leu Leu Arg Leu Ala Lys Lys Tyr
1220 1225 1230

Glu Ala Thr Leu Glu Lys Cys Cys Ala Glu Ala Asn Pro Pro Ala

1235 1240 1245

Cys Tyr Gly Thr Val Leu Ala Glu Phe Gln Pro Leu Val Glu Glu

1250 1255 1260

Pro Lys Asn Leu Val Lys Thr Asn Cys Asp Leu Tyr Glu Lys Leu

1265 1270 1275

Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val Arg Tyr Thr Gln

1280 1285 1290

Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu Ala Ala Arg

1295 1300 1305

Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu Pro Glu Asp

1310 1315 1320

Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile Leu Asn

1325 1330 1335

Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His Val

[0358] 1340 1345 1350

Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe

1355

Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys

1370 1375 1380

Ala Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu

1385 1390 1395

Lys Glu Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val

1400 1405 1410

Lys His Lys Pro Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met

1415 1420 1425

Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp

1430 1435 1440

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

1445 1450 1455

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

[0359] 1460 1465 1470

Lys

[0360] 单下划线:信号肽序列;双下划线-ENPP1序列的起始和结束;**=在信号肽序列上的切割位置;粗体残基表示白蛋白序列

[0361] SEQ.ID NO:14-ENPP5-NPP3-Fc序列

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

1 5 10 15

Leu Ser Thr Thr Phe Ser**Lys Gln Gly Ser Cys Arg Lys Lys Cys Phe

20 25 30

Asp Ala Ser Phe Arg Gly Leu Glu Asn Cys Arg Cys Asp Val Ala Cys

35 40 45

Lys Asp Arg Gly Asp Cys Cys Trp Asp Phe Glu Asp Thr Cys Val Glu

50 55 60

Ser Thr Arg Ile Trp Met Cys Asn Lys Phe Arg Cys Gly Glu Arg Leu

65 70 75 80

[0362]

Glu Ala Ser Leu Cys Ser Cys Ser Asp Asp Cys Leu Gln Arg Lys Asp

85 90 95

Cys Cys Ala Asp Tyr Lys Ser Val Cys Gln Gly Glu Thr Ser Trp Leu

100 105 110

Glu Glu Asn Cys Asp Thr Ala Gln Gln Ser Gln Cys Pro Glu Gly Phe

115 120 125

Asp Leu Pro Pro Val Ile Leu Phe Ser Met Asp Gly Phe Arg Ala Glu

130 135 140

Tyr Leu Tyr Thr Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys

145 150 155 160

Thr Cys Gly Ile His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys
165 170 175
Thr Phe Pro Asn His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser
180 185 190
His Gly Ile Ile Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn
195 200 205
Phe Ser Leu Ser Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly
210 215 220
Gln Pro Met Trp Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr
225 230 235 240
Tyr Phe Trp Pro Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser
245 250 255
Ile Tyr Met Pro Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser
260 265 270

[0363] Thr Leu Leu Lys Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe
275 280 285
Tyr Thr Met Tyr Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly
290 295 300
Pro Val Ser Ala Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala
305 310 315 320
Phe Gly Met Leu Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys
325 330 335
Val Asn Ile Ile Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys
340 345 350
Asn Lys Met Glu Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe
355 360 365
Tyr Met Tyr Glu Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro
370 375 380
His Asp Phe Phe Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser

385 390 395 400

Cys Arg Lys Pro Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu

405 410 415

Pro Lys Arg Leu His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His

420 425 430

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

435 440 445

Asn Cys Gly Gly Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met

450 455 460

Glu Ala Ile Phe Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu

465 470 475 480

Val Glu Pro Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu

485 490 495

Leu Arg Ile Gln Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn

[0364] 500 505 510

His Leu Leu Lys Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val

515 520 525

Ser Lys Phe Ser Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser

530 535 540

Leu Asp Cys Phe Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln

545 550 555 560

Val Asn Gln Met Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val

565 570 575

Lys Val Asn Leu Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val

580 585 590

Asp His Cys Leu Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys

595 600 605

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

610 615 620

Asp Thr Ser Pro Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp
625 630 635 640
Val Arg Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala
645 650 655
Asp Lys Asn Ile Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg
660 665 670
Thr Ser Asp Ser Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro
675 680 685
Met Tyr Glu Glu Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu
690 695 700
Leu Ile Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly
705 710 715 720
Pro Ile Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu
725 730 735

[0365] Ile Thr Lys His Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr
740 745 750
Phe Val Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn
755 760 765
Cys Pro Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro
770 775 780
Thr Asn Val Glu Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val
785 790 795 800
Glu Glu Arg Phe Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu
805 810 815
Leu Thr Gly Leu Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu
820 825 830
Ile Leu Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile **Asp**
835 840 845
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly

850 855 860

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile

865 870 875 880

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu

885 890 895

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His

900 905 910

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg

915 920 925

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys

930 935 940

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu

945 950 955 960

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr

[0366] 965 970 975

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu

980 985 990

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp

995 1000 1005

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro

1010 1015 1020

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

1025 1030 1035

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser

1040 1045 1050

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

1055 1060 1065

Ser Leu Ser Pro Gly Lys

1070

[0367] 单下划线:信号肽序列;双下划线-ENPP3序列的起始和结束;**=在信号肽序列上的切割位置;粗体残基表示白蛋白序列

[0368] SEQ.ID NO:15-ENPP5-NPP3-白蛋白序列

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

1 5 10 15

Leu Ser Thr Thr Phe Ser**Lys Gln Gly Ser Cys Arg Lys Lys Cys Phe

20 25 30

Asp Ala Ser Phe Arg Gly Leu Glu Asn Cys Arg Cys Asp Val Ala Cys

35 40 45

Lys Asp Arg Gly Asp Cys Cys Trp Asp Phe Glu Asp Thr Cys Val Glu

50 55 60

Ser Thr Arg Ile Trp Met Cys Asn Lys Phe Arg Cys Gly Glu Arg Leu

65 70 75 80

Glu Ala Ser Leu Cys Ser Cys Ser Asp Asp Cys Leu Gln Arg Lys Asp

[0369] 85 90 95

Cys Cys Ala Asp Tyr Lys Ser Val Cys Gln Gly Glu Thr Ser Trp Leu

100 105 110

Glu Glu Asn Cys Asp Thr Ala Gln Gln Ser Gln Cys Pro Glu Gly Phe

115 120 125

Asp Leu Pro Pro Val Ile Leu Phe Ser Met Asp Gly Phe Arg Ala Glu

130 135 140

Tyr Leu Tyr Thr Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys

145 150 155 160

Thr Cys Gly Ile His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys

165 170 175

Thr Phe Pro Asn His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser

180 185 190

His Gly Ile Ile Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn

195 200 205

Phe Ser Leu Ser Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly

210 215 220

Gln Pro Met Trp Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr

225 230 235 240

Tyr Phe Trp Pro Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser

245 250 255

Ile Tyr Met Pro Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser

260 265 270

Thr Leu Leu Lys Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe

275 280 285

Tyr Thr Met Tyr Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly

[0370] 290 295 300

Pro Val Ser Ala Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala

305 310 315 320

Phe Gly Met Leu Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys

325 330 335

Val Asn Ile Ile Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys

340 345 350

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

355 360 365

Tyr Met Tyr Glu Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro

370 375 380

His Asp Phe Phe Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser

385 390 395 400

Cys Arg Lys Pro Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu

405 410 415

Pro Lys Arg Leu His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His
420 425 430
Leu Phe Val Asp Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr
435 440 445
Asn Cys Gly Gly Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met
450 455 460
Glu Ala Ile Phe Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu
465 470 475 480
Val Glu Pro Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu
485 490 495
Leu Arg Ile Gln Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn
500 505 510
His Leu Leu Lys Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val
515 520 525

[0371] Ser Lys Phe Ser Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser
530 535 540
Leu Asp Cys Phe Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln
545 550 555 560
Val Asn Gln Met Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val
565 570 575
Lys Val Asn Leu Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val
580 585 590
Asp His Cys Leu Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys
595 600 605
Ala Met Arg Met Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly
610 615 620
Asp Thr Ser Pro Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp
625 630 635 640
Val Arg Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala

645 650 655

Asp Lys Asn Ile Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg

660 665 670

Thr Ser Asp Ser Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro

675 680 685

Met Tyr Glu Glu Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu

690 695 700

Leu Ile Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly

705 710 715 720

Pro Ile Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu

725 730 735

Ile Thr Lys His Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr

740 745 750

Phe Val Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn

[0372] 755 760 765

Cys Pro Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro

770 775 780

Thr Asn Val Glu Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val

785 790 795 800

Glu Glu Arg Phe Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu

805 810 815

Leu Thr Gly Leu Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu

820 825 830

Ile Leu Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile **Gly**

835 840 845

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Met Lys Trp

850 855 860

Val Thr Phe Leu Leu Leu Leu Phe Val Ser Gly Ser Ala Phe Ser Arg

865 870 875 880

Gly Val Phe Arg Arg Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr
885 890 895

Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe
900 905 910

Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val
915 920 925

Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
930 935 940

Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
945 950 955 960

Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys
965 970 975

Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
980 985 990

[0373] Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met
995 1000 1005

Cys Thr Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly His Tyr
1010 1015 1020

Leu His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
1025 1030 1035

Leu Leu Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys
1040 1045 1050

Cys Ala Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp
1055 1060 1065

Gly Val Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met
1070 1075 1080

Lys Cys Ser Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala
1085 1090 1095

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

1100 1105 1110

Ala Glu Ile Thr Lys Leu Ala Thr Asp Leu Thr Lys Val Asn Lys

1115 1120 1125

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala

1130 1135 1140

Glu Leu Ala Lys Tyr Met Cys Glu Asn Gln Ala Thr Ile Ser Ser

1145 1150 1155

Lys Leu Gln Thr Cys Cys Asp Lys Pro Leu Leu Lys Lys Ala His

1160 1165 1170

Cys Leu Ser Glu Val Glu His Asp Thr Met Pro Ala Asp Leu Pro

1175 1180 1185

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

1190 1195 1200

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Thr Phe Leu Tyr Glu

[0374] 1205 1210 1215

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

1220 1225 1230

Leu Ala Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys Cys Ala Glu

1235 1240 1245

Ala Asn Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu Phe Gln

1250 1255 1260

Pro Leu Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys Asp

1265 1270 1275

Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu

1280 1285 1290

Val Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu

1295 1300 1305

Val Glu Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys

1310 1315 1320

Thr Leu Pro Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu

1325 1330 1335

Ser Ala Ile Leu Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro

1340 1345 1350

Val Ser Glu His Val Thr Lys Cys Cys Ser Gly Ser Leu Val Glu

1355 1360 1365

Arg Arg Pro Cys Phe Ser Ala Leu Thr Val Asp Glu Thr Tyr Val

1370 1375 1380

Pro Lys Glu Phe Lys Ala Glu Thr Phe Thr Phe His Ser Asp Ile

1385 1390 1395

[0375]

Cys Thr Leu Pro Glu Lys Glu Lys Gln Ile Lys Lys Gln Thr Ala

1400 1405 1410

Leu Ala Glu Leu Val Lys His Lys Pro Lys Ala Thr Ala Glu Gln

1415 1420 1425

Leu Lys Thr Val Met Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys

1430 1435 1440

Cys Lys Ala Ala Asp Lys Asp Thr Cys Phe Ser Thr Glu Gly Pro

1445 1450 1455

Asn Leu Val Thr Arg Cys Lys Asp Ala Leu Ala

1460 1465

[0376] 单下划线:信号肽序列;双下划线-NPP3序列的起始和结束;**=在信号肽序列上的切割位置;粗体残基表示白蛋白序列

[0377] SEQ.ID NO:16-ENPP5蛋白输出信号序列

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

[0378] 1 5 10 15

Leu Ser Thr Thr Phe Ser Xaa

[0379] 20

[0380] SEQ.ID NO:17-ENPP5-1-Fc

[0381]

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

1 5 10 15

Leu Ser Thr Thr Phe Ser**Gly Leu Lys Pro Ser Cys Ala Lys Glu Val

20 25 30

Lys Ser Cys Lys Gly Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg

35 40 45

Cys Asp Ala Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln

50 55 60

Glu Thr Cys Ile Glu Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg

65 70 75 80

Cys Gly Glu Lys Arg Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp

85 90 95

Cys Lys Asp Lys Gly Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln

100 105 110

Gly Glu Lys Ser Trp Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro

115 120 125

Gln Cys Pro Ala Gly Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu

130 135 140

Asp Gly Phe Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro

145 150 155 160

Val Ile Ser Lys Leu Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg

165 170 175

Pro Val Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr

180 185 190

Gly Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp

195 200 205

Pro Lys Met Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn
210 215 220
Pro Glu Trp Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln
225 230 235 240
Gly Leu Lys Ser Gly Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile
245 250 255
Asn Gly Ile Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro
260 265 270
Phe Glu Glu Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys
275 280 285
Asp Glu Arg Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser
290 295 300
Ser Gly His Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu
305 310 315 320

[0382] Gln Arg Val Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu
325 330 335
Leu Asn Leu His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly
340 345 350
Met Glu Gln Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu
355 360 365
Gly Asp Val Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu
370 375 380
Arg Pro Ser Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly
385 390 395 400
Ile Ala Arg Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro
405 410 415
Tyr Leu Lys His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp
420 425 430
Arg Ile Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala

435 440 445

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

450 455 460

Asp Asn Val Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro

465 470 475 480

Gly Phe Lys His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val

485 490 495

Tyr Asn Leu Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn

500 505 510

Gly Thr His Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr

515 520 525

Pro Lys His Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr

530 535 540

Arg Asn Pro Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu

[0383] 545 550 555 560

Pro Ile Glu Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu

565 570 575

Lys Ile Ile Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu

580 585 590

Gln Lys Glu Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser

595 600 605

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

610 615 620

Asp Arg Asn Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr

625 630 635 640

Gln Asp Phe Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr

645 650 655

Lys Asn Asn Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu

660 665 670

Asn Lys Asn Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn
675 680 685
Ile Val Pro Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His
690 695 700
Asp Thr Leu Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val
705 710 715 720
Val Ser Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser
725 730 735
Leu Glu Asn Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile
740 745 750
Leu Ile Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr
755 760 765
Ser Gln Thr Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile
770 775 780

[0384] Leu Pro His Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His
785 790 795 800
Asp Ser Ser Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile
805 810 815
Thr Asp Val Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys
820 825 830
Glu Pro Val Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe
835 840 845
Ser Gln Glu Asp Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
850 855 860
Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
865 870 875 880
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
885 890 895
Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp

900 905 910

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

915 920 925

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

930 935 940

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu

945 950 955 960

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg

965 970 975

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys

980 985 990

[0385] Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp

995 1000 1005

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr

1010 1015 1020

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

1025 1030 1035

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn

1040 1045 1050

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr

1055 1060 1065

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

1070 1075

[0386] 单下划线:信号肽序列;双下划线-NPP3序列的起始和结束;**=在信号肽序列上的切割位置;粗体残基表示Fc序列

[0387] SEQ.ID NO:18-ENPP7-1-Fc氨基酸序列

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

1 5 10 15

Ala Pro Gly Ala Gly Ala**Gly Leu Lys Pro Ser Cys Ala Lys Glu Val

20 25 30

Lys Ser Cys Lys Gly Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg

35 40 45

Cys Asp Ala Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln

50 55 60

Glu Thr Cys Ile Glu Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg

65 70 75 80

Cys Gly Glu Lys Arg Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp

85 90 95

Cys Lys Asp Lys Gly Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln

100 105 110

[0388] Gly Glu Lys Ser Trp Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro

115 120 125

Gln Cys Pro Ala Gly Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu

130 135 140

Asp Gly Phe Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro

145 150 155 160

Val Ile Ser Lys Leu Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg

165 170 175

Pro Val Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr

180 185 190

Gly Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp

195 200 205

Pro Lys Met Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn

210 215 220

Pro Glu Trp Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln

225 230 235 240

Gly Leu Lys Ser Gly Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile

245 250 255

Asn Gly Ile Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro

260 265 270

Phe Glu Glu Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys

275 280 285

Asp Glu Arg Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser

290 295 300

Ser Gly His Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu

305 310 315 320

Gln Arg Val Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu

325 330 335

Leu Asn Leu His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly

[0389] 340 345 350

Met Glu Gln Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu

355 360 365

Gly Asp Val Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu

370 375 380

Arg Pro Ser Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly

385 390 395 400

Ile Ala Arg Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro

405 410 415

Tyr Leu Lys His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp

420 425 430

Arg Ile Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala

435 440 445

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

450 455 460

Asp Asn Val Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro
465 470 475 480
Gly Phe Lys His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val
485 490 495
Tyr Asn Leu Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn
500 505 510
Gly Thr His Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr
515 520 525
Pro Lys His Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr
530 535 540
Arg Asn Pro Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu
545 550 555 560
Pro Ile Glu Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu
565 570 575

[0390] Lys Ile Ile Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu
580 585 590
Gln Lys Glu Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser
595 600 605
Gly Tyr Ser Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val
610 615 620
Asp Arg Asn Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr
625 630 635 640
Gln Asp Phe Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr
645 650 655
Lys Asn Asn Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu
660 665 670
Asn Lys Asn Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn
675 680 685
Ile Val Pro Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His

690 695 700

Asp Thr Leu Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val

705 710 715 720

Val Ser Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser

725 730 735

Leu Glu Asn Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile

740 745 750

Leu Ile Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr

755 760 765

Ser Gln Thr Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile

770 775 780

Leu Pro His Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His

785 790 795 800

Asp Ser Ser Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile

[0391] 805 810 815

Thr Asp Val Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys

820 825 830

Glu Pro Val Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe

835 840 845

Ser Gln Glu Asp Leu Ile Asn **Asp Lys Thr His Thr Cys Pro Pro Cys**

850 855 860

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro

865 870 875 880

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

885 890 895

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp

900 905 910

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu

915 920 925

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu

930 935 940

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn

945 950 955 960

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly

965 970 975

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu

980 985 990

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr

995 1000 1005

[0392]

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu

1010 1015 1020

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser

1025 1030 1035

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln

1040 1045 1050

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His

1055 1060 1065

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

1070 1075 1080

[0393] 单下划线:信号肽序列;双下划线-NPP1序列的起始和结束;**=在信号肽序列上的切割位置;粗体残基表示Fc序列

[0394] SEQ.ID NO:19-ENPP71(缺乏NPP1 N端GLK)氨基酸序列:

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

1 5 10 15

[0395]

Ala Pro Gly Ala Gly Ala**Pro Ser Cys Ala Lys Glu Val Lys Ser Cys

20 25 30

Lys Gly Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala
35 40 45
Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys
50 55 60
Ile Glu Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu
65 70 75 80
Lys Arg Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp
85 90 95
Lys Gly Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys
100 105 110
Ser Trp Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro
115 120 125
Ala Gly Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe
130 135 140

[0396] Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser
145 150 155 160
Lys Leu Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr
165 170 175
Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr
180 185 190
Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met
195 200 205
Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp
210 215 220
Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys
225 230 235 240
Ser Gly Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile
245 250 255
Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu

260 265 270

Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg

275 280 285

Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His

290 295 300

Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val

305 310 315 320

Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu

325 330 335

His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln

340 345 350

Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val

355 360 365

Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser

[0397] 370 375 380

Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg

385 390 395 400

Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys

405 410 415

His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu

420 425 430

Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro

435 440 445

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

450 455 460

Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys

465 470 475 480

His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu

485 490 495

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

[0398] Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn
610 615 620
Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe
625 630 635 640
Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn
645 650 655
Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn
660 665 670
Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro
675 680 685
Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu
690 695 700
Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly
705 710 715 720
Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn

725 730 735

Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro

740 745 750

Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr

755 760 765

Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His

770 775 780

Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser

[0399]

785 790 795 800

Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val

805 810 815

Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val

820 825 830

Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu

835 840 845

Asp

[0400] 单下划线:信号肽序列;双下划线-NPP3序列的起始和结束;**=在信号肽序列上的切割位置

[0401] SEQ.ID NO:20-ENPP71(缺乏NPP1 N端GLK)-Fc氨基酸序列:

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

1 5 10 15

Ala Pro Gly Ala Gly Ala**Pro Ser Cys Ala Lys Glu Val Lys Ser Cys

20 25 30

[0402] Lys Gly Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala

35 40 45

Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys

50 55 60

Ile Glu Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu

65 70 75 80

Lys Arg Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp

85 90 95

Lys Gly Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys

100 105 110

Ser Trp Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro

115 120 125

Ala Gly Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe

130 135 140

Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser

145 150 155 160

Lys Leu Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr

165 170 175

Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr

[0403] 180 185 190

Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met

195 200 205

Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp

210 215 220

Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys

225 230 235 240

Ser Gly Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile

245 250 255

Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu

260 265 270

Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg

275 280 285

Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His

290 295 300

Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val
305 310 315 320
Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu
325 330 335
His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln
340 345 350
Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val
355 360 365
Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser
370 375 380
Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg
385 390 395 400
Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys
405 410 415

[0404] His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu
420 425 430
Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro
435 440 445
Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val
450 455 460
Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys
465 470 475 480
His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu
485 490 495
Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His
500 505 510
Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His
515 520 525
Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro

530 535 540

Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu

545 550 555 560

Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile

565 570 575

Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu

580 585 590

Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser

595 600 605

Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn

610 615 620

Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe

625 630 635 640

Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn

[0405] 645 650 655

Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn

660 665 670

Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro

675 680 685

Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu

690 695 700

Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly

705 710 715 720

Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn

725 730 735

Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro

740 745 750

Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr

755 760 765

Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His

770 775 780

Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser

785 790 795 800

Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val

805 810 815

Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val

820 825 830

Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu

835 840 845

Asp Leu Ile Asn Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro

850 855 860

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys

865 870 875 880

[0406] Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val

885 890 895

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp

900 905 910

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

915 920 925

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

930 935 940

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu

945 950 955 960

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg

965 970 975

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys

980 985 990

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

995 1000 1005

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr

1010 1015 1020

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

1025 1030 1035

[0407] Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn

1040 1045 1050

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr

1055 1060 1065

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

1070 1075

[0408] 单下划线:信号肽序列;双下划线-NPP1序列的起始和结束;**=在信号肽序列上的切割位置;粗体残基表示Fc序列

[0409] SEQ.ID NO:21-ENPP7-1(缺乏NPP1 N端GLK)-ALB氨基酸序列

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

1 5 10 15

Ala Pro Gly Ala Gly Ala**Pro Ser Cys Ala Lys Glu Val Lys Ser Cys

20 25 30

Lys Gly Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala

35 40 45

Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys

[0410]

50 55 60

Ile Glu Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu

65 70 75 80

Lys Arg Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp

85 90 95

Lys Gly Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys

100 105 110

Ser Trp Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro
115 120 125
Ala Gly Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe
130 135 140
Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser
145 150 155 160
Lys Leu Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr
165 170 175
Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr
180 185 190
Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met
195 200 205
Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp
210 215 220

[0411] Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys
225 230 235 240
Ser Gly Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile
245 250 255
Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu
260 265 270
Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg
275 280 285
Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His
290 295 300
Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val
305 310 315 320
Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu
325 330 335
His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln

340 345 350

Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val

355 360 365

Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser

370 375 380

Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg

385 390 395 400

Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys

405 410 415

His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu

420 425 430

Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro

435 440 445

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

[0412] 450 455 460

Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys

465 470 475 480

His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu

485 490 495

Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His

500 505 510

Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His

515 520 525

Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro

530 535 540

Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu

545 550 555 560

Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile

565 570 575

Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu
580 585 590
Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser
595 600 605
Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn
610 615 620
Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe
625 630 635 640
Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn
645 650 655
Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn
660 665 670
Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro
675 680 685

[0413] Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu
690 695 700
Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly
705 710 715 720
Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn
725 730 735
Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro
740 745 750
Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr
755 760 765
Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His
770 775 780
Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser
785 790 795 800
Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val

805 810 815

Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val

820 825 830

Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu

835 840 845

Asp Arg Ser Gly Ser Gly Gly Ser Met Lys Trp Val Thr Phe Leu Leu

850 855 860

Leu Leu Phe Val Ser Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg

865 870 875 880

Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu

885 890 895

Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln

900 905 910

Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu Val Thr Asp

[0414] 915 920 925

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys

930 935 940

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu

945 950 955 960

Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro

965 970 975

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Ser Leu

980 985 990

Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met Cys Thr Ser Phe Lys

995 1000 1005

Glu Asn Pro Thr Thr Phe Met Gly His Tyr Leu His Glu Val Ala

1010 1015 1020

Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Tyr Tyr Ala

1025 1030 1035

Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys Ala Glu Ala Asp
1040 1045 1050

Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val Lys Glu Lys
1055 1060 1065

Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys Ser Ser Met
1070 1075 1080

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
1085 1090 1095

Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr Lys
1100 1105 1110

Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly
1115 1120 1125

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr
1130 1135 1140

[0415] Met Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys
1145 1150 1155

Cys Asp Lys Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val
1160 1165 1170

Glu His Asp Thr Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp
1175 1180 1185

Phe Val Glu Asp Gln Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys
1190 1195 1200

Asp Val Phe Leu Gly Thr Phe Leu Tyr Glu Tyr Ser Arg Arg His
1205 1210 1215

Pro Asp Tyr Ser Val Ser Leu Leu Leu Arg Leu Ala Lys Lys Tyr
1220 1225 1230

Glu Ala Thr Leu Glu Lys Cys Cys Ala Glu Ala Asn Pro Pro Ala
1235 1240 1245

Cys Tyr Gly Thr Val Leu Ala Glu Phe Gln Pro Leu Val Glu Glu

1250 1255 1260

Pro Lys Asn Leu Val Lys Thr Asn Cys Asp Leu Tyr Glu Lys Leu

1265 1270 1275

Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val Arg Tyr Thr Gln

1280 1285 1290

Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu Ala Ala Arg

1295 1300 1305

Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu Pro Glu Asp

1310 1315 1320

Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile Leu Asn

1325 1330 1335

Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His Val

1340 1345 1350

Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe

[0416] 1355 1360 1365

Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys

1370 1375 1380

Ala Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu

1385 1390 1395

Lys Glu Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val

1400 1405 1410

Lys His Lys Pro Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met

1415 1420 1425

Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp

1430 1435 1440

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

1445 1450 1455

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

1460 1465 1470

[0417] Lys

[0418] 单下划线:信号肽序列;双下划线-NPP1序列的起始和结束;**=在信号肽序列上

的切割位置;粗体残基表示白蛋白序列

[0419] SEQ.ID NO:22-ENPP7-NPP3-Fc序列:

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

[0420]

180 185 190

Ile Ile Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser

195 200 205

Leu Ser Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro

210 215 220

Met Trp Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe

225 230 235 240

Trp Pro Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr

245 250 255

Met Pro Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu

260 265 270

Leu Lys Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr

275 280 285

Met Tyr Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val

[0421] 290 295 300

Ser Ala Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala Phe Gly

305 310 315 320

Met Leu Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn

325 330 335

Ile Ile Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys

340 345 350

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

355 360 365

Tyr Glu Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro His Asp

370 375 380

Phe Phe Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg

385 390 395 400

Lys Pro Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys

405 410 415

Arg Leu His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His Leu Phe
420 425 430
Val Asp Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys
435 440 445
Gly Gly Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala
450 455 460
Ile Phe Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu
465 470 475 480
Pro Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg
485 490 495
Ile Gln Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His Leu
500 505 510
Leu Lys Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys
515 520 525

[0422] Phe Ser Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu Asp
530 535 540
Cys Phe Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn
545 550 555 560
Gln Met Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val
565 570 575
Asn Leu Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val Asp His
580 585 590
Cys Leu Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala Met
595 600 605
Arg Met Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp Thr
610 615 620
Ser Pro Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp Val Arg
625 630 635 640
Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys

645 650 655

Asn Ile Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser

660 665 670

Asp Ser Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro Met Tyr

675 680 685

Glu Glu Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu Leu Ile

690 695 700

Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile

705 710 715 720

Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr

725 730 735

Lys His Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val

740 745 750

Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro

[0423] 755 760 765

Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn

770 775 780

Val Glu Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu

785 790 795 800

Arg Phe Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr

805 810 815

Gly Leu Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu

820 825 830

Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile **Asp Lys Thr**

835 840 845

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser

850 855 860

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg

865 870 875 880

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro

885 890 895

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala

900 905 910

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val

915 920 925

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr

930 935 940

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr

945 950 955 960

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu

965 970 975

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys

[0424]

980 985 990

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

995 1000 1005

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu

1010 1015 1020

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

1025 1030 1035

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met

1040 1045 1050

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

1055 1060 1065

Ser Pro Gly Lys

1070

[0425] 单下划线:信号肽序列;双下划线-NPP3序列的起始和结束;**=在信号肽序列上的切割位置;粗体残基表示Fc序列

[0426] SEQ.ID NO:23-ENPP7-1-白蛋白

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

1 5 10 15

Ala Pro Gly Ala Gly Leu Lys**Pro Ser Cys Ala Lys Glu Val Lys Ser

20 25 30

Cys Lys Gly Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp

35 40 45

Ala Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr

50 55 60

Cys Ile Glu Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly

65 70 75 80

Glu Lys Arg Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys

85 90 95

Asp Lys Gly Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu

100 105 110

Lys Ser Trp Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys

115 120 125

Pro Ala Gly Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly

130 135 140

Phe Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile

145 150 155 160

Ser Lys Leu Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val

165 170 175

Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu

180 185 190

Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys

195 200 205

Met Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu

210 215 220

Trp Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu
225 230 235 240
Lys Ser Gly Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly
245 250 255
Ile Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu
260 265 270
Glu Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu
275 280 285
Arg Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly
290 295 300
His Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg
305 310 315 320
Val Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn
325 330 335

[0427] Leu His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu
340 345 350
Gln Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp
355 360 365
Val Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro
370 375 380
Ser Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala
385 390 395 400
Arg Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu
405 410 415
Lys His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile
420 425 430
Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn
435 440 445
Pro Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn

450 455 460

Val Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe

465 470 475 480

Lys His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn

485 490 495

Leu Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr

500 505 510

His Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys

515 520 525

His Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn

530 535 540

Pro Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile

545 550 555 560

Glu Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile

[0428] 565 570 575

Ile Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys

580 585 590

Glu Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr

595 600 605

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

610 615 620

Asn Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp

625 630 635 640

Phe Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn

645 650 655

Asn Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys

660 665 670

Asn Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val

675 680 685

Pro Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr

690 695 700

Leu Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser

705 710 715 720

Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu

725 730 735

Asn Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile

740 745 750

Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln

755 760 765

Thr Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro

770 775 780

His Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His Asp Ser

785 790 795 800

[0429] Ser Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp

805 810 815

Val Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro

820 825 830

Val Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln

835 840 845

Glu Asp Gly Gly Ser Gly Gly Ser **Met Lys Trp Val Thr Phe Leu Leu**

850 855 860

Leu Leu Phe Val Ser Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg

865 870 875 880

Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu

885 890 895

Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln

900 905 910

Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu Val Thr Asp

915 920 925

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys

930 935 940

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu

945 950 955 960

Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro

965 970 975

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Ser Leu

980 985 990

Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met Cys Thr Ser Phe Lys

995 1000 1005

Glu Asn Pro Thr Thr Phe Met Gly His Tyr Leu His Glu Val Ala

1010 1015 1020

Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Tyr Tyr Ala

[0430] 1025 1030 1035

Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys Ala Glu Ala Asp

1040 1045 1050

Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val Lys Glu Lys

1055 1060 1065

Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys Ser Ser Met

1070 1075 1080

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg

1085 1090 1095

Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr Lys

1100 1105 1110

Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly

1115 1120 1125

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr

1130 1135 1140

Met Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys
1145 1150 1155

Cys Asp Lys Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val
1160 1165 1170

Glu His Asp Thr Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp
1175 1180 1185

Phe Val Glu Asp Gln Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys
1190 1195 1200

Asp Val Phe Leu Gly Thr Phe Leu Tyr Glu Tyr Ser Arg Arg His
1205 1210 1215

Pro Asp Tyr Ser Val Ser Leu Leu Leu Arg Leu Ala Lys Lys Tyr
1220 1225 1230

Glu Ala Thr Leu Glu Lys Cys Cys Ala Glu Ala Asn Pro Pro Ala
1235 1240 1245

[0431] Cys Tyr Gly Thr Val Leu Ala Glu Phe Gln Pro Leu Val Glu Glu
1250 1255 1260

Pro Lys Asn Leu Val Lys Thr Asn Cys Asp Leu Tyr Glu Lys Leu
1265 1270 1275

Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val Arg Tyr Thr Gln
1280 1285 1290

Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu Ala Ala Arg
1295 1300 1305

Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu Pro Glu Asp
1310 1315 1320

Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile Leu Asn
1325 1330 1335

Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His Val
1340 1345 1350

Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe

1355 1360 1365

Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys

[0432] 1370 1375 1380

Ala Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu

1385 1390 1395

[0433] 单下划线:信号肽序列;双下划线-NPP3序列的起始和结束;**=在信号肽序列上的切割位置;粗体残基表示Fc序列

[0434] SEQ.ID NO:24-ENPP7-NPP3-白蛋白

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

1 5 10 15

Ala Pro Gly Ala**Lys Gln Gly Ser Cys Arg Lys Lys Cys Phe Asp Ala

20 25 30

Ser Phe Arg Gly Leu Glu Asn Cys Arg Cys Asp Val Ala Cys Lys Asp

35 40 45

Arg Gly Asp Cys Cys Trp Asp Phe Glu Asp Thr Cys Val Glu Ser Thr

50 55 60

Arg Ile Trp Met Cys Asn Lys Phe Arg Cys Gly Glu Arg Leu Glu Ala

[0435] 65 70 75 80

Ser Leu Cys Ser Cys Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys Cys

85 90 95

Ala Asp Tyr Lys Ser Val Cys Gln Gly Glu Thr Ser Trp Leu Glu Glu

100 105 110

Asn Cys Asp Thr Ala Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp Leu

115 120 125

Pro Pro Val Ile Leu Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr Leu

130 135 140

Tyr Thr Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys Thr Cys

145 150 155 160

Gly Ile His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr Phe

165 170 175

Pro Asn His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly

180 185 190

Ile Ile Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser

195 200 205

Leu Ser Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro

210 215 220

Met Trp Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe

225 230 235 240

Trp Pro Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr

245 250 255

Met Pro Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu

[0436] 260 265 270

Leu Lys Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr

275 280 285

Met Tyr Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val

290 295 300

Ser Ala Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala Phe Gly

305 310 315 320

Met Leu Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn

325 330 335

Ile Ile Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys

340 345 350

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

355 360 365

Tyr Glu Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro His Asp

370 375 380

Phe Phe Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg
385 390 395 400
Lys Pro Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys
405 410 415
Arg Leu His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His Leu Phe
420 425 430
Val Asp Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys
435 440 445
Gly Gly Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala
450 455 460
Ile Phe Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu
465 470 475 480
Pro Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg
485 490 495

[0437] Ile Gln Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His Leu
500 505 510
Leu Lys Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys
515 520 525
Phe Ser Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu Asp
530 535 540
Cys Phe Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn
545 550 555 560
Gln Met Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val
565 570 575
Asn Leu Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val Asp His
580 585 590
Cys Leu Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala Met
595 600 605
Arg Met Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp Thr

610 615 620

Ser Pro Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp Val Arg

625 630 635 640

Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys

645 650 655

Asn Ile Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser

660 665 670

Asp Ser Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro Met Tyr

675 680 685

Glu Glu Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu Leu Ile

690 695 700

Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile

705 710 715 720

Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr

[0438] 725 730 735

Lys His Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val

740 745 750

Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro

755 760 765

Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn

770 775 780

Val Glu Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu

785 790 795 800

Arg Phe Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr

805 810 815

Gly Leu Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu

820 825 830

Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile Gly Gly Gly

835 840 845

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Met Lys Trp Val Thr

850 855 860

Phe Leu Leu Leu Leu Phe Val Ser Gly Ser Ala Phe Ser Arg Gly Val

865 870 875 880

Phe Arg Arg Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp

885 890 895

Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln

900 905 910

Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu

915 920 925

Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn

930 935 940

Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile

945 950 955 960

[0439] Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys

965 970 975

Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn

980 985 990

Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met Cys Thr

995 1000 1005

Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly His Tyr Leu His

1010 1015 1020

Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu

1025 1030 1035

Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys Ala

1040 1045 1050

Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val

1055 1060 1065

Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys

1070 1075 1080

Ser Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala

1085 1090 1095

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

1100 1105 1110

Ile Thr Lys Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys

1115 1120 1125

Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu

1130 1135 1140

Ala Lys Tyr Met Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu

1145 1150 1155

Gln Thr Cys Cys Asp Lys Pro Leu Leu Lys Lys Ala His Cys Leu

1160 1165 1170

Ser Glu Val Glu His Asp Thr Met Pro Ala Asp Leu Pro Ala Ile

[0440] 1175 1180 1185

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

1190 1195 1200

Glu Ala Lys Asp Val Phe Leu Gly Thr Phe Leu Tyr Glu Tyr Ser

1205 1210 1215

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

1220 1225 1230

Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys Cys Ala Glu Ala Asn

1235 1240 1245

Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu Phe Gln Pro Leu

1250 1255 1260

Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys Asp Leu Tyr

1265 1270 1275

Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val Arg

1280 1285 1290

Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu
1295 1300 1305

Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu
1310 1315 1320

Pro Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala
1325 1330 1335

Ile Leu Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser
1340 1345 1350

Glu His Val Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg
1355 1360 1365

Pro Cys Phe Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys
1370 1375 1380

[0441]

Glu Phe Lys Ala Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr
1385 1390 1395

Leu Pro Glu Lys Glu Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala
1400 1405 1410

Glu Leu Val Lys His Lys Pro Lys Ala Thr Ala Glu Gln Leu Lys
1415 1420 1425

Thr Val Met Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys Cys Lys
1430 1435 1440

Ala Ala Asp Lys Asp Thr Cys Phe Ser Thr Glu Gly Pro Asn Leu
1445 1450 1455

Val Thr Arg Cys Lys Asp Ala Leu Ala
1460 1465

[0442] 单下划线:信号肽序列;双下划线-NPP3序列的起始和结束;**=在信号肽序列上的切割位置;粗体残基表示白蛋白序列

[0443] SEQ.ID NO:25-ENPP7-ENPP3-白蛋白

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

1 5 10 15

Ala Pro Gly Ala**Lys Gln Gly Ser Cys Arg Lys Lys Cys Phe Asp Ala

20 25 30

Ser Phe Arg Gly Leu Glu Asn Cys Arg Cys Asp Val Ala Cys Lys Asp

35 40 45

Arg Gly Asp Cys Cys Trp Asp Phe Glu Asp Thr Cys Val Glu Ser Thr

50 55 60

Arg Ile Trp Met Cys Asn Lys Phe Arg Cys Gly Glu Arg Leu Glu Ala

65 70 75 80

Ser Leu Cys Ser Cys Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys Cys

85 90 95

Ala Asp Tyr Lys Ser Val Cys Gln Gly Glu Thr Ser Trp Leu Glu Glu

100 105 110

[0444] Asn Cys Asp Thr Ala Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp Leu

115 120 125

Pro Pro Val Ile Leu Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr Leu

130 135 140

Tyr Thr Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys Thr Cys

145 150 155 160

Gly Ile His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr Phe

165 170 175

Pro Asn His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly

180 185 190

Ile Ile Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser

195 200 205

Leu Ser Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro

210 215 220

Met Trp Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe

225 230 235 240

Trp Pro Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr

245 250 255

Met Pro Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu

260 265 270

Leu Lys Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr

275 280 285

Met Tyr Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val

290 295 300

Ser Ala Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala Phe Gly

305 310 315 320

Met Leu Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn

325 330 335

Ile Ile Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys

[0445] 340 345 350

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

355 360 365

Tyr Glu Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro His Asp

370 375 380

Phe Phe Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg

385 390 395 400

Lys Pro Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys

405 410 415

Arg Leu His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His Leu Phe

420 425 430

Val Asp Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys

435 440 445

Gly Gly Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala

450 455 460

Ile Phe Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu
465 470 475 480
Pro Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg
485 490 495
Ile Gln Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His Leu
500 505 510
Leu Lys Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys
515 520 525
Phe Ser Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu Asp
530 535 540
Cys Phe Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn
545 550 555 560
Gln Met Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val
565 570 575

[0446] Asn Leu Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val Asp His
580 585 590
Cys Leu Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala Met
595 600 605
Arg Met Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp Thr
610 615 620
Ser Pro Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp Val Arg
625 630 635 640
Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys
645 650 655
Asn Ile Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser
660 665 670
Asp Ser Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro Met Tyr
675 680 685
Glu Glu Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu Leu Ile

690 695 700

Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile

705 710 715 720

Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr

725 730 735

Lys His Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val

740 745 750

Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro

755 760 765

Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn

770 775 780

Val Glu Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu

785 790 795 800

Arg Phe Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr

[0447] 805 810 815

Gly Leu Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu

820 825 830

Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile Asp Lys Thr

835 840 845

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser

850 855 860

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg

865 870 875 880

Thr Pro Glu Val Thr Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly

885 890 895

Gly Gly Ser **Met Lys Trp Val Thr Phe Leu Leu Leu Leu Phe Val Ser**

900 905 910

Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg Glu Ala His Lys Ser

915 920 925

Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly

930 935 940

Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp

945 950 955 960

Glu His Ala Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys

965 970 975

Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu

980 985 990

Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly

995 1000 1005

Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu

1010 1015 1020

Cys Phe Leu Gln His Lys Asp Asp Asn Pro Ser Leu Pro Pro Phe

1025 1030 1035

[0448] Glu Arg Pro Glu Ala Glu Ala Met Cys Thr Ser Phe Lys Glu Asn

1040 1045 1050

Pro Thr Thr Phe Met Gly His Tyr Leu His Glu Val Ala Arg Arg

1055 1060 1065

His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Tyr Tyr Ala Glu Gln

1070 1075 1080

Tyr Asn Glu Ile Leu Thr Gln Cys Cys Ala Glu Ala Asp Lys Glu

1085 1090 1095

Ser Cys Leu Thr Pro Lys Leu Asp Gly Val Lys Glu Lys Ala Leu

1100 1105 1110

Val Ser Ser Val Arg Gln Arg Met Lys Cys Ser Ser Met Gln Lys

1115 1120 1125

Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser

1130 1135 1140

Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr Lys Leu Ala

1145 1150 1155

Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly Asp Leu

1160 1165 1170

Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met Cys

1175 1180 1185

Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys Cys Asp

1190 1195 1200

Lys Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val Glu His

1205 1210 1215

Asp Thr Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp Phe Val

1220 1225 1230

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

1235 1240 1245

Phe Leu Gly Thr Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Asp

[0449] 1250 1255 1260

Tyr Ser Val Ser Leu Leu Leu Arg Leu Ala Lys Lys Tyr Glu Ala

1265 1270 1275

Thr Leu Glu Lys Cys Cys Ala Glu Ala Asn Pro Pro Ala Cys Tyr

1280 1285 1290

Gly Thr Val Leu Ala Glu Phe Gln Pro Leu Val Glu Glu Pro Lys

1295 1300 1305

Asn Leu Val Lys Thr Asn Cys Asp Leu Tyr Glu Lys Leu Gly Glu

1310 1315 1320

Tyr Gly Phe Gln Asn Ala Ile Leu Val Arg Tyr Thr Gln Lys Ala

1325 1330 1335

Pro Gln Val Ser Thr Pro Thr Leu Val Glu Ala Ala Arg Asn Leu

1340 1345 1350

Gly Arg Val Gly Thr Lys Cys Cys Thr Leu Pro Glu Asp Gln Arg

1355 1360 1365

Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile Leu Asn Arg Val

1370 1375 1380

Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His Val Thr Lys

1385 1390 1395

Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe Ser Ala

1400 1405 1410

Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys Ala Glu

1415 1420 1425

Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu Lys Glu

1430 1435 1440

[0450]

Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val Lys His

1445 1450 1455

Lys Pro Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met Asp Asp

1460 1465 1470

Phe Ala Gln Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp Lys Asp

1475 1480 1485

Thr Cys Phe Ser Thr Glu Gly Pro Asn Leu Val Thr Arg Cys Lys

1490 1495 1500

Asp Ala Leu Ala

1505

[0451] 单下划线:信号肽序列;双下划线-NPP3序列的起始和结束;**=在信号肽序列上的切割位置;粗体残基表示白蛋白序列

[0452] SEQ.ID NO:26-ENPP71-GLK氨基酸序列

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

1 5 10 15

[0453]

Ala Pro Gly Ala Gly Ala**Gly Leu Lys Pro Ser Cys Ala Lys Glu Val

20 25 30

Lys Ser Cys Lys Gly Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg
35 40 45
Cys Asp Ala Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln
50 55 60
Glu Thr Cys Ile Glu Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg
65 70 75 80
Cys Gly Glu Lys Arg Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp
85 90 95
Cys Lys Asp Lys Gly Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln
100 105 110
Gly Glu Lys Ser Trp Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro
115 120 125
Gln Cys Pro Ala Gly Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu
130 135 140

[0454] Asp Gly Phe Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro
145 150 155 160
Val Ile Ser Lys Leu Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg
165 170 175
Pro Val Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr
180 185 190
Gly Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp
195 200 205
Pro Lys Met Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn
210 215 220
Pro Glu Trp Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln
225 230 235 240
Gly Leu Lys Ser Gly Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile
245 250 255
Asn Gly Ile Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro

260 265 270

Phe Glu Glu Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys

275 280 285

Asp Glu Arg Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser

290 295 300

Ser Gly His Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu

305 310 315 320

Gln Arg Val Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu

325 330 335

Leu Asn Leu His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly

340 345 350

Met Glu Gln Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu

355 360 365

Gly Asp Val Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu

[0455] 370 375 380

Arg Pro Ser Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly

385 390 395 400

Ile Ala Arg Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro

405 410 415

Tyr Leu Lys His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp

420 425 430

Arg Ile Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala

435 440 445

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

450 455 460

Asp Asn Val Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro

465 470 475 480

Gly Phe Lys His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val

485 490 495

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

[0456]

Gly Tyr Ser Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val
610 615 620
Asp Arg Asn Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr
625 630 635 640
Gln Asp Phe Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr
645 650 655
Lys Asn Asn Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu
660 665 670
Asn Lys Asn Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn
675 680 685
Ile Val Pro Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His
690 695 700
Asp Thr Leu Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val
705 710 715 720
Val Ser Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser

725 730 735

Leu Glu Asn Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile

740 745 750

Leu Ile Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr

755 760 765

Ser Gln Thr Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile

770 775 780

Leu Pro His Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His

[0457] 785 790 795 800

Asp Ser Ser Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile

805 810 815

Thr Asp Val Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys

820 825 830

Glu Pro Val Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe

835 840 845

Ser Gln Glu Asp

850

[0458] 单下划线:信号肽序列;双下划线-NPP1序列的起始和结束;**=在信号肽序列上的切割位置;

[0459] SEQ.ID NO:27-ENPP121氨基酸序列

Met Glu Arg Asp Gly Cys Ala Gly Gly Gly Ser Arg Gly Gly Glu Gly

1 5 10 15

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

20 25 30

[0460]

Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala Ser

35 40 45

Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala

50 55 60

Arg Ala Arg Thr Ala Lys Asp Pro Asn Thr Tyr Lys Ile Ile Ser Leu

65 70 75 80

Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly**Phe Thr Ala Gly

85 90 95

Leu Lys Pro Ser Cys Ala Lys Glu Val Lys Ser Cys Lys Gly Arg Cys

100 105 110

Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala Ala Cys Val Glu

115 120 125

Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys Ile Glu Pro Glu

130 135 140

His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu Lys Arg Leu Thr

145 150 155 160

Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp Lys Gly Asp Cys

165 170 175

[0461] Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp Val Glu

180 185 190

Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro Ala Gly Phe Glu

195 200 205

Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe Arg Ala Glu Tyr

210 215 220

Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser Lys Leu Lys Lys

225 230 235 240

Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr Lys Thr

245 250 255

Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu Ser His

260 265 270

Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala Ser Phe

275 280 285

Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys Gly Glu

290 295 300

Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly Thr Phe

305 310 315 320

Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro Asp Ile

325 330 335

Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Leu Ala

340 345 350

Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His Phe Tyr

355 360 365

Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr Gly Pro

370 375 380

Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly Met Val

385 390 395 400

Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg Cys Leu

[0462] 405 410 415

Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser Cys Lys

420 425 430

Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn Ile Lys

435 440 445

Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val Pro Asp

450 455 460

Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu Ser Cys

465 470 475 480

Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe Leu Pro

485 490 495

Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu Thr Phe

500 505 510

Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu Arg Lys

515 520 525

Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser Asn Met
530 535 540
Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys His Gly Ile Glu
545 550 555 560
Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu
565 570 575
Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn
580 585 590
His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His Pro Lys Glu Val
595 600 605
His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp Asn Leu
610 615 620
Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe Gln Thr
625 630 635 640

[0463] Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His Glu Thr
645 650 655
Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr Ile Cys
660 665 670
Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp Ile Leu
675 680 685
Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser Phe Ser
690 695 700
Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile Pro Leu
705 710 715 720
Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val Ser
725 730 735
Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser Gly Ile
740 745 750
Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln Ser

755 760 765

Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys Tyr

770 775 780

Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val Phe Asp

785 790 795 800

Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln Lys

805 810 815

Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe Phe

820 825 830

Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His Cys

[0464] 835 840 845

Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp Asn

850 855 860

Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu Glu

865 870 875 880

Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile Thr

885 890 895

Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile Leu

900 905 910

Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp

915 920 925

[0465] 单下划线:信号肽序列;双下划线-NPP1序列的起始和结束;**=在信号肽序列上的切割位置;

[0466] SEQ.ID.NO:28-ENPP121-Fc氨基酸序列

Met Glu Arg Asp Gly Cys Ala Gly Gly Gly Ser Arg Gly Gly Glu Gly

1 5 10 15

[0467]

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

20 25 30

Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala Ser

35 40 45

Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala

50 55 60

Arg Ala Arg Thr Ala Lys Asp Pro Asn Thr Tyr Lys Ile Ile Ser Leu

65 70 75 80

Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly**Phe Thr Ala Gly

85 90 95

Leu Lys Pro Ser Cys Ala Lys Glu Val Lys Ser Cys Lys Gly Arg Cys

100 105 110

Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala Ala Cys Val Glu

115 120 125

Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys Ile Glu Pro Glu

130 135 140

[0468] His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu Lys Arg Leu Thr

145 150 155 160

Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp Lys Gly Asp Cys

165 170 175

Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp Val Glu

180 185 190

Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro Ala Gly Phe Glu

195 200 205

Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe Arg Ala Glu Tyr

210 215 220

Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser Lys Leu Lys Lys

225 230 235 240

Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr Lys Thr

245 250 255

Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu Ser His

260 265 270

Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala Ser Phe

275 280 285

Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys Gly Glu

290 295 300

Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly Thr Phe

305 310 315 320

Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro Asp Ile

325 330 335

Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Leu Ala

340 345 350

Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His Phe Tyr

355 360 365

Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr Gly Pro

[0469] 370 375 380

Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly Met Val

385 390 395 400

Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg Cys Leu

405 410 415

Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser Cys Lys

420 425 430

Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn Ile Lys

435 440 445

Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val Pro Asp

450 455 460

Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu Ser Cys

465 470 475 480

Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe Leu Pro

485 490 495

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

[0470]
His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp Asn Leu
610 615 620
Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe Gln Thr
625 630 635 640
Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His Glu Thr
645 650 655
Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr Ile Cys
660 665 670
Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp Ile Leu
675 680 685
Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser Phe Ser
690 695 700
Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile Pro Leu
705 710 715 720
Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val Ser

725 730 735

Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser Gly Ile

740 745 750

Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln Ser

755 760 765

Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys Tyr

770 775 780

Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val Phe Asp

785 790 795 800

Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln Lys

805 810 815

Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe Phe

820 825 830

Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His Cys

[0471] 835 840 845

Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp Asn

850 855 860

Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu Glu

865 870 875 880

Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile Thr

885 890 895

Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile Leu

900 905 910

Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp Leu Ile Asn

915 920 925

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly

930 935 940

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met

945 950 955 960

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Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
                965                 970                 975
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
            980                 985                 990
His Asn Ala Lys Thr Lys Pro Arg  Glu Glu Gln Tyr Asn  Ser Thr Tyr
        995                 1000                1005
Arg Val  Val Ser Val Leu Thr  Val Leu His Gln Asp  Trp Leu Asn
    1010                1015                1020
Gly Lys  Glu Tyr Lys Cys Lys  Val Ser Asn Lys Ala  Leu Pro Ala
    1025                1030                1035
Pro Ile  Glu Lys Thr Ile Ser  Lys Ala Lys Gly Gln  Pro Arg Glu
    1040                1045                1050
Pro Gln  Val Tyr Thr Leu Pro  Pro Ser Arg Glu Glu  Met Thr Lys
    1055                1060                1065
Asn Gln  Val Ser Leu Thr Cys  Leu Val Lys Gly Phe  Tyr Pro Ser
    1070                1075                1080
Asp Ile  Ala Val Glu Trp Glu  Ser Asn Gly Gln Pro  Glu Asn Asn
    1085                1090                1095
Tyr Lys  Thr Thr Pro Pro Val  Leu Asp Ser Asp Gly  Ser Phe Phe
    1100                1105                1110
Leu Tyr  Ser Lys Leu Thr Val  Asp Lys Ser Arg Trp  Gln Gln Gly
    1115                1120                1125
Asn Val  Phe Ser Cys Ser Val  Met His Glu Ala Leu  His Asn His
    1130                1135                1140
Tyr Thr  Gln Lys Ser Leu Ser  Leu Ser Pro Gly Lys
    1145                1150                1155
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[0472]

[0473] 单下划线:信号肽序列;双下划线-NPP1序列的起始和结束;**=在信号肽序列上的切割位置;粗体残基表示Fc序列

[0474] SEQ.ID NO:29-ENPP121-ALB氨基酸序列:

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

[0475]

Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala Ala Cys Val Glu
115 120 125
Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys Ile Glu Pro Glu
130 135 140
His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu Lys Arg Leu Thr
145 150 155 160
Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp Lys Gly Asp Cys
165 170 175
Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp Val Glu
180 185 190
Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro Ala Gly Phe Glu
195 200 205
Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe Arg Ala Glu Tyr
210 215 220

Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser Lys Leu Lys Lys
225 230 235 240
Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr Lys Thr
245 250 255
Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu Ser His
260 265 270
Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala Ser Phe
275 280 285
Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys Gly Glu
290 295 300
Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly Thr Phe
305 310 315 320
Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro Asp Ile
325 330 335

[0476] Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Leu Ala
340 345 350
Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His Phe Tyr
355 360 365
Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr Gly Pro
370 375 380
Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly Met Val
385 390 395 400
Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg Cys Leu
405 410 415
Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser Cys Lys
420 425 430
Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn Ile Lys
435 440 445
Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val Pro Asp

450 455 460

Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu Ser Cys

465 470 475 480

Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe Leu Pro

485 490 495

Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu Thr Phe

500 505 510

Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu Arg Lys

515 520 525

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

530 535 540

Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys His Gly Ile Glu

545 550 555 560

Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu

[0477] 565 570 575

Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn

580 585 590

His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His Pro Lys Glu Val

595 600 605

His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp Asn Leu

610 615 620

Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe Gln Thr

625 630 635 640

Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His Glu Thr

645 650 655

Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr Ile Cys

660 665 670

Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp Ile Leu

675 680 685

Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser Phe Ser
690 695 700
Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile Pro Leu
705 710 715 720
Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val Ser
725 730 735
Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser Gly Ile
740 745 750
Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln Ser
755 760 765
Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys Tyr
770 775 780
Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val Phe Asp
785 790 795 800

[0478] Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln Lys
805 810 815
Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe Phe
820 825 830
Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His Cys
835 840 845
Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp Asn
850 855 860
Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu Glu
865 870 875 880
Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile Thr
885 890 895
Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile Leu
900 905 910
Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp Arg Ser Gly

915 920 925

Ser Gly Gly Ser Met Lys Trp Val Thr Phe Leu Leu Leu Leu Phe Val

930 935 940

Ser Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg Glu Ala His Lys

945 950 955 960

Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys

965 970 975

Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr

980 985 990

Asp Glu His Ala Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr

995 1000 1005

Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys Ser Leu His

1010 1015 1020

Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu Arg Glu

[0479] 1025 1030 1035

Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro Glu

1040 1045 1050

Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Ser Leu

1055 1060 1065

Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met Cys Thr Ser Phe

1070 1075 1080

Lys Glu Asn Pro Thr Thr Phe Met Gly His Tyr Leu His Glu Val

1085 1090 1095

Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Tyr Tyr

1100 1105 1110

Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys Ala Glu Ala

1115 1120 1125

Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val Lys Glu

1130 1135 1140

Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys Ser Ser

1145 1150 1155

Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala

1160 1165 1170

Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr

1175 1180 1185

Lys Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His

1190 1195 1200

Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys

1205 1210 1215

Tyr Met Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr

1220 1225 1230

Cys Cys Asp Lys Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu

1235 1240 1245

[0480] Val Glu His Asp Thr Met Pro Ala Asp Leu Pro Ala Ile Ala Ala

1250 1255 1260

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

1265 1270 1275

Lys Asp Val Phe Leu Gly Thr Phe Leu Tyr Glu Tyr Ser Arg Arg

1280 1285 1290

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

1295 1300 1305

Tyr Glu Ala Thr Leu Glu Lys Cys Cys Ala Glu Ala Asn Pro Pro

1310 1315 1320

Ala Cys Tyr Gly Thr Val Leu Ala Glu Phe Gln Pro Leu Val Glu

1325 1330 1335

Glu Pro Lys Asn Leu Val Lys Thr Asn Cys Asp Leu Tyr Glu Lys

1340 1345 1350

Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val Arg Tyr Thr

1355 1360 1365

Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu Ala Ala

1370 1375 1380

Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu Pro Glu

1385 1390 1395

Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile Leu

1400 1405 1410

Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His

1415 1420 1425

Val Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys

1430 1435 1440

Phe Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe

1445 1450 1455

[0481] Lys Ala Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro

1460 1465 1470

Glu Lys Glu Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu

1475 1480 1485

Val Lys His Lys Pro Lys Ala Thr Ala Glu Gln Leu Lys Thr Val

1490 1495 1500

Met Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys Cys Lys Ala Ala

1505 1510 1515

Asp Lys Asp Thr Cys Phe Ser Thr Glu Gly Pro Asn Leu Val Thr

1520 1525 1530

Arg Cys Lys Asp Ala Leu Ala Arg Ser Trp Ser His Pro Gln Phe

1535 1540 1545

Glu Lys

1550

[0482] 单下划线:信号肽序列;双下划线-NPP1序列的起始和结束;**=在信号肽序列上的切割位置;粗体残基表示白蛋白序列

[0483] SEQ.ID NO:30-ENPP121-NPP3-Fc序列

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Met Glu Arg Asp Gly Cys Ala Gly Gly Gly Ser Arg Gly Gly Glu Gly
1               5                  10                  15
Gly Arg Ala Pro Arg Glu Gly Pro Ala Gly Asn Gly Arg Asp Arg Gly
            20                  25                  30
Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala Ser
        35                  40                  45
Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala
    50                  55                  60
Arg Ala Arg Thr Ala Lys Asp Pro Asn Thr Tyr Lys Ile Ile Ser Leu
65                  70                  75                  80
Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly Phe Thr Ala**Lys
                85                  90                  95
Gln Gly Ser Cys Arg Lys Lys Cys Phe Asp Ala Ser Phe Arg Gly Leu
            100                 105                 110
Glu Asn Cys Arg Cys Asp Val Ala Cys Lys Asp Arg Gly Asp Cys Cys
        115                 120                 125
Trp Asp Phe Glu Asp Thr Cys Val Glu Ser Thr Arg Ile Trp Met Cys
    130                 135                 140
Asn Lys Phe Arg Cys Gly Glu Arg Leu Glu Ala Ser Leu Cys Ser Cys
145                 150                 155                 160
Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys Cys Ala Asp Tyr Lys Ser
                165                 170                 175
Val Cys Gln Gly Glu Thr Ser Trp Leu Glu Glu Asn Cys Asp Thr Ala
            180                 185                 190
Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp Leu Pro Pro Val Ile Leu
        195                 200                 205
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[0484]

Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr Leu Tyr Thr Trp Asp Thr
210 215 220
Leu Met Pro Asn Ile Asn Lys Leu Lys Thr Cys Gly Ile His Ser Lys
225 230 235 240
Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Thr
245 250 255
Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Asn
260 265 270
Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser Leu Ser Ser Lys Glu
275 280 285
Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro Met Trp Leu Thr Ala
290 295 300
Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe Trp Pro Gly Ser Glu
305 310 315 320

[0485] Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr Met Pro Tyr Asn Gly
325 330 335
Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu Leu Lys Trp Leu Asp
340 345 350
Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr Met Tyr Phe Glu Glu
355 360 365
Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val Ser Ala Arg Val Ile
370 375 380
Lys Ala Leu Gln Val Val Asp His Ala Phe Gly Met Leu Met Glu Gly
385 390 395 400
Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn Ile Ile Leu Leu Ala
405 410 415
Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys Met Glu Tyr Met Thr
420 425 430
Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr Met Tyr Glu Gly Pro Ala

435 440 445

Pro Arg Ile Arg Ala His Asn Ile Pro His Asp Phe Phe Ser Phe Asn

450 455 460

Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg Lys Pro Asp Gln His

465 470 475 480

Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys Arg Leu His Tyr Ala

485 490 495

Lys Asn Val Arg Ile Asp Lys Val His Leu Phe Val Asp Gln Gln Trp

500 505 510

Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys Gly Gly Gly Asn His

515 520 525

Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala Ile Phe Leu Ala His

530 535 540

Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu Pro Phe Glu Asn Ile

[0486] 545 550 555 560

Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg Ile Gln Pro Ala Pro

565 570 575

Asn Asn Gly Thr His Gly Ser Leu Asn His Leu Leu Lys Val Pro Phe

580 585 590

Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys Phe Ser Val Cys Gly

595 600 605

Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu Asp Cys Phe Cys Pro His

610 615 620

Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn Gln Met Leu Asn Leu

625 630 635 640

Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val Asn Leu Pro Phe Gly

645 650 655

Arg Pro Arg Val Leu Gln Lys Asn Val Asp His Cys Leu Leu Tyr His

660 665 670

Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala Met Arg Met Pro Met Trp
675 680 685
Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp Thr Ser Pro Leu Pro Pro
690 695 700
Thr Val Pro Asp Cys Leu Arg Ala Asp Val Arg Val Pro Pro Ser Glu
705 710 715 720
Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys Asn Ile Thr His Gly
725 730 735
Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser Asp Ser Gln Tyr Asp
740 745 750
Ala Leu Ile Thr Ser Asn Leu Val Pro Met Tyr Glu Glu Phe Arg Lys
755 760 765
Met Trp Asp Tyr Phe His Ser Val Leu Leu Ile Lys His Ala Thr Glu
770 775 780

[0487] Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile Phe Asp Tyr Asn Tyr
785 790 795 800
Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr Lys His Leu Ala Asn
805 810 815
Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val Val Leu Thr Ser Cys
820 825 830
Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro Gly Trp Leu Asp Val
835 840 845
Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn Val Glu Ser Cys Pro
850 855 860
Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu Arg Phe Thr Ala His
865 870 875 880
Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr Gly Leu Asp Phe Tyr
885 890 895
Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu Gln Leu Lys Thr Tyr

900 905 910

Leu Pro Thr Phe Glu Thr Thr Ile Asp Lys Thr His Thr Cys Pro Pro

915 920 925

Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro

930 935 940

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

945 950 955 960

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn

965 970 975

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg

980 985 990

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val

995 1000 1005

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val

[0488] 1010 1015 1020

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys

1025 1030 1035

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro

1040 1045 1050

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu

1055 1060 1065

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser

1070 1075 1080

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu

1085 1090 1095

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

1100 1105 1110

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met

1115 1120 1125

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

1130 1135 1140

[0489]

Ser Pro Gly Lys

1145

[0490] 单下划线:信号肽序列;双下划线-NPP1序列的起始和结束;**=在信号肽序列上的切割位置;粗体残基表示Fc序列

[0491] SEQ.ID NO:31-ENPP121-NPP3-白蛋白序列

Met Glu Arg Asp Gly Cys Ala Gly Gly Gly Ser Arg Gly Gly Glu Gly

1 5 10 15

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

20 25 30

Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala Ser

35 40 45

Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala

50 55 60

Arg Ala Arg Thr Ala Lys Asp Pro Asn Thr Tyr Lys Ile Ile Ser Leu

65 70 75 80

[0492]

Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly Phe Thr Ala**Lys

85 90 95

Gln Gly Ser Cys Arg Lys Lys Cys Phe Asp Ala Ser Phe Arg Gly Leu

100 105 110

Glu Asn Cys Arg Cys Asp Val Ala Cys Lys Asp Arg Gly Asp Cys Cys

115 120 125

Trp Asp Phe Glu Asp Thr Cys Val Glu Ser Thr Arg Ile Trp Met Cys

130 135 140

Asn Lys Phe Arg Cys Gly Glu Arg Leu Glu Ala Ser Leu Cys Ser Cys

145 150 155 160

Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys Cys Ala Asp Tyr Lys Ser
165 170 175

Val Cys Gln Gly Glu Thr Ser Trp Leu Glu Glu Asn Cys Asp Thr Ala
180 185 190

Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp Leu Pro Pro Val Ile Leu
195 200 205

Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr Leu Tyr Thr Trp Asp Thr
210 215 220

Leu Met Pro Asn Ile Asn Lys Leu Lys Thr Cys Gly Ile His Ser Lys
225 230 235 240

Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Thr
245 250 255

Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Asn
260 265 270

[0493] Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser Leu Ser Ser Lys Glu
275 280 285

Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro Met Trp Leu Thr Ala
290 295 300

Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe Trp Pro Gly Ser Glu
305 310 315 320

Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr Met Pro Tyr Asn Gly
325 330 335

Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu Leu Lys Trp Leu Asp
340 345 350

Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr Met Tyr Phe Glu Glu
355 360 365

Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val Ser Ala Arg Val Ile
370 375 380

Lys Ala Leu Gln Val Val Asp His Ala Phe Gly Met Leu Met Glu Gly

385 390 395 400

Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn Ile Ile Leu Leu Ala

405 410 415

Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys Met Glu Tyr Met Thr

420 425 430

Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr Met Tyr Glu Gly Pro Ala

435 440 445

Pro Arg Ile Arg Ala His Asn Ile Pro His Asp Phe Phe Ser Phe Asn

450 455 460

Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg Lys Pro Asp Gln His

465 470 475 480

Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys Arg Leu His Tyr Ala

485 490 495

Lys Asn Val Arg Ile Asp Lys Val His Leu Phe Val Asp Gln Gln Trp

[0494] 500 505 510

Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys Gly Gly Gly Asn His

515 520 525

Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala Ile Phe Leu Ala His

530 535 540

Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu Pro Phe Glu Asn Ile

545 550 555 560

Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg Ile Gln Pro Ala Pro

565 570 575

Asn Asn Gly Thr His Gly Ser Leu Asn His Leu Leu Lys Val Pro Phe

580 585 590

Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys Phe Ser Val Cys Gly

595 600 605

Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu Asp Cys Phe Cys Pro His

610 615 620

Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn Gln Met Leu Asn Leu
625 630 635 640
Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val Asn Leu Pro Phe Gly
645 650 655
Arg Pro Arg Val Leu Gln Lys Asn Val Asp His Cys Leu Leu Tyr His
660 665 670
Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala Met Arg Met Pro Met Trp
675 680 685
Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp Thr Ser Pro Leu Pro Pro
690 695 700
Thr Val Pro Asp Cys Leu Arg Ala Asp Val Arg Val Pro Pro Ser Glu
705 710 715 720
Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys Asn Ile Thr His Gly
725 730 735

[0495] Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser Asp Ser Gln Tyr Asp
740 745 750
Ala Leu Ile Thr Ser Asn Leu Val Pro Met Tyr Glu Glu Phe Arg Lys
755 760 765
Met Trp Asp Tyr Phe His Ser Val Leu Leu Ile Lys His Ala Thr Glu
770 775 780
Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile Phe Asp Tyr Asn Tyr
785 790 795 800
Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr Lys His Leu Ala Asn
805 810 815
Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val Val Leu Thr Ser Cys
820 825 830
Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro Gly Trp Leu Asp Val
835 840 845
Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn Val Glu Ser Cys Pro

850 855 860

Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu Arg Phe Thr Ala His

865 870 875 880

Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr Gly Leu Asp Phe Tyr

885 890 895

Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu Gln Leu Lys Thr Tyr

900 905 910

Leu Pro Thr Phe Glu Thr Thr Ile Gly Gly Gly Ser Gly Gly Gly Gly

915 920 925

Ser Gly Gly Gly Gly Ser Met Lys Trp Val Thr Phe Leu Leu Leu Leu

930 935 940

Phe Val Ser Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg Glu Ala

945 950 955 960

His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His

[0496] 965 970 975

Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys

980 985 990

Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu Val Thr Asp Phe Ala

995 1000 1005

Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys Ser

1010 1015 1020

Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu

1025 1030 1035

Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu

1040 1045 1050

Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro

1055 1060 1065

Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met Cys Thr

1070 1075 1080

Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly His Tyr Leu His

1085 1090 1095

Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu

1100 1105 1110

Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys Ala

1115 1120 1125

Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val

1130 1135 1140

Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys

1145 1150 1155

Ser Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala

1160 1165 1170

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

1175 1180 1185

[0497] Ile Thr Lys Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys

1190 1195 1200

Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu

1205 1210 1215

Ala Lys Tyr Met Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu

1220 1225 1230

Gln Thr Cys Cys Asp Lys Pro Leu Leu Lys Lys Ala His Cys Leu

1235 1240 1245

Ser Glu Val Glu His Asp Thr Met Pro Ala Asp Leu Pro Ala Ile

1250 1255 1260

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

1265 1270 1275

Glu Ala Lys Asp Val Phe Leu Gly Thr Phe Leu Tyr Glu Tyr Ser

1280 1285 1290

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

1295 1300 1305

Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys Cys Ala Glu Ala Asn

1310 1315 1320

Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu Phe Gln Pro Leu

1325 1330 1335

Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys Asp Leu Tyr

1340 1345 1350

Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val Arg

1355 1360 1365

Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu

1370 1375 1380

Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu

1385 1390 1395

Pro Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala

[0498] 1400 1405 1410

Ile Leu Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser

1415 1420 1425

Glu His Val Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg

1430 1435 1440

Pro Cys Phe Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys

1445 1450 1455

Glu Phe Lys Ala Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr

1460 1465 1470

Leu Pro Glu Lys Glu Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala

1475 1480 1485

Glu Leu Val Lys His Lys Pro Lys Ala Thr Ala Glu Gln Leu Lys

1490 1495 1500

Thr Val Met Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys Cys Lys

1505 1510 1515

Ala Ala Asp Lys Asp Thr Cys Phe Ser Thr Glu Gly Pro Asn Leu

1520 1525 1530

[0499]

Val Thr Arg Cys Lys Asp Ala Leu Ala

1535 1540

[0500] 单下划线:信号肽序列;双下划线-NPP3序列的起始和结束;**=在信号肽序列上的切割位置;粗体残基表示白蛋白序列

[0501] SEQ.ID NO:32-ENPP121GLK蛋白输出信号序列

Met Glu Arg Asp Gly Cys Ala Gly Gly Gly Ser Arg Gly Gly Glu Gly

1 5 10 15

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

20 25 30

Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala Ser

35 40 45

[0502] Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala

50 55 60

Arg Ala Arg Thr Ala Lys Asp Pro Asn Thr Tyr Lys Ile Ile Ser Leu

65 70 75 80

Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly Phe Thr Ala Gly

85 90 95

Leu Lys

[0503] SEQ.ID NO:33-白蛋白序列

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Met

1 5 10 15

[0504]

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

20 25 30

Ser Arg Gly Val Phe Arg Arg Glu Ala His Lys Ser Glu Ile Ala His
35 40 45
Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile
50 55 60
Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys
65 70 75 80
Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu
85 90 95
Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys
100 105 110
Leu Cys Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala Asp
115 120 125
Cys Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His
130 135 140

[0505] Lys Asp Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala Glu
145 150 155 160
Ala Met Cys Thr Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly His
165 170 175
Tyr Leu His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
180 185 190
Leu Leu Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys
195 200 205
Ala Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val
210 215 220
Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys Ser
225 230 235 240
Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala
245 250 255
Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr Lys

260 265 270

Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly Asp

275 280 285

Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met Cys

290 295 300

Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys Cys Asp Lys

305 310 315 320

Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val Glu His Asp Thr

325 330 335

Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp Phe Val Glu Asp Gln

340 345 350

Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Thr

355 360 365

Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Asp Tyr Ser Val Ser Leu

[0506] 370 375 380

Leu Leu Arg Leu Ala Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys Cys

385 390 395 400

Ala Glu Ala Asn Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu Phe

405 410 415

Gln Pro Leu Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys Asp

420 425 430

Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val

435 440 445

Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu

450 455 460

Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu Pro

465 470 475 480

Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile Leu

485 490 495

Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His Val
500 505 510
Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe Ser
515 520 525
Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys Ala Glu
530 535 540
Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu Lys Glu Lys
545 550 555 560

[0507]

Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val Lys His Lys Pro
565 570 575
Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met Asp Asp Phe Ala Gln
580 585 590
Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp Lys Asp Thr Cys Phe Ser
595 600 605
Thr Glu Gly Pro Asn Leu Val Thr Arg Cys Lys Asp Ala Leu Ala
610 615 620

[0508] SEQ.ID NO:34-人IgG Fc结构域,Fc

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1 5 10 15
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

[0509]

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65 70 75 80
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly

85 90 95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile

100 105 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val

115 120 125

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser

130 135 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu

145 150 155 160

[0510] Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro

165 170 175

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

180 185 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met

195 200 205

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

210 215 220

Pro Gly Lys

225

[0511] SEQ.ID NO:35-白蛋白序列

Met Lys Trp Val Thr Phe Leu Leu Leu Leu Phe Val Ser Gly Ser Ala

1 5 10 15

Phe Ser Arg Gly Val Phe Arg Arg Glu Ala His Lys Ser Glu Ile Ala

20 25 30

His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu

35 40 45

Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala

50 55 60

Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp
65 70 75 80
Glu Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
85 90 95
Lys Leu Cys Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala
100 105 110
Asp Cys Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
115 120 125
His Lys Asp Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala
130 135 140
Glu Ala Met Cys Thr Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly
145 150 155 160
His Tyr Leu His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
165 170 175

[0512]
Glu Leu Leu Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys
180 185 190
Cys Ala Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly
195 200 205
Val Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys
210 215 220
Ser Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240
Ala Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr
245 250 255
Lys Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly
260 265 270
Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met
275 280 285
Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys Cys Asp

290 295 300

Lys Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val Glu His Asp

305 310 315 320

Thr Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp Phe Val Glu Asp

325 330 335

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

340 345 350

Thr Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Asp Tyr Ser Val Ser

355 360 365

Leu Leu Leu Arg Leu Ala Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys

370 375 380

Cys Ala Glu Ala Asn Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu

385 390 395 400

Phe Gln Pro Leu Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys

[0513] 405 410 415

Asp Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu

420 425 430

Val Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val

435 440 445

Glu Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu

450 455 460

Pro Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile

465 470 475 480

Leu Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His

485 490 495

Val Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe

500 505 510

Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys Ala

515 520 525

Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu Lys Glu

530 535 540

Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val Lys His Lys

545 550 555 560

Pro Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met Asp Asp Phe Ala

565 570 575

[0514]

Gln Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp Lys Asp Thr Cys Phe

580 585 590

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

595 600 605

Arg Ser Trp Ser His Pro Gln Phe Glu Lys

610 615

[0515] SEQ.ID NO:36-ENPP2信号肽

Leu Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly

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Phe Thr Ala

[0516] SEQ.ID NO:37-信号序列ENPP7

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

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[0517]

Ala Pro Gly Ala

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[0518] SEQ.ID NO:38-信号序列ENPP7

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

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Ala Pro Gly Ala Gly Ala

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[0521] SEQ.ID NO:39-信号序列ENPP1-2-1

Met Glu Arg Asp Gly Cys Ala Gly Gly Gly Ser Arg Gly Gly Glu Gly

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

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Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala Ser

35 40 45

[0522]

Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala

50 55 60

Arg Ala Arg Thr Ala Lys Asp Pro Asn Thr Tyr Lys Ile Ile Ser Leu

65 70 75 80

Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly Phe Thr Ala

85 90 95

[0523] SEQ.ID NO:40-exENPP3

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

[0524] 1 5 10 15

Lys

[0525] SEQ.ID NO:41-信号序列ENPP5:

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

1 5 10 15

[0526]

Leu Ser Thr Thr Phe Ser

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[0527] SEQ ID NO:42-天青杀素-ENPP1-FC核苷酸序列

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[0530] SEQ ID NO:43-天青杀素-ENPP1-白蛋白核苷酸序列

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[0533] SEQ ID NO:44-天青杀素-ENPP1核苷酸序列

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[0557] SEQ.ID NO:50-NPP121-NPP3-Fc的核苷酸序列

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gaaaaggccg ccagggccag gactgccaag gaccccaaca cctacaagat catctccctc 240

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cgaatatgga tgtgcaataa atttcgttgt ggagagacca gattagaggc cagcctttgc 480

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gaagggtttg acctgccacc agttatcttg ttttctatgg atggatttag agctgaatat 660

ttatacacat gggatacttt aatgccaaat atcaataaac tgaaaacatg tggaattcat 720

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tttggaaaag ctatgaggat gcccatgtgg agttcataca cagtccccca gttgggagac 2100

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[0562] SEQ.ID NO:51-NPP121-NPP3-Fc的核苷酸序列

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tggagttccg cgttacataa cttacggtaa atggcccgcc tggctgaccg cccaacgacc 360

cccgcccatt gacgtcaata atgacgtatg ttcccatagt aacgccaata gggactttcc 420

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gtttgtggct ttgctaatcc attgcccaca gagtctcttg actgtttctg ccctcaccta 1740

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cccatgtgga gttcatacac agtccccccag ttgggagaca catcgcctct gcctcccact 1980

gtcccagact gtctgcgggc tgatgtcagg gttcctcctt ctgagagcca aaaatgttcc 2040

ttctatttag cagacaagaa tatcacccac ggcttcctct atcctcctgc cagcaataga 2100

acatcagata gccaatatga tgctttaatt actagcaatt tggtacctat gtatgaagaa 2160

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[0595] SEQ.ID NO:56-ENPP1核苷酸序列:

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gtgctgtccg tgtgcgtgct gaccaccatc ctgggctgca tcttcggcct gaagcccagc 300

tgcgccaaag aagtgaagtc ctgcaagggc cggtgcttcg agcggacctt cggcaactgc 360

agatgcgacg ccgcctgtgt ggaactgggc aactgctgcc tggactacca ggaaacctgc 420

atcgagcccg agcacatctg gacctgcaac aagttcagat gcggcgagaa gcggctgacc 480

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gaccccaaga tgaacgccag cttcagcctg aagtccaaag agaagttcaa ccccgagtgg 900

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taccagcagc ggaaagaacc cgtgtccgat atcctgaagc tgaaaaccca tctgcccacc 2760

ttcagccagg aagat 2775

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[0601] Asp Ser Ser

[0602] SEQ.ID NO:58-接头

[0603] Glu Ser Ser

[0604] SEQ.ID NO:59-接头

[0605] Arg Gln Gln

[0606] SEQ.ID NO:60-接头

[0607] Lys Arg

[0608] SEQ.ID NO:61-接头

[0609] $(Arg)_m$;m=0-15

[0610] SEQ.ID NO:62-接头

[0611] Asp Ser Ser Ser Glu Glu Lys Phe Leu Arg Arg Ile Gly Arg Phe Gly

[0612] SEQ.ID NO:63-接头

[0613] Glu Glu Glu Glu Glu Glu Glu Pro Arg Gly Asp Thr

1 5 10

[0614] SEQ.ID NO:64-接头

[0615] Ala Pro Trp His Leu Ser Ser Gln Tyr Ser Arg Thr

1 5 10

[0616] SEQ.ID NO:65-接头

[0617] Ser Thr Leu Pro Ile Pro His Glu Phe Ser Arg Glu

1 5 10

[0618] SEQ.ID NO:66-接头

[0619] Val Thr Lys His Leu Asn Gln Ile Ser Gln Ser Tyr

1 5 10

[0620] SEQ.ID NO:67-接头

[0621] $(Glu)_m$;m=1-15

[0622] SEQ.ID NO:68-接头

[0623] Leu Ile Asn

[0624] SEQ.ID NO:69-接头

[0625] Gly Gly Ser Gly Gly Ser

1 5

[0626] SEQ.ID NO:70-接头

[0627] Arg Ser Gly Ser Gly Gly Ser

1 5

[0628] SEQ.ID NO:71-接头

[0629] $(Asp)_m$;m=1-15

[0630] 1

[0631] SEQ.ID NO:72-接头

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

[0632]

1 5 10 15

[0633] SEQ.ID NO:73-接头

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

[0634]

1 5 10 15

[0635] SEQ.ID NO:74-接头

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

[0636]

1 5 10

[0637] SEQ.ID NO:75-接头

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

[0638]

1 5 10

[0639] SEQ.ID NO:76-接头

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

[0640]

1 5 10

[0641] SEQ.ID NO:77-接头

Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys

[0642]

1 5 10

[0643] SEQ.ID NO:78-接头

Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys

[0644]

1 5 10

[0645] SEQ.ID NO:79-接头

Leu Gly Leu Gly Leu Gly Leu Arg Lys

[0646]

1 5

[0647] SEQ.ID NO:80-接头

Gly Leu Gly Leu Gly Leu Arg Lys

[0648]

1 5

[0649] SEQ.ID NO:81-接头

Leu Gly Leu Gly Leu Arg Lys

[0650]

1 5

[0651] SEQ.ID NO:82-接头

Gly Leu Gly Leu Arg Lys

[0652]

1 5

[0653] SEQ.ID NO:83-接头

Leu Gly Leu Arg Lys

[0654]

1 5

[0655] SEQ.ID NO:84-接头

Gly Leu Arg Lys

[0656]

1

[0657] SEQ.ID NO:85-接头

Leu Arg Lys

[0658]

1

[0659] SEQ.ID NO:86-接头

Arg Lys

[0660]

1

[0661] SEQ.ID NO:87-接头

[0662] $(Lys)_m$;m＝0-15

[0663] 1

[0664] SEQ.ID NO:88-接头

[0665] D_m;m＝1-15

[0666] 1

[0667] SEQ ID NO:89-可溶性NPP1-Fc融合蛋白序列

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

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

[0669] **Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys** Ser Leu Ser Leu Ser Pro Gly Lys

[0670] 双下划线-NPP1序列的起始和结束;粗体残基表示Fc序列

[0671] SEQ ID NO:90-可溶性NPP1-Fc核苷酸序列

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agatgcgacg ccgcctgtgt ggaactgggc aactgctgcc tggactacca ggaaacctgc

atcgagcccg agcacatctg gacctgcaac aagttcagat gcggcgagaa gcggctgacc

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aacggcagcg tgcccttcga ggaacggatc ctggctgtgc tgcagtggct gcagctgccc

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[0677] SEQ ID NO:91-可溶性NPP1-(GLK)-Fc融合蛋白序列

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Asn Cys Arg Cys Asp Ala Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys Ile Glu
Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu Lys Arg Leu Thr Arg Ser Leu Cys Ala Cys
Ser Asp Asp Cys Lys Asp Lys Gly Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp
Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro Ala Gly Phe Glu Thr Pro Pro Thr Leu Leu
Phe Ser Leu Asp Gly Phe Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser Lys Leu
Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Ser
Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala
Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala
Lys Tyr Gln Gly Leu Lys Ser Gly Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro
Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Leu Ala Val Leu Gln Trp Leu Gln
Leu Pro Lys Asp Glu Arg Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr
Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly Met Val Gly Met Leu Met Asp Gly
Leu Lys Glu Leu Asn Leu His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser
[0678] Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala
Ala Arg Leu Arg Pro Ser Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu
Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe Leu Pro Lys Arg Leu His Phe Ala
Lys Ser Asp Arg Ile Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu
Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser Asn Met Gln Ala Leu Phe Val Gly
Tyr Gly Pro Gly Phe Lys His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys
Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His Leu Leu Lys Asn Pro
Val Tyr Thr Pro Lys His Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp
Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe Gln Thr Gln Phe Asn Leu Thr Val
Ala Glu Glu Lys Ile Ile Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr
Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp Ile Leu Met Pro Leu Trp Thr Ser
Tyr Thr Val Asp Arg Asn Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile
Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro
Pro Gln Leu Asn Lys Asn Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr

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

[0679] **Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys**

[0680] 双下划线-NPP1序列的起始和结束;粗体残基表示Fc序列

[0681] SEQ ID NO:92-可溶性NPP1-Fc融合蛋白序列

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

[0682] Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser Cys Lys Lys

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

[0683] Val Ser Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp Leu Ile Asn **Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys**

[0684] 双下划线-NPP1序列的起始和结束;粗体残基表示Fc序列

[0685] SEQ ID NO:93-可溶性NPP1-Fc融合蛋白序列

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

[0686] Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly
Pro Gly Phe Lys His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu
Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr
Thr Pro Lys His Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp Asn Leu
Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu
Glu Lys Ile Ile Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr Ile Cys
Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr
Val Asp Arg Asn Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile Pro Leu
Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln
Leu Asn Lys Asn Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln Ser
Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn
Val Val Ser Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln Lys
Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp
Thr Ser Gln Thr Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp Asn
Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg
Ile Thr Asp Val Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile Leu
Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp Leu Ile Asn **Asp Lys Thr His Thr Cys Pro Pro**
Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn

[0687] Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

[0688] 双下划线-NPP1序列的起始和结束;粗体残基表示Fc序列

[0689] SEQ ID NO:94-接头

[0690] Gly Gly Gly Gly Ser

[0691] 根据本发明的药物组合物

[0692] 根据本发明的AAV载体(vector)可以通过常规方法施用于人或动物体,其需要在药物组合物中配制载体(vector)。在一个实施方案中,本发明涉及包括AAV载体(vector)的药物组合物(下文称为“根据本发明的药物组合物”),AAV载体(vector)包括重组病毒基因组,其中重组病毒基因组包括表达盒,表达盒包括与编码ENPP1或ENPP3或其功能等效变体的核苷酸序列可操作连接的转录调节区。

[0693] 在根据本发明的腺相关病毒载体(vector)、单纯疱疹病毒载体(vector)、腺病毒载体(vector)、甲病毒载体(vector)和慢病毒载体(vector)的上下文中公开的所有实施方案也适用于根据本发明的药物组合物。

[0694] 在一些实施方案中,药物组合物可以包括治疗有效量的根据本发明的AAV载体(vector)和药学上可接受的载体(carrier)。在一些实施方案中,药物组合物可以包括治疗有效量的根据本发明的腺病毒载体(vector)和药学上可接受的载体(carrier)。

[0695] 在一些实施方案中,药物组合物可以包括治疗有效量的根据本发明的慢病毒载体(vector)和药学上可接受的载体(carrier)。

[0696] 在一些实施方案中,药物组合物可包括治疗有效量的根据本发明的甲病毒属载体(vector)和药学上可接受的载体(carrier)。

[0697] 在一些实施方案中,药物组合物可包括治疗有效量的根据本发明的单纯疱疹病毒载体(vector)和药学上可接受的载体(carrier)。

[0698] 术语“治疗有效量”是指根据本发明的AAV载体(vector)的经计算产生所需效果的量,并且除其它原因外,通常由根据本发明的病毒载体(vector)的自身特征和待获得的治疗效果来确定。有效治疗疾病的根据本发明的病毒载体(vector)的量可以通过本文所述的标准临床技术或本领域已知的其它技术来确定。此外,体外测试也可任选地用于帮助鉴定最佳剂量范围。制剂中使用的精确剂量将取决于给药途径和病症的严重程度,并且应当根据医生的判断和根据每个患者的情况来决定。

[0699] 启动子

[0700] 用于基因治疗的载体(vector)需要表达盒。表达盒由三个重要组分组成:启动子、治疗基因和聚腺苷酸化信号。启动子对于控制治疗性基因的表达是必需的。组织特异性启动子是仅在某些细胞类型中具有活性的启动子。在表达盒中使用组织特异性启动子可以限制不需要的转基因表达以及促进持续的转基因表达。用于基因治疗的常用启动子包括巨细

胞病毒即刻早期(CMV-IE)启动子、劳斯氏肉瘤病毒长端重复序列(RSV-LTR)、莫洛尼鼠白血病病毒(MoMLV)LTR和其它逆转录病毒LTR启动子。真核启动子可用于基因治疗,常见实例包括人a1-抗胰蛋白酶(hAAT)和鼠RNA聚合酶II(大亚基)启动子。非组织特异性启动子如小核RNA U1b启动子,EF1α启动子和PGK1启动子也可用于基因治疗。组织特异性启动子如Apo A-I、ApoE和a1-抗胰蛋白酶(hAAT)能够在基因治疗中组织特异性表达目的蛋白。Papadakis等人的表I。(启动子和控制元件:基因治疗的表达盒的设计,《当前基因治疗》,2004,4,89-113)(Promoters and ControlElements:Designing Expression Cassettes for Gene Therapy,Current Gene Therapy,2004,4,89-113))列出了在基因治疗中使用真核启动子的转录靶向的实例,所有这些在此全文引入作为参考。

[0701] 给药剂量和模式

[0702] AAV滴度以载体(vector)或病毒基因组每毫升(vg/ml)或(vg/kg)载体(vector)或病毒基因组每公斤剂量的“物理”滴度给出。纯化的载体(vector)颗粒的QPCR可用于测定滴度。一种进行AAV VG数字滴定的方法是首先用DNase处理纯化的AAV载体(vector)样本,以从生产过程中除去未包被的AAV基因组DNA或污染的质粒DNA。然后对DNase抗性颗粒进行热处理以从衣壳中释放基因组。使用靶向病毒基因组的特定区域的引物/探针组,通过实时PCR定量释放的基因组。

[0703] 病毒组合物可以以剂量单位配制以含有对于人类患者在约1.0×10^{9}vg/kg至约1.0×10^{15}vg/kg并且优选地1.0×10^{12}vg/kg至1.0×10^{14}vg/kg范围内的量的病毒载体(vector)。优选地,制剂中病毒的剂量为1.0×10^{9}vg/kg、5.0×10^{9}vg/kg、1.0×10^{10}vg/kg、5.0×10^{10}vg/kg、1.0×10^{11}vg/kg、5.0×10^{11}vg/kg、1.0×10^{12}vg/kg、5.0×10^{12}vg/kg、或1.0×10^{13}vg/kg、5.0×10^{13}vg/kg、1.0×10^{14}vg/kg、5.0×10^{14}vg/kg、或1.0×10^{15}vg/kg或5.0×10^{15}vg/kg。

[0704] 在一些实施方案中,在根据本发明的上下文中,施用给哺乳动物,特别是人的剂量随特定病毒载体(vector)、包括载体(vector)和其载体(carrier)的组合物(如上文)以及给药模式而变化。该剂量足以在所需的时间范围内实现所需的反应,例如,治疗或预防反应。就病毒载体(vector)而言,剂量最高可达1×10^{15}vg/kg。

[0705] 本发明的载体(vector)允许长期基因表达,导致治疗性蛋白的长期作用。短语“长期表达”,“持续表达”和“持久表达”可互换使用。根据本发明的长期表达意指治疗性基因和/或蛋白的表达,优选以治疗性水平表达至少45天、至少60天、至少90天、至少120天、至少180天、至少250天、至少360天、至少450天、至少730天或更多。优选地,长期表达意指表达至少90天、至少120天、至少180天、至少250天、至少360天、至少450天、至少720天或更多,更优选地,至少360天、至少450天、至少720天或更多。这种长期表达可以通过重复剂量(如果可能)或通过单次剂量实现。

[0706] 重复剂量可以每天给药两次、每天给药一次、每周给药两次、每周给药一次、每月给药一次、每两个月给药一次、每三个月给药一次、每四个月给药一次、每六个月给药一次、每年给药一次、每两年给药一次或更多次。计量加入可以持续需要的时间,例如至少6个月、至少1年、2年、3年、4年、5年、10年、15年、20年或更长,直至待治疗患者的一生。

[0707] 根据本发明的药物组合物可以局部或全身给药、肌肉内给药、静脉内给药和胃肠外给药。根据本发明的治疗组合物的递送可以针对中枢神经系统、心脏系统和肺系统。通常

的递送策略是直接肌肉注射。作为非限制性实例,已显示骨骼肌是有效转导的靶组织类型。一旦被转导,肌肉细胞充当可以通过许多AAV变体局部或全身作用的蛋白产物的生产位点。

[0708] 在一个实施方案中,药物组合物在其细胞待转导的组织或器官附近施用。在一个具体的实施方案中,根据本发明的药物组合物在肝脏中通过注射到肝脏实质中而局部施用。在另一个实施方案中,根据本发明的药物组合物是全身施用的。

[0709] 作为非限制性实例,全身给药包括根据本发明的AAV载体(vector)的全身注射,例如肌内注射、血管内注射、动脉内注射、静脉内注射、腹膜内注射或皮下注射。优选地,全身给药是经由im、ip、is或iv注射。在一些实施方案中,通过静脉注射施用根据本发明的AAV载体(vector)。

[0710] 在另一个实施方案中,根据本发明的药物组合物被递送至受试对象的肝脏。使用本领域已知的方法实现对肝脏的给药,包括但不限于静脉内给药、门静脉给药、胆管内给药、动脉内给药和直接注射到肝实质中。在另一个实施方案中,静脉内施用药物组合物。

[0711] 根据本发明的药物组合物可以以单剂量施用,或者在根据本发明的具体实施方案中,可以采用多剂量(例如两次、三次、四次或更多次施用)来实现治疗效果。优选地,当需要多剂量以消除中和抗体的作用时,包括在根据本发明的药物组合物中的AAV载体(vector)来自不同的血清型。

[0712] 制剂

[0713] 制剂还可含有缓冲盐。或者,组合物可以是粉末形式,在使用前用合适的载体(vehicle)(例如无菌无热原的水)配制。必要时,组合物还可以包括局部麻醉剂如利多卡因以缓解注射部位的疼痛。当组合物将要通过渗透施用时,其可以用含有药用质量的水或盐水溶液的渗透瓶配制。当通过注射施用组合物时,可以提供用于注射的水小瓶或无菌盐水溶液,使得成分可以在给药前混合。优选地,药学上可接受的载体(carrier)是盐水溶液和去污剂如Pluronic®。

[0714] 根据本发明的组合物可以被配制用于递送至用于兽用目的的动物(例如,家畜(牛、猪、其他动物)和其他非人类哺乳动物受试对象,以及人类受试对象。AAV载体(vector)可以与生理学上可接受的载体(carrier)配制用于基因转移和基因治疗应用。作为非限制性实例,还包括与根据本发明的AAV载体(vector)组合或与根据本发明的AAV载体(vector)混合的佐剂的使用。所考虑的佐剂包括但不限于无机盐佐剂或无机盐凝胶佐剂,颗粒佐剂,微粒佐剂,粘膜佐剂。佐剂可以作为与根据本发明的AAV载体(vector)的混合物施用于受试对象或与AAV载体(vector)组合使用。

[0715] 本文可互换使用的术语“药学上可接受的载体(carrier)”、“药学上可接受的稀释剂”、“药学上可接受的赋形剂”或“药学上可接受的载体(vehicle)”是指无毒的固体,半固体或液体填充剂,稀释剂,包封材料或任何常规类型的制剂助剂。药学上可接受的载体(carrier)在所使用的剂量和浓度下对接受者基本上无毒,并且与制剂的其它成分相容。药学上可接受的载体(carrier)的数量和性质取决于所需的给药形式。药学上可接受的载体(vector)是已知的并且可以通过本领域熟知的方法制备(Faulii TrilloC,“Tratado de Farmacia Galénica”.Ed.Luzán 5,S.A.,Madrid,ES,1993;Gennaro A,Ed.,“《雷明顿:药学的科学与实践》(Remington:The Science and Practice of Pharmacy)”第20版.LippincottWilliams&Wilkins,Philadelphia,Pa.,US,2003)。

[0716] 作为非限制性实例,AAV载体(vector)可以配制用于通过注射(例如通过弹丸式注射或连续输注)胃肠外给药。用于注射的制剂可以以含有添加的防腐剂的单位剂型(例如在安瓿或多剂量容器中)存在。病毒组合物可以采取在油性或水性载体(vector)中的混悬液、溶液或乳液的形式,并且可以含有配制试剂,例如悬浮剂、稳定剂或分散剂。AAV制剂的液体药剂可以通过常规方式用药学上可接受的添加剂制备,药学上可接受的添加剂例如悬浮剂(例如山梨糖醇糖浆、纤维素衍生物或氢化可食用脂肪)、乳化剂(例如卵磷脂或阿拉伯胶)、非水性载体(vector)(例如杏仁油、油性酯、乙醇或分馏植物油)以及防腐剂(例如对羟基苯甲酸甲酯或丙酯或山梨酸)。

[0717] 适用于胃肠外给药的制剂包括水性和非水性,等渗无菌注射溶液,其可含有抗氧化剂、缓冲剂、抑菌剂和使制剂与预期接受者的血液等渗的溶质,以及水性和非水性无菌悬浮液,其可包括悬浮剂、增溶剂、增稠剂、稳定剂和防腐剂。制剂可以存在于单位剂量或多剂量密封容器如安瓿和小瓶中,并且可以储存在冷冻干燥(冻干)条件下,仅需要在使用前即刻添加用于注射的无菌液体赋形剂,例如水。临时注射溶液和悬浮液可由前述种类的无菌粉末、颗粒和片剂制备。

[0718] 此外,该组合物可以包括另外的治疗剂或生物活性剂。例如,可存在用于治疗特定适应症的治疗因子。控制炎症的因子,例如布洛芬或类固醇,可以是组合物的一部分以减少与载体(vector)的体内给药和生理痛苦相关的肿胀和炎症。免疫系统抑制剂可与组合物方法一起施用以减少对载体(vector)自身或与病症相关的任何免疫应答。免疫抑制药物或免疫抑制剂给药是故意诱导免疫抑制的主要方法,在最佳情况下,免疫抑制药物仅靶向免疫系统的任何活动过度的组分。

[0719] 免疫抑制药物或免疫抑制剂或抗排异药物是抑制或阻止免疫系统活性的药物。这类药物包括糖皮质激素、细胞抑制剂、抗体、作用于免疫亲和素的药物。在药理学(超生理学)剂量中,糖皮质激素如泼尼松、地塞米松和氢化可的松用于抑制各种过敏和炎症反应。细胞抑制剂,例如嘌呤类似物、烷化剂,例如氮芥(环磷酰胺)、亚硝基脲、铂化合物等。环磷酰胺((Baxter's Cytoxan)可能是最有效的免疫抑制化合物。抗代谢物,例如叶酸类似物如甲氨蝶呤、嘌呤类似物如硫唑嘌呤和巯嘌呤、嘧啶类似物如氟尿嘧啶,和蛋白合成抑制剂。细胞毒性抗生素其中,更生霉素是最重要的。用于肾移植。其它细胞毒性抗生素是蒽环类抗生素、丝裂霉素C、博来霉素、光神霉素。抗体有时用作快速且有效的免疫抑制疗法以防止急性排斥反应(例如,抗CD20单克隆抗体)。

[0720] 或者,免疫增强子可包括在组合物中以上调机体针对疾病的天然防御。

[0721] 可存在抗生素(即,杀微生物剂和杀真菌剂)以降低与基因转移程序和其它病症相关的感染风险。

[0722] 药物组合物可以根据常规程序配制为适用于对人静脉内、皮下或肌内给药的药物组合物。

[0723] 根据本发明的治疗方法

[0724] 作为非限制性实例,将编码人ENPP1或ENPP3的病毒载体(vector)施用于哺乳动物,导致编码ENPP1或ENPP3的DNA的递送和该蛋白在哺乳动物中的表达,从而恢复减少软组织中的钙化或骨化所需的ENPP1或ENPP3的水平。

[0725] 在一个方面,本发明涉及用于治疗和/或预防病理性钙化或骨化疾病的包括重组

病毒基因组的腺相关病毒载体(vector)或包括该病毒载体(vector)的药物组合物,其中重组病毒基因组包括表达盒,表达盒包括与编码ENPP1或ENPP3或其功能等效变体的核苷酸序列可操作连接的转录调节区。

[0726] 在另一方面,本发明涉及包括重组病毒基因组的腺相关病毒载体(vector)或包括病毒载体(vector)的药物组合物在制备用于治疗和/或预防疾病、病理性钙化或骨化疾病的药物中的用途,其中重组病毒基因组包括表达盒,表达盒包括与编码ENPP1或ENPP3或其功能等同变体的核苷酸序列可操作连接的转录调节区。

[0727] 在另一方面,本发明提供治疗和/或预防有需要的受试对象中病理性钙化或骨化的疾病的方法,其包括向受试对象施用腺相关病毒载体(vector)或包括病毒载体(vector)的药物组合物,该腺相关病毒载体(vector)包括:重组病毒基因组,其中重组病毒基因组包括表达盒,表达盒包括与编码ENPP1或ENPP3或其功能等效变体的核苷酸序列可操作连接的转录调节区。

[0728] 在另一方面,通过本发明的组合物和方法治疗的病理性钙化或骨化的疾病选自由以下组成的组:X连锁低磷酸血症(XLH)、慢性肾病(CKD)、矿物质和骨代谢紊乱(MBD)、血管钙化、软组织的病理性钙化、软组织的病理性骨化、婴儿全身性动脉钙化(GACI)、后纵韧带骨化(OPLL)。

[0729] 根据本发明的多核苷酸、载体(vector)和质粒

[0730] 本发明还涉及用于生产病毒载体(vector),例如根据本发明的AAV载体(vector)的多核苷酸。在一个实施方案中,本发明涉及包括侧接腺相关病毒ITR的表达盒的多核苷酸(根据本发明的多核苷酸),其中表达盒包括与编码ENPP1或ENPP3或其功能等同变体的核苷酸序列可操作连接的转录调节区。

[0731] 在一个实施方案中,根据本发明的多核苷酸包括转录调节区,转录调节区包括启动子;优选组成型启动子;更优选肝特异性启动子;更优选肝特异性启动子选自:白蛋白启动子、磷酸烯醇丙酮酸羧激酶(PEPCK)启动子和α1-抗胰蛋白酶启动子组成的组;最优选的是人α1-抗胰蛋白酶启动子。在另一个实施方案中,根据本发明的多核苷酸的转录调节区还包括与启动子可操作连接的增强子,优选肝特异性增强子,更优选肝控制区增强子(HCR)。

[0732] 在另一个实施方案中,根据本发明的多核苷酸的表达盒还包括聚腺苷酸化信号,更优选为SV40聚腺苷酸。在另一个实施方案中,由根据本发明的多核苷酸编码的ENPP1选自人ENPP1和人ENPP3组成的组。

[0733] 可以将根据本发明的多核苷酸并入载体(vector)例如质粒中。因此,在另一方面,本发明涉及包括根据本发明的多核苷酸的载体(vector)或质粒。在特定实施方案中,根据本发明的多核苷酸并入腺相关病毒载体(vector)或质粒中。

[0734] 优选地,用于生产腺伴随病毒所必需的所有其它结构和非结构编码序列不存在于病毒载体(vector)中,因为它们可以通过另一种载体(vector)例如质粒,或通过将序列稳定整合到包装细胞系中来反式提供。

[0735] 用于获得根据本发明的AAV的方法

[0736] 本发明还涉及用于获得根据本发明的病毒载体(vector)的方法,作为非限制性实例,AAV载体(vector)。AAV载体(vector)可以通过将本发明的多核苷酸导入组成型表达Rep和Cap蛋白的细胞中获得,或者其中Rep和Cap编码序列在质粒或载体(vector)中提供。因

此,在另一方面,本发明涉及用于获得腺相关病毒载体(vector)的方法,其包括以下步骤:

[0737] (i)提供包括根据本发明的多核苷酸、AAV Cap蛋白、AAV Rep蛋白和任选的AAV依赖于其复制的病毒蛋白的细胞,

[0738] (ii)在足以组装AAV的条件下维持细胞,

[0739] (iii)纯化由细胞产生的腺相关病毒载体(vector)。

[0740] 先前已经描述了用于载体(vector)化转基因的重组AAV(rAAV)的生产(Ayuso E等人,《当今基因疗法》(Curr.Gene Ther.)2010,10:423-436;Okada T等人,《人类基因疗法》(Hum.Gene Ther.)2009,20:1013-1021;Zhang H等人,《人类基因疗法》(Hum.Gene Ther.)2009,20:922-929;和Virag T,et al.,《人类基因疗法》(Hum.Gene Ther.)2009,20:807-817)。这些方案可用于或适于产生根据本发明的AAV。能够产生腺相关病毒载体(vector)的任何细胞都可用于本发明,包括哺乳动物和昆虫细胞。

[0741] 在一个实施方案中,生产细胞系用本发明的多核苷酸(包括侧接ITR的表达盒)和编码Rep和Cap蛋白并提供辅助功能的构建体瞬时转染。在另一个实施方案中,细胞系稳定提供辅助功能,并用本发明的多核苷酸(包括侧接ITR的表达盒)和编码Rep和Cap蛋白的构建体瞬时转染。

[0742] 在另一个实施方案中,细胞系稳定地提供Rep和Cap蛋白以及辅助功能,并用本发明的多核苷酸顺转。在另一个实施方案中,细胞系稳定地提供Rep和Cap蛋白,并用本发明的多核苷酸和编码辅助功能的多核苷酸瞬时转染。在另一个实施方案中,细胞系稳定地提供根据本发明的多核苷酸,Rep和Cap蛋白以及辅助功能。本领域已经描述了制备和使用这些和其它AAV生产系统的方法。

[0743] 在另一个实施方案中,生产细胞系是用提供Rep和Cap蛋白的杆状病毒表达载体(vector)感染的昆虫细胞系(通常是Sf9细胞)。该系统不需要腺病毒辅助基因(Ayuso E等人,《当今基因疗法》(Curr.GeneTher.)2010,10:423-436)。

[0744] 在另一个实施方案中,AAV的转基因递送能力可以通过提供两个基因组的AAV ITR来增加,这两个基因组可以退火形成头对尾多联体。通常,在AAV进入宿主细胞后,含有转基因的单链DNA被宿主细胞DNA聚合酶复合物转化为双链DNA,之后ITR帮助在细胞核中形成多联体。作为替代方案,AAV可以被工程化为自身互补(sc)AAV,其使得病毒载体(vector)能够在进入靶细胞时绕过第二链合成的步骤,从而提供具有更快和潜在更高(例如高达100倍)转基因表达的scAAV病毒载体(vector)。

[0745] 例如,AAV可以被工程化以具有包括两个连接的单链DNA的基因组,单链DNA分别编码转基因单元及其互补体,其可以在递送到靶细胞中之后咬合在一起,产生编码目的转基因单元的双链DNA。自身互补AAV已在本领域中描述(Carter B,美国专利6,596,535,Carter B,美国专利7,125,717,and Takano H等人,美国专利7,456,683)。

[0746] 优选地,所有结构和非结构编码序列(Cap蛋白和Rep蛋白)不存在于AAV载体(vector)中,因为它们可以通过载体(vector)如质粒反式提供。已经报道Cap蛋白对AAV病毒的宿主靶向性、细胞、组织或器官特异性、受体用途、感染效率和免疫原性有影响。因此,可考虑例如受试对象的物种(例如人或非人物种),受试对象的免疫状态,受试对象对于长期或短期治疗的适合性,或特定治疗应用(例如特定疾病或病症的治疗,或递送至特定细胞)来选择用于rAAV的AAV Cap。

[0747] 在另一个实施方案中,Cap蛋白衍生自AAV,AAV选自AAV2、AAV5、AAV7、AAV8、AAV9、AAV10和AAVrh10血清型组成的组。在另一个实施方案中,Cap蛋白衍生自AAV8。

[0748] 在一些实施方案中,用于本发明方法的AAV Cap可以通过上述AAV Cap或其编码核酸之一的诱变(即通过插入、缺失或取代)产生。在一些实施方案中,AAV Cap与一种或多种前述AAV Cap至少70%、75%、80%、85%、90%、95%、98%或99%或更多相似。

[0749] 在一些实施方案中,AAV Cap是嵌合的,包括来自两个、三个、四个或更多个上述AAV Cap的结构域。在一些实施方案中,AAV Cap是源于两种或三种不同AAV或重组AAV的VP1、VP2和VP3单体的嵌合体。在一些实施方案中,rAAV组合物包括多于一种的上述Cap。

[0750] 在一些实施方案中,用于rAAV组合物的AAV Cap被工程化以含有异源序列或其它修饰。例如,可将赋予选择性靶向或免疫逃避的肽或蛋白序列工程化到Cap蛋白中。可替换地或附加地,可以化学修饰Cap,使得rAAV的表面被聚乙二醇化(即聚乙二醇化),这可以促进免疫逃避。还可以诱变Cap蛋白(例如去除其天然受体结合,或掩蔽免疫原性表位)。

[0751] 在一些实施方案中,用于本发明方法的AAV Rep蛋白可以通过上述AAV Rep之一或其编码核酸的诱变(即通过插入、缺失或取代)产生。在一些实施方案中,AAV Rep与一种或多种前述AAV Rep至少70%、75%、80%、85%、90%、95%、98%或99%或更多相似。

[0752] 在另一个实施方案中,AAV Rep和Cap蛋白衍生自AAV2、AAV5、AAV7、AAV8、AAV9、AAV10和AAVrh10组成的组。

[0753] 在一些实施方案中,用于本发明方法的AAV依赖于其复制的病毒蛋白可以通过上述病毒蛋白或其编码核酸之一的诱变(即通过插入、缺失或取代)产生。在一些实施方案中,病毒蛋白与一种或多种上述病毒蛋白至少70%、75%、80%、85%、90%、95%、98%或99%或更高相似。

[0754] 测定AAV依赖的Cap蛋白、Rep蛋白和病毒蛋白的功能的方法是本领域熟知的。可以通过将AAV rep基因,AAV cap基因和提供辅助功能的基因引入载体(vector)(例如质粒)并将载体(vector)引入细胞中来引入细胞。基因可以整合到同一质粒或不同质粒中。在另一个实施方案中,AAV rep和cap基因整合到一个质粒中,而提供辅助功能的基因整合到另一个质粒中。适用于本发明方法的包括AAV Rep和cap基因的质粒的实例包括pHLP19和pRep6cap6载体(vector)(Colisi P,美国专利6,001,650和Russell D等人,美国专利6,156,303)。

[0755] 根据本发明的多核苷酸和包括AAV rep和cap基因或提供辅助功能的基因的多核苷酸可以通过使用本领域熟知的任何合适的方法引入细胞中。转染方法的实例包括但不限于用磷酸钙共沉淀、DEAE-葡聚糖、聚凝胺、电穿孔、显微注射、脂质体介导的融合、脂质转染、逆转录病毒感染和生物弹道转染。在一个具体的实施方案中,通过与磷酸钙共沉淀进行转染。当细胞缺乏任何AAV rep和cap基因以及提供腺病毒辅助功能的基因的表达时,基因可以与根据本发明的多核苷酸同时引入细胞中。

[0756] 或者,可以在导入本发明的多核苷酸之前或之后将基因导入细胞中。在具体实施方案中,用三种质粒同时转染细胞:

[0757] 1)包括根据本发明的多核苷酸的质粒

[0758] 2)包括AAV rep和cap基因的质粒

[0759] 3)包括提供辅助功能的基因的质粒。

[0760] 或者,AAV rep和cap基因以及提供辅助功能的基因可由包装细胞携带,或者游离地携带和/或整合到包装细胞的基因组中。

[0761] 本发明包括涉及在足以组装AAV的条件下维持细胞的方法。培养包装细胞的方法和促进AAV载体(vector)颗粒释放的示例性条件,例如产生细胞裂解液,可以如本文实施例中所述进行。生产细胞生长合适的时间以促进AAV的组装和病毒载体(vector)向培养基中的释放。通常,细胞可以生长约24小时、约36小时、约48小时、约72小时、约4天、约5天、约6天、约7天、约8天、约9天、至多约10天。在约10天后(或更早,取决于培养条件和所用的具体生产细胞),生产水平通常显著降低。通常,培养时间从病毒产生的点开始测量。例如,在AAV的情况下,病毒生产通常在如本文所述在合适的生产细胞中提供辅助病毒功能后开始。通常,在辅助病毒感染后(或在病毒生产开始后)约48至约100、优选约48至约96、优选约72至约96、优选约68至约72小时收获细胞。

[0762] 本发明包括纯化细胞产生的腺相关病毒载体(vector)的方法。根据本发明的AAV可以从i)用根据本发明的多核苷酸转染的细胞和ii)转染后一段时间,优选72小时的细胞的培养基两者获得。用于从细胞或培养基纯化AAV的任何方法可用于获得根据本发明的AAV。在一个具体的实施方案中,按照基于聚乙二醇沉淀步骤和两个连续氯化铯(CsCl)梯度的优化方法纯化根据本发明的AAV。根据本发明纯化的AAV可以用PBS透析,过滤并保存在-80℃。病毒基因组的滴度可以通过定量PCR,按照AAV2参考标准物质的方案,使用线性化的质粒DNA作为标准曲线来测定(Lock M,等人,《人类基因疗法》(Hum.Gene Ther.)2010;21:1273-1285)。

[0763] 在另一个实施方案中,进一步通过聚乙二醇沉淀步骤或氯化铯梯度分馏进行纯化。在一些实施方案中,方法还包括纯化步骤,例如用核酸酶处理细胞裂解液,在CsCl梯度上纯化细胞裂解液,或使用硫酸肝素层析纯化细胞裂解液(Halbert C等人,《分子生物学方法》(Methods Mol.Biol.)2004;246:201-212)。

[0764] 各种天然存在的和重组的AAV、它们的编码核酸、AAV Cap和Rep蛋白和它们的序列,以及分离或产生、繁殖和纯化这种AAV的方法,特别它们的衣壳,是适合用于生产AAV的是本领域已知的。

[0765] 动物模型

[0766] 以下是可用于测试施用ENPP1或ENPP3以预防或减少病理性骨化或钙化进展的功效的非限制性动物模型。

[0767] 1.《$Enpp1^{asj/asj}$模型用于婴儿期广泛动脉钙化(GACI)》($Enpp1^{asj/asj}$ model of Generalized ArterialCalcification of Infancy(GACI));Li,等人,2013,Disease Models&Mech.6(5):1227-35.

[0768] 2.《$Enpp1^{asj/asj}$模型用于婴儿期广泛动脉钙化(GACI)》($Enpp1^{asj/asj}$ model of Generalized ArterialCalcification of Infancy(GACI));Li,等人,2014,PloS one 9(12):el 13542.

[0769] 3.《$ABCC6^{-/-}$小鼠弹性纤维假黄瘤模型(PXE)》($ABCC6^{-/-}$mouse model of Pseudoxanthoma Elasticum(PXE));Jiang,等人,2007,J.Invest.Derm.127(6):1392-4102.

[0770] 4.《X连锁低磷酸血症(XLH)HYP小鼠模型》(HYP mouse model of X-linked

hypophosphatasia(XLH));Liang,等人.,2009,Calcif.Tissue Int.85(3):235-46.

[0771] 5.《Hutchison-Gilford早衰综合征LmnaG609G/+小鼠模型》(LmnaG609G/+mouse model ofHutchison-Gilford Progeria Syndrome);Villa-Bellosta,等人,2013,Circulation 127(24):2442-51.

[0772] 6.《后纵韧带骨化(OPLL)小鼠足尖行走(ttw)模型》(Tip toe walking(ttw)mouse model ofOssification of the Posterior Longitudinal Ligament(OPLL))(Okawa,等人,1998,Nature Genetics19(3):271-3;Nakamura,等人,1999,Human Genetics 104(6):492-7)和《骨关节炎》(osteoarthritis)(Bertrand,等人,2012,Annals Rheum.Diseases 71(7):1249-53).

[0773] 7.《腺嘌呤饮食对慢性肾病影响的大鼠模型》(Rat model of chronic kidney disease(CKD)onthe adenine diet);Schibler,等人,1968,Clin.Sci.35(2):363-72;O'Neill,等人,2011,KidneyInt.79(5):512-7.

[0774] 8.《腺嘌呤饮食对慢性肾病(CKD)影响的小鼠模型》(Mouse model of chronic kidney disease(CKD)on the adenine diet);Jia,等人.,2013,BMC Nephrol.14:116.

[0775] 9.《5/6肾切除术CKD大鼠模型》(5/6th nephrectomy rat model of CKD);Morrison,1962,Lab Invest.11:321-32;

[0776] Shimamura&Morrison,1975,Am.J.Pathol.79(1):95-106.

[0777] 10.《GACI和骨量减少的ENPP1基因敲除小鼠模型》(ENPP1 knockout mouse model of GACI andosteopenia);Mackenzie,等人,2012,PloS one 7(2):e32177.

[0778] 根据本发明,使用如上所述的动物模型测试编码ENPP1或ENPP3的载体(vector)给药后软组织钙化和骨化的变化。例如,以下小鼠模型:(a)Npt2a$^{-/-}$(b)双重突变体Npt2a$^{-/-}$/Enpp1 $^{asj/asj}$和(c)经过饮食诱导引起肾结石形成的C57BL/6小鼠(Jackson实验室),饮食为高钙、低镁饮食(如Teklad实验室饮食TD.00042,Harlan实验室,Madison,WI)。

[0779] 使用正常食物饲养的Npt2a$^{-/-}$小鼠在断奶日龄开始显示肾结石形成并持续至少至10周龄。相反,当与正常食物饲养的Npt2a-/-小鼠相比时,双突变体Npt2a$^{-/-}$/Enpp1 $^{asj/asj}$小鼠呈现肾结石形成水平的两倍。Npt2a$^{-/-}$小鼠和Npt2a$^{-/-}$/Enpp1 $^{asj/asj}$小鼠从Jackson实验室,ME商购获得。按照本领域已知的标准方案(《杰克逊实验室资源手册》(Jackson Laboratory Recourse Manual),(2007,1-29))通过将Npt2a$^{-/-}$小鼠与Enpp 1$^{asj/asj}$小鼠杂交育种来创造双突变小鼠(Npt2a$^{-/-}$/Enpp1 $^{asj/asj}$)。可使用用于肾结石相关疾病的Npt2a$^{-/-}$或Npt2a$^{-/-}$/Enpp1 $^{asj/asj}$双突变小鼠模型来测试根据本发明的治疗功效(Khan&Canales,2011,《泌尿学杂志》(J.Urol.)186(3):1107-13;Wu,2015,《尿结石病》(Urolithiasis)43(增刊1):65-76)。形成草酸盐结石的啮齿动物模型,即,乙二醇、羟基嘌呤饲养的小鼠或大鼠,或腹膜内注射草酸钠小的鼠和大鼠(Khan&Glenton,《泌尿学杂志》(J.Urology)184:1189-1196),尿酸盐结石形成(Wu等人,1994,《美国科学院院报》(Proc.Natl.Acad.Sci.U S A)91(2):742-6)和胱氨酸尿小鼠模型(Zee等人,2017,《自然医学》(Nat.Med.)23(3):288-290;Sahota等人,2014,Urology 84(5):1249e9-15)中也可以进行测试。

[0780] 在某些实施方案中,不存在重述人类疾病GACI的成人形式的啮齿动物模型,在文献中也被称为常染色体隐性低磷血症性佝偻病2型(ARHR2)(Levy-Litan等人,2010,《美国人类遗传学期刊》(Am.J.HumanGen.)86(2):273-8)。

[0781] 关于ENPP1的酶活性、ENPP3的酶活性、血浆PPi的定量、显微CT扫描、血浆PPi摄取的定量的实验细节,在PCT/US2016/33236-Braddock等人,WO 2014/126965-Braddock等人,WO 2017/087936-Braddock等人,和US2015/0359858-Braddock等人的专利申请和出版物中详细描述了全部内容,将其全部内容整体并入本文。

[0782] 通过以下实施例进一步说明本发明,实施例绝不应解释为进一步限制。在本申请中引用的所有引用的参考文献(包括参考文献、授权专利、公开的专利申请和共同未决的专利申请)的内容通过引用明确地并入本文。

[0783] 实施例

[0784] 实施例:1——将NPP1序列克隆到AAV系统中,产生用于AAV感染、AAV生产和纯化的构建体

[0785] 本实施例中使用的AAV质粒含有侧接来自AAV2的两个ITR的表达盒。AAV2的基因组可能是AAV8的假型。表达盒可在5′至3′方向上具有以下元件:肝特异性增强子肝控制区(HCR)、肝特异性启动子人α抗胰蛋白酶(hAAT)、内含子、包括N端天青杀素信号序列的多核苷酸、NPP1 cDNA、C端Fc序列和SV40聚腺苷酸化信号。表达盒侧接来自AAV2的5′ITR和3′ITR。所产生的构建体显示在图1的示意图中。

[0786] ENPP1蛋白是位于细胞表面的跨膜蛋白,具有不同的膜内结构域。通过省略跨膜结构域使ENPP1蛋白可溶。将人NPP1(NCBI登录号NP_006199)修饰为表达可溶性重组蛋白,通过将其跨膜区(例如,ENPP1的残基77-98,NCBI登录号NP_006199)替换为选自以下组成的组的合适的信号肽序列:(a)人NPP2的残基12-30(NCBI登录号NP_001124335)或(b)ENPP7的残基1-22或(c)ENPP5的残基1-24或(d)人血清白蛋白或(e)人天青杀素

[0787] SEQ IDS(1-4、6-15、17-31和42-56)表示几种ENPP1-Fc和ENPP3-Fc构建体,它们都可用于将ENPP1或ENPP3序列克隆到AAV系统中,产生用于AAV感染的构建体。

[0788] 使用标准分子生物学方案将修饰的NPP1序列克隆到质粒中。使用携带与构建体相同组分但没有NPP1cDNA并具有多克隆位点的非编码质粒产生空颗粒作为对照。

[0789] 将125μg的载体(vector)质粒(含有ITR和表达盒)以及125μg的rep/cap质粒(表达AAV颗粒的衣壳蛋白和病毒复制所必需的蛋白)和150μg的表达腺病毒辅助功能的辅助质粒通过磷酸钙共沉淀共转染每个滚瓶,在滚瓶中培养的HEK293细胞中产生感染性AAV载体(vector)颗粒。每个载体(vector)制备总共使用10个滚瓶。转染后大约3天,收获细胞并在2500g离心10min。然后分别处理细胞团块和培养基。在TBS(50mM TrisHCl、150mM NaCl、2mM $MgCl_2$、pH 8.0)中充分重构细胞团块。

[0790] 3次冷冻/解冻循环后,将裂解液以2500g离心30min。将离心的上清液加入到培养基中,通过与8%的PEG 8000(Sigma)孵育15小时沉淀载体(vector)颗粒,在2500g离心30min沉淀。将含有来自细胞和培养基的载体(vector)的团块在TBS中充分重构,用核酸酶(Merck)在37℃处理30min,在10,000g离心10min。将上清液上样到含有1.3-1.5g/ml CsCl密度梯度的37.5ml超明亮管(Beckman)中,并在SW28转头(Beckman)中以28,000rpm离心17h。用10ml注射器和18号针头收集病毒带,转移到新的12.5ml超明亮管中,用1.379g/ml CsCl溶液充满以产生连续梯度。将管在SW40Ti转头(Beckman)中以38,000rpm离心48h。最后,收集全颗粒带,使用10KDa膜(Slide-A-lyzer透析产品,Pierce)在PBS中透析,并用0.45μm的Millipore过滤器过滤。这种基于PEG和CsCl的纯化方案显著减少了空AAV衣壳以及来

自病毒原种的DNA和蛋白杂质,从而增加了AAV纯度,最终导致更高的体内转导。相同的方案用于产生携带不编码任何ENPP蛋白的“空”载体(vector)的感染性AAV颗粒。

[0791] 实施例2——使用不同信号序列表达ENPP1

[0792] ENPP1通过在CHO或HEK293哺乳动物细胞中建立稳定转染而产生。为了建立稳定的细胞系,将编码ENPP1融合蛋白的核酸序列(例如本文别处公开的序列)置于用于大规模蛋白生产的合适载体(vector)中。有多种这样的载体(vector)可从商业来源获得。

[0793] 例如,图3显示克隆到pcDNA3质粒中的NPP2信号-NPP1-Fc、克隆到pcDNA3质粒中的NPP7信号-NPP1-Fc和克隆到pcDNA3质粒中的天青杀素信号-NPP1-Fc的质粒图,pcDNA3质粒具有适当的核酸内切酶限制性位点。使用已建立的技术如电穿孔或脂质体转染将含有所需蛋白构建体的pcDNA3质粒稳定转染到表达质粒中,并使细胞在抗生素选择下生长以增强稳定转染的细胞。

[0794] 然后建立单个稳定转染细胞的克隆并筛选所需融合蛋白的高表达克隆。筛选用于ENPP1蛋白表达的单细胞克隆在96孔板中以高通量方式使用合成酶底物pNP-TMP完成,如先前对于ENPP1的描述那样(Saunders等人,2008,《分子癌症治疗学》(Mol.Cancer Ther.)7(10):3352-62;Albright等人,2015,《自然通讯》(Nat Commun.)6:10006)。

[0795] 在通过筛选鉴定出高表达克隆后,蛋白生产在摇瓶或使用生物反应器中完成,如前面针对ENPP1所描述的那样(Albright等人,2015,《自然通讯》(Nat Commun.)6:10006)。使用本领域已知的标准纯化技术的组合完成ENPP1的纯化。

[0796] 如图2所示,包括天青杀素信号序列的构建体产生最高量的NPP1蛋白。与使用NPP2(127mg/升)或使用NPP7(136mg/升)信号序列产生的ENPP1蛋白相比,使用天青杀素信号序列(731mg/升)产生的ENPP1蛋白的量令人惊奇地高5倍。使用如上所述的另外的技术和/或色谱步骤进一步纯化由此产生的ENPP1蛋白,以达到基本上更高的纯度,例如~99%的纯度。

[0797] 通过使用HPLC测定人NPP1对ATP的稳态水解来测量由此产生的ENPP1的酶活性。简单地说,通过将10nM的ENPP1加入到含有20mM Tris,pH 7.4,150mM的NaCl,4.5nM KCl,14μM $ZnCl_2$,1mM $MgCl_2$和1mM $CaCl_2$的反应缓冲液中的不同浓度的ATP中来开始酶反应。在不同时间点,移除50μl反应溶液并且用等体积的3M甲酸淬灭。将淬灭的反应溶液上样在用5mM乙酸铵(pH 6.0)溶液平衡并用0%至20%甲醇梯度洗脱的C-18(5μm,250×4.6mm)柱(Higgins Analytical)上。通过259nm处的UV吸光度监测底物和产物,并根据它们的相应峰和标准曲线的整合进行定量。因此,ENPP1蛋白根据本文和在其他地方中PCT/2014/015945-Braddock等人;PCT/2016/033236-Braddock等人和PCT/2016/063034-Braddock等人讨论的方案来表征。

[0798] 实施例3——将编码ENPP1-Fc的AAV病毒颗粒注射至小鼠并测量体重增加、骨密度、骨强度和骨体积。

[0799] 使用小鼠模型例如Enpp1 $^{asj/asj}$小鼠模型、ABCC6$^{-/-}$小鼠模型、HYP小鼠模型、ttw小鼠模型、慢性肾病(CKD)的小鼠模型或CKD的5/6肾切除术大鼠模型测试编码NPP1或NPP3并能够表达NPP1或NPP3的载体(vector)的递送功效。作为非限制性实例,以下实验使用Enpp1 $^{asj/asj}$小鼠作为小鼠模型,天青杀素-NPP1-Fc构建体作为多核苷酸递送至小鼠模型,并且通过使用编码ENPP1-Fc蛋白的AAV颗粒(如实施例1中所示制备)在体内完成递送。

[0800] 普通技术人员将认识到相同的实验可以通过使用替代的小鼠模型、替代的多核苷酸构建体,替代的多核苷酸构建体包括编码不同ENPP1融合蛋白(ENPP1-白蛋白或ENPP1-Fc或ENPP1功能等同物或ENPP1缺乏Fc或白蛋白结构域等)的替代的信号序列(NPP2、NPP5、NPP7、白蛋白或天青杀素),或本发明公开的不同ENPP3融合蛋白(ENPP3-Fc或ENPP3-白蛋白或ENPP3缺乏Fc或白蛋白结构域或ENPP3功能等同物等)用于测试治疗病理性钙化或骨化疾病的基因疗法的功效。本实验中使用的天青杀素-NPP1-Fc构建体编码人ENPP1-Fc蛋白作为构思的证据,并且可以用编码人ENPP3-Fc的天青杀素-NPP3-Fc构建体重复相同的实验。

[0801] 在该实验中使用四组小鼠,每组具有至少五只小鼠(6至8周龄),在注射AAV颗粒之前,所有组小鼠通过腹膜内注射浓度为1000μg/ml(最终剂量为25-40μg/动物)的Titer GK1.5CD4抗体而减少小鼠中对AAV构建体产生的人蛋白的免疫应答,作为对照组的第一队列ENPP1 ^{wt}小鼠注射包括空载体(vector)的AAV颗粒,作为对照组的第二队列ENPP1 $^{asj/asj}$小鼠注射包括空载体(vector)的AAV颗粒,作为研究组的第三队列ENPP1 ^{wt}小鼠注射包括编码ENPP1-Fc蛋白的多核苷酸的AAV颗粒,以及作为试验组的第四队列ENPP1 $^{asj/as}$小鼠注射包括编码ENPP1-Fc蛋白的多核苷酸的AAV颗粒。每个队列在AAV注射后每周(即AAV给药后的第7、14、21、28、35、42、49、56、63、70、77、84、91、98和105天)重复进行耐受注射。

[0802] 给实验小鼠喂食加速饮食((Harlan Teklad,Rodent diet TD.00442,Madison,WI)其富含磷,镁含量降低)或常规食物(实验室高压灭菌鼠粮5010(Laboratory Autoclavable Rodent Diet 5010);PMINutritional International,Brentwood,MO)并且在6-8周龄后,所有小鼠接受在PBS pH 7.4中的约1×10^{12}至1×10^{15}vg/kg,优选1×10^{13}至1×10^{14}vg/kg的眶后注射或尾静脉注射。注射的载体(vector)是空的"无效的"(对照组)或携带NPP1基因(研究组)。每天测量体重以记录AAV注射后体重的任何增加或减少。如下收集和分析来自小鼠的血液、尿液、骨和组织样本。实验方案详见Albright等人,《自然通讯》(Nat Commun.)2015年12月1日;6:10006和Caballero等人,PLoS One.2017;12(7):e0180098,其全部内容通过引用并入本文。在研究结束时(在7、28和112天,在用异氟烷深度麻醉的眼眶放血后对所有小鼠实施安乐死,并且如本领域中所述去除重要器官。(Npt2a-/-小鼠尿中骨桥蛋白排泄受损(Impaired urinary osteopontin excretion in Npt2a-/-mice.),Caballero等人,《美国生理学杂志肾生理学》(Am J Physiol Renal Physiol.)2017年1月1日;312(1):F77-F83;Npt2a基因敲除小鼠对膳食钙和磷的反应(Response of Npt2a knockout mice to dietary calcium and phosphorus),LiY等人,PLoS One.2017;12(4):e0176232.)。

[0803] 血浆PPi的定量

[0804] 使用肝素化的微量移液管对动物进行眶后放血,并将血液分配到肝素处理的eppendorf管中并置于湿冰上。样本在4℃预冷微离心机中以4,000r.p.m旋转5min,收集血浆并稀释于1体积的50mM的Tris-醋酸盐pH=8.0中。收集的血浆通过300KDa膜超速离心过滤(NanoSep 300 K,Pall Corp.,Ann Arbour,MI),并在-80℃下冷冻。焦磷酸盐用标准的三步酶分析法定量,使用尿苷5'-二磷酸[^{14}C]葡萄糖记录反应产物,尿苷5'-二磷酸[^{14}C]葡萄糖酸(皮摩尔级无机焦磷酸盐的分析(Analysis of inorganicpyrophosphate at the picomole level).Cheung CP,Suhadolnik RJ,《分析生物化学》(Anal Biochem.)1977年11月;83(1):61-3)。简单地说,含有5mM的$MgCl_2$、90mM KCL、63mM Tris-HCL(pH7.6)、1nmol

NADP+、2nmol葡萄糖1,6-二磷酸、400pmol尿苷5'-二磷酸葡萄糖、0.02μCi尿苷5'-二磷酸[^{14}C]葡萄糖、0.25单位尿苷5'-二磷酸葡萄糖焦磷酸化酶、0.25单位磷酸葡糖变位酶、0.5单位葡萄糖6-磷酸脱氢酶和无机焦磷酸盐(50-200pmol)的反应混合物(100μl)在37℃孵育30分钟。加入200μl悬浮于水中的2％活性炭终止反应。然后在闪烁溶液中对200μl上清液的等分试样进行计数。

[0805] 体内^{99m}PYP成像

[0806] 如果需要,可以进行骨成像。使用具有双重1mm针孔准直器的临床前microSPECT/CT混合成像系统(Gamma Medica-Ideas)38在动物组中评价骨成像剂99mTc-焦磷酸盐(X-SPECT,Pharmalucence,Inc)。给每只动物腹膜内注射2-5mCi放射性标记的示踪剂,并在注射后1-1.5h成像。获得CT扫描(在50kVp,800uA和1.25的放大倍数下的512个投影)用于与SPECT图像的解剖共定位。SPECT成像通过如下获取,每个准直器头180°逆时针旋转,32个投影,每个投影60s,ROR为7.0cm,FOV为8.95cm,能量窗为140keV+-20。CT图像应使用FLEX X-O CT软件(Gamma Medica-Ideas)使用滤波反投影算法(filteredback-projection algorithm)重构。SPECT图像应使用FLEX SPECT软件(5次迭代,4个子集)重构,随后与CT图像融合,并使用AMIRA软件进行分析。

[0807] ^{99}mPYP摄取的定量

[0808] 对于^{99}mPYP鼠扫描,在注射的7天内对动物成像。将所得到的SPECT扫描导入NIH的ImageJ图像处理软件中,并且在每个动物的头部(靶器官)和全身周围绘制感目的区域。通过比较头部中的计数与全身中的计数的比率来计算百分比注射活性(PIA),通常称为'百分比注射剂量',并表示为百分比注射剂量,以给出关于目的区域(头部)摄取放射性示踪剂的亲和力的测量。每次扫描的总计数作为注射剂量的全身测量。

[0809] 血液和尿液参数

[0810] 还可以使用血液样本(通过眼眶放血采集)和在10AM和2PM之间的同一时间整夜禁食后收集的点尿进行生物化学分析。通过过滤(NanoSep 300K,Pall Corp.,Ann Arbor,MI)使肝素化血浆去蛋白化之后,用荧光探针(AB112155,ABCAM,Cambridge,MA)测定血浆和尿总焦磷酸盐(PPi)浓度。针对尿肌酐校正尿PPi,通过LC-MS/MS或通过ELISA使用适当的对照测量尿肌酐,以调整测定间可变性。

[0811] 肾脏组织学

[0812] 将左肾在4℃的4％福尔马林/PBS中固定12小时,然后用浓度增加的乙醇和二甲苯脱水,然后石蜡包埋。在用1％甲基绿复染的10μm von Kossa染色切片上测定矿物质沉积。苏木精/伊红用作形态学评价的复染剂。包括皮质、髓质和肾盂的矢状肾切片的组织形态学评估由两个独立的观察员使用Osteomeasure系统盲法进行(Osteometrics,Atlanta,GA)。用下式确定钙化面积百分比:％钙化面积＝100*钙化面积/总面积(包括皮质、髓质和肾盂内腔),并取决于每个切片的观察面积数。矿化尺寸通过使用下式确定:钙化尺寸＝钙化面积/每个切片上观察到的钙化面积的数量。

[0813] 透射电镜下,左肾1mm^{3}块在含2.5％戊二醛和2％多聚甲醛的磷酸盐缓冲盐水中固定2小时,然后在1％锇液中固定2小时。使用一系列乙醇浓度(50％至100％)进行脱水。将肾脏组织包埋在环氧树脂中,并在60℃过夜进行聚合。制备薄切片(50nm)后,将组织用铀和铅双重染色,并使用Tecnai Biotwin(LaB6,80kV)(FEI,Thermo Fisher,Hillsboro,OR)观察。

[0814] 组织学、组织形态测量和显微CT

[0815] 将小鼠的胫骨和股骨剥去软组织,在70%乙醇中固定,脱水,并包埋在甲基丙烯酸甲酯中,然后切片并用甲苯胺蓝染色(C.B.Ware等人,靶向破坏低亲和力白血病抑制因子受体基因导致胎盘、骨骼、神经和代谢缺陷,并导致围产期死亡(Targeted disruption of the low-affinity leukemia inhibitory factorreceptor gene causes placental, skeletal,neural and metabolic defects and results in perinataldeath.) Development 121,1283-1299(1995))。在刚好在对应于原发性海绵病的生长板下方的固定区域上进行组织形态学测量(A.M.Parfitt等人,骨组织形态学:命名、符号和单位的标准化(Bonehistomorphometry:standardization of nomenclature,symbols,and units.) Report of the ASBMRHistomorphometry Nomenclature Committee.J Bone Miner Res 2,595-610(1987))并用Osteomeasure测量软件进行分析(Osteometrics,Atlanta,GA)。使用ScancoμCT-35(Scanco,Bruttissellen,Switzerland)对骨进行扫描,并针对刚好在生长板(松质骨)下方的近侧胫骨和远侧股骨以及胫骨或股骨中段(皮质骨)处的众多结构参数进行分析。

[0816] 骨生物力学测试

[0817] 用三点弯曲将加速饮食的小鼠股骨负载至失效;用四点弯曲将常规饮食的小鼠股骨负载至失效。通过向后到前方向加载股骨进行全部骨测试,使前象限承受拉伸载荷。四点弯曲设备的下支架和上支架的宽度分别为7mm和3mm。使用伺服液压试验机(Instron model 8874;Instron Corp.,Norwood,MA,USA)以0.05mm/s的偏转率进行测试。载荷和跨中挠度直接以200Hz的采样频率采集。分析了载荷-挠度曲线的刚度、最大负荷和断裂功。屈服(yield)被定义为割线刚度(针对挠曲范围归一化的载荷范围)相对于初始切线刚度降低10%。在室温下测试股骨,并用磷酸盐缓冲盐水(PBS)保持湿润。还测量屈服后挠曲,其定义为失效时的挠曲减去屈服时的挠曲。

[0818] 实施例4——使用表达ENPP1或ENPP3的病毒载体(vector)治疗慢性肾病

[0819] 以下实施例提供表达ENPP1或ENPP3的AAV,其预期有效治疗血管钙化和与CKD相关的症状。为了说明的目的在实施例中使用ENPP1-Fc和ENPP3-Fc并且通过使用本发明的其他ENPP1或ENPP3融合体可以获得类似结果。

[0820] 根据实施例1制备表达ENPP1-Fc和ENPP3-Fc蛋白的AAV病毒体并对CKD小鼠施用(其为慢性肾病(CKD)模型)(BMC Nephrology,2013,14:116)。用ENPP1和ENPP3治疗六组小鼠。

[0821] 对照队列:在该实验中,作为对照组的第一队列ENPP1 wt小鼠注射包括空载体(vector)的AAV颗粒,作为对照组的第二队列CKD小鼠注射包括空载体(vector)的AAV颗粒。

[0822] ENPP1处理的小鼠队列:第三队列ENPP1^{wt}小鼠注射工程化以表达ENPP1-Fc蛋白的AAV颗粒,第四队列CKD小鼠注射工程化以表达ENPP1-Fc蛋白的AAV颗粒。

[0823] ENPP3处理的小鼠队列:第五队列ENPP1^{wt}小鼠注射工程化以表达ENPP3-Fc蛋白的AAV颗粒,第六队列CKD小鼠注射工程化以表达ENPP3-Fc蛋白的AAV颗粒。

[0824] 腺嘌呤饮食:CKD小鼠维持腺嘌呤饮食,而野生型小鼠维持常规饮食((实验室高压灭菌鼠粮5010)Laboratory Autoclavable Rodent Diet 5010;PMI Nutritional International,Brentwood,MO)。为了提供CKD小鼠食用的含腺嘌呤的食物,将腺嘌呤与以

酪蛋白为基础的饮食混合,以钝化气味和味道。腺嘌呤购自Sigma Aldrich(MO,USA),粉末状酪蛋白基饮食购自Special Diets Services(SDS,UK)(参考编号824522)。饮食的其他成分还有玉米淀粉(39.3%)、酪蛋白(20.0%)、麦芽糊精(14.0%)、蔗糖(9.2%)、玉米/玉米油(5%)、纤维素(5%)、维生素混合物(1.0%)、DL-蛋氨酸(0.3%)和酒石酸胆碱(0.2%)。

[0825] 载体(vector)注射:2周龄后,所有小鼠接受约1×10^{12}至1×10^{15}vg/kg的眶后注射或尾静脉注射,优选每只小鼠在PBS pH 7.4中1×10^{13}至1×10^{14}vg/kg。注射的载体(vector)是空的"无效的"(对照组)或携带NPP1或NPP3基因(研究组)。

[0826] 测定:如实施例3所述,对每个队列的肾脏组织学、PPi水平和血尿参数,如FGF-23水平、维生素D、甲状旁腺激素(PTH)水平、血清/血尿素水平、血尿素氮(BUN)水平、血清/血液肌酸水平和血浆焦磷酸(PPi)水平)进行分析。自发排尿后收集尿液作为点尿液样本。血清和尿液的钙、磷、肌酐和尿素水平在Konelab 20XTi(Thermo Scientific,Finland)上测量。肌酐浓度用比色测定法(BioChain,CA USA)验证。通过小鼠完整PTH ELISA试剂盒(Immutopics,CA,USA)测量PTH,使用完整FGF23 ELISA(Kainos,Japan)测量FGF23水平,并且使用EIA试剂盒(Immunodiagnostic Systems,UK)测量维生素D。实验细节在BMC Nephrology,2013,14:116,和PLoS One.2017Jul 13;12(7)中列出。

[0827] 结果:未治疗的CKD小鼠通常表现出体重降低和肾功能下降的迹象,例如尿尿素/血清尿素和尿肌酐/血清肌酐之间的比率降低。相反,用表达ENPP1或ENPP3蛋白的AAV治疗的CKD小鼠的体重有望增加,接近正常WT小鼠的体重范围。通常认为8至100mg/dL的血清尿素水平是最佳的。高于100mg/dL的尿素水平与增加的发病率以及体重减轻和身体活动减少有关。预期治疗的(有ENPP1或ENPP3的AAV)CKD小鼠表现出改善的肾功能,表现为血清尿素水平降低和尿尿素水平增加,导致更高的尿尿素/血清尿素比率。

[0828] CKD小鼠的肾组织的肾组织学分析预期显示晶体结构在诸如管腔、微脓肿和扩张的小管的区域中沉积,高碘酸-Schiff(Periodic acid-Schiff,PAS)染色显示扩张的鲍曼空间,存在具有蛋白管型的萎缩性小管("甲状腺化")和具有小管基底膜增厚的小管萎缩,通过Ladewig染色观察到轻度间质纤维化的存在,并且通过von Kossa染色观察到管状结构的广泛钙化的发生。相反,预期根据本发明用ENPP1或ENPP3处理的CKD小鼠显示出小管腔和软组织脉管系统中肾矿物质沉积物的减少或缺乏,组织学类似于健康野生型小鼠的组织学。

[0829] 当与健康野生型小鼠(正常PPi约为2-4μM;PTH约为10-65ng/L;FGF23中位数为13RU/ml,正常FGF23范围为5-210RU/ml;正常维生素D水平为20-50ng/mL)相比时,预期未治疗的CKD小鼠表现出血清无机磷的显著增加(pi),PTH和FGF23水平增加,但1,25$(OH)_2$-维生素D水平降低和较低的PPi水平(~0.5μM)。相反,预期治疗的CKD小鼠显示出PPi水平升高(~4-5μM),其预期高于在未治疗的CKD小鼠中发现的PPi水平(~0.5μM)。因此,普通技术人员可以通过观察一个或多个因素来确定基于载体(vector)的ENPP1或ENPP3治疗慢性肾脏疾病的疗效,这些因素包括组织学分析显示的肾脏和冠状动脉软组织钙化减少(25%、或50%、或70%、或90%或100%)、血清PPi水平升高、维生素D水平正常化、FGF23水平降至正常范围、血液分析PTH水平正常化、存活率增加以及随着体重增加而观察到的尿尿素和肌酸增加所观察到的肾功能改善。

[0830] 人类受试对象的治疗:

[0831] 通过提供含pH 7.4下1X PBS中5×10^{11}至$5\times10^{15vg/kg}$的静脉注射来治疗患有CKD的人类患者,在一些实施方案中,能够递送和表达ENPP1或ENPP3的每个受试对象大约为在pH 7.4的1X PBS中提供大约1×10^{12}至1×10^{15}Vg/kg的静脉注射。通过如针对小鼠模型所讨论的周期性血液和尿液测试来监测上述一种或多种参数,观察CKD治疗成功。取而代之的是需要肾切片或动脉组织染色的组织学分析,这在活体患者中是不可行的,而是使用本领域中常见的非侵入性可视化技术,如CT扫描、超声或静脉肾盂造影,以响应基于载体(vector)的递送和表达ENPP1或ENPP3,可视化CKD患者中钙化的存在和钙化的减少。静脉肾盂造影术是使用用作染料的造影剂来帮助使泌尿道可视化并检测肾钙化的存在的X射线检查。计算机断层摄影是使用X射线技术来描绘身体的内部结构(例如泌尿道)的无创成像技术。CT扫描可见肾脏钙化。CT扫描从身体周围的不同角度收集X射线图像以产生身体内部结构和器官的详细横截面图像以及三维图像。CT扫描也可用于动脉中以检测治疗后钙化的存在和随后的减少。计算机分析透过身体的辐射以重构内部结构和器官的图像。

[0832] 具有可视化软组织钙化、心脏钙化、心肌梗死的技能的医生通过施用表达人ENPP1或人ENPP3的AAV病毒体对患有CKD的受试对象进行治疗。医生施用递送hENPP1或hENPP3构建体并在诱导型启动子控制下表达相应蛋白的病毒颗粒。因此,医师可选择基于症状改善的速率和程度来控制剂量(所表达的hENPP1或hENPP3的量)。本领域技术人员通过观察一种或多种阳性症状观察到成功的治疗,阳性症状例如肾功能改善,尿肌酸水平改善(尿液中的正常肌酸水平男性为40-278mg/dL,女性为29-226mg/dL)和尿液-尿素水平改善(成人尿液中的正常尿素水平为26-43g/24h),正常血清-肌酸水平(正常血清肌酸酐范围女性为0.6-1.1mg/dL,男性为0.7-1.3mg/dL),正常维生素D水平(20ng/ml-50ng/mL被认为适合健康人。小于12ng/mL的水平表示维生素D缺乏),正常血尿素氮水平(健康成人的BUN水平为7-20mg/dL),体重增长,血清PPi水平增加(至少约4-5μm),通过无创技术如CT或超声扫描可视化的动脉组织钙化减少(25%、或50%、或70%、或90%或100%减少)和或肾小管钙化减少。

[0833] 实施例5——使用表达ENPP1或ENPP3的病毒载体(vector)治疗GACI

[0834] 以下实施例提供表达ENPP1或ENPP3的AAV,其预期有效治疗血管钙化和与GACI相关的症状。为了说明的目的在实施例中使用ENPP1-Fc和ENPP3-Fc并且通过使用本发明的其他ENPP1或ENPP3融合体可以获得类似结果。

[0835] 根据实施例1制备表达ENPP1-Fc和ENPP3-Fc蛋白的AAV病毒体,并对Enpp1 $^{asj/asj}$小鼠施用(其是婴儿全身性动脉钙化的模型)(Li等人,2013,《疾病模型与机制》(Disease Models&Mech.),6(5):1227-35)。用ENPP1和ENPP3治疗六组小鼠。

[0836] 对照队列:在该实验中,作为对照组的第一队列ENPP1 wt小鼠注射包括空载体(vector)的AAV颗粒,作为对照组的第二队列Enpp1 $^{asj/asj}$小鼠注射包括空载体(vector)的AAV颗粒。

[0837] ENPP1处理的小鼠队列:第三队列ENPP1 ^{wt}小鼠注射工程化以表达ENPP1-Fc蛋白的AAV颗粒,第四队列Enpp1 $^{asj/asj}$小鼠注射工程化以表达ENPP1-Fc蛋白的AAV颗粒。

[0838] ENPP3处理的小鼠队列:第五队列ENPP1 ^{wt}小鼠注射工程化以表达ENPP3-Fc蛋白的AAV颗粒,第六队列Enpp1 $^{asj/asj}$小鼠注射工程化以表达ENPP3-Fc蛋白的AAV颗粒。用常规饲料喂养野生型小鼠,用高磷酸盐Teklad饮食饲养Enpp1 $^{asj/asj}$小鼠。

[0839] 载体(vector)注射:2周龄后,所有小鼠接受约1×10^{12}至1×10^{15}vg/kg的眶后注射

或尾静脉注射,优选每只小鼠在PBS pH 7.4中1×10^{13}至1×10^{14}vg/kg。注射的载体(vector)是空的"无效的"(对照组)或携带NPP1或NPP3基因(研究组)。

[0840] 测定:如实施例3和4所述,对每个队列的肾脏组织学、PPi水平和血尿参数,如FGF-23水平、维生素D、甲状旁腺激素(PTH)水平、血清/血尿素水平、血尿素氮(BUN)水平、血清/血液肌酸水平和血浆焦磷酸(PPi)水平)进行分析。

[0841] 结果:未治疗的Enpp1 $^{asj/asj}$小鼠通常表现出体重降低和死亡率增加。相反,用表达ENPP1蛋白或ENPP3蛋白的AAV治疗的Enpp1 $^{asj/asj}$小鼠的体重有望增加,接近正常WT小鼠的体重范围。

[0842] 预期用空载体(vector)处理的Enpp1 $^{asj/asj}$小鼠在其心脏、主动脉和冠状动脉中显示钙化,并且在右心室的游离壁中显示心肌梗塞的组织学证据,显示冠状动脉、心脏、升主动脉和降主动脉的钙化,在冠状动脉钙化区域附近的心肌组织中显示心肌细胞坏死和心肌纤维化。相反,预期用表达ENPP1-Fc或ENPP3-Fc的AAV处理的Enpp1 $^{asj/asj}$动物在组织学或尸检显微CT上显示不存在心脏、动脉或主动脉钙化。使用空载体(vector)治疗的Enpp1 $^{asj/asj}$小鼠也显示出以肾髓质为中心的钙化,以及大量的、广泛的钙化,以髓质为中心,并延伸到肾皮质。相反,预期根据本发明用ENPP1或ENPP3处理的Enpp1 $^{asj/asj}$小鼠显示出小管腔和软组织脉管系统中肾矿物质沉积物的减少或缺乏,组织学类似于健康野生型小鼠的组织学。

[0843] 除了存活率、每日动物重量和终末组织学之外,通过尸检后高分辨率显微CT扫描对血管钙化、血浆PPi浓度和99mTc PPi(99mPYP)摄取成像以评估治疗反应。WT或经治疗(表达ENPP1或ENPP3的载体(vector))的Enpp1 $^{asj/asj}$通过显微CT预计都不会有任何血管钙化,相比之下,未治疗(空载体(vector))Enpp1 $^{asj/asj}$队列的主动脉、冠状动脉和心脏预计会有明显的钙化。此外,预期治疗的(表达ENPP1或ENPP3的载体(vector))Enpp1 $^{asj/asj}$动物的血清PPi浓度(5.2μM)升高至WT水平(4.4μM)并且显著高于未治疗的enpp1asj/asj水平(0.5μM)。

[0844] 99mPYP是通常用于心脏成像和骨重建的成像剂。它对异常高骨重建活性的区域敏感,因为它位于羟磷灰石表面,然后可以被破骨细胞吸收。与治疗的Enpp1 $^{asj/asj}$动物相比,未治疗的Enpp1 $^{asj/asj}$动物的每周系列成像预期在头部显示出更大的99mPYP摄取。在含有空载体(vector)或表达ENPP1的载体(vector)的病毒颗粒给药后的第30-35天和第50-65天进行测量。预期这些实验组的比较显示ENPP1-Fc或ENPP3-Fc治疗使GACI小鼠中的99mPYP摄取恢复至WT水平,表明ENPP1-Fc或ENPP3-Fc治疗能够通过升高胞外PPi浓度来消除Enpp1 $^{asj/asj}$小鼠中的未调节组织、触须和颅骨矿化。这些观察结果预期显示给予含有表达ENPP1-Fc或ENPP3-Fc的载体(vector)的病毒颗粒的Enpp1 $^{asj/asj}$小鼠没有血管钙化并且具有正常血浆PPi浓度。

[0845] 与健康野生型小鼠(PP正常水平约为2-4μM;PTH约为10-65ng/L;FGF23中位数为13RU/ml,正常FGF23范围为5-210RU/ml;正常维生素D水平为20-50ng/mL)相比,未治疗的Enpp1 $^{asj/asj}$小鼠的血清无机磷(pi)显著升高,PTH和FGF23水平升高,1,25$(OH)_2$-维生素D水平下降,PPi水平降低(~0.5μM)。相反,预期治疗的Enpp1 $^{asj/asj}$小鼠显示出PPi水平升高(~4-5μM),其预期高于在未治疗的CKD小鼠中发现的PPi水平(~0.5μM)。因此,普通技术人员可以通过观察一个或多个因素来确定基于载体(vector)的ENPP1或ENPP3治疗GACI的疗

效,这些因素包括组织学分析显示的肾脏和冠状动脉软组织钙化减少(25%、或50%、或70%、或90%或100%)、血清PPi水平升高、维生素D水平正常化、FGF23水平降至正常范围、血液分析PTH水平正常化、存活率增加以及随着体重增加而观察到的尿尿素和肌酸增加所观察到的肾功能改善。

[0846] 人类受试对象的治疗

[0847] 通过提供含pH 7.4下1X PBS中5×10^{11}至$5\times10^{15vg/kg}$的静脉注射来治疗患有GACI的人类患者,在一些实施方案中,能够递送和表达hENPP1或hENPP3的每个受试对象大约为在pH 7.4的1X PBS中提供大约1×10^{12}至1×10^{15}Vg/kg的静脉注射。通过如针对小鼠模型所讨论的周期性血液和尿液测试来监测上述一种或多种参数,观察GACI治疗成功。代替需要对肾脏切片或动脉组织染色的组织学分析,其在活患者中不可行,取而代之的是使用如实施例4中讨论的非侵入性可视化技术。

[0848] 具有可视化软组织钙化、心脏钙化、心肌梗死的技能的医生通过施用表达hENPP1或hENPP3的AAV病毒体对患有GACI的受试对象进行治疗。医生施用递送编码hENPP1或hENPP3的构建体的病毒颗粒,载体(vector)在诱导型启动子的控制下表达ENPP蛋白。因此,医师可基于症状改善的速率和程度来控制剂量(所表达的hENPP1或hENPP3的量)。本领域的医学专业人员通过观察一个或多个阳性症状观察到成功的治疗,如正常的维生素D水平(认为20ng/ml到50ng/mL对健康人来说是足够的。水平低于12ng/mL表示缺乏维生素D),正常血尿素氮水平(健康成人的BUN水平为7-20mg/dL),体重增长,血清PPi水平增加(至少约4-5μm),动脉组织钙化减少(25%、或50%、或70%、或90%或100%减少)和/或通过无创技术如CT或超声扫描可视化的肾小管钙化减少。

[0849] 实施例6——使用表达ENPP1或ENPP3的病毒载体(vector)治疗PXE

[0850] 以下实施例提供表达ENPP1或ENPP3的AAV,其预期有效治疗血管钙化和与PXE相关的症状。为了说明的目的在实施例中使用ENPP1-Fc和ENPP3-Fc并且通过使用本发明的其他ENPP1或ENPP3融合体可以获得类似结果。

[0851] 根据实施例1制备表达ENPP1-Fc蛋白和ENPP3-Fc蛋白的AAV病毒体,并对$ABCC6^{asj/asj}$小鼠施用(其是弹性纤维假黄瘤的模型;Jiang等人,2007,《皮肤病学研究杂志》(J.Invest.Derm.)127(6):1392-4102)。用ENPP1和ENPP3治疗六组小鼠。

[0852] 对照队列:在该实验中,作为对照组的第一队列ENPP1 wt小鼠注射包括空载体(vector)的AAV颗粒,作为对照组的第二队列$ABCC6^{-/-}$小鼠注射包括空载体(vector)的AAV颗粒。

[0853] ENPP1处理的小鼠队列:第三队列$ENPP1^{wt}$小鼠注射工程化以表达ENPP1-Fc蛋白的AAV颗粒,第四队列$ABCC6^{-/-}$小鼠注射工程化以表达ENPP1-Fc蛋白的AAV颗粒。

[0854] ENPP3处理的小鼠队列:第五队列$ENPP1^{wt}$小鼠注射工程化以表达ENPP3-Fc蛋白的AAV颗粒,第六队列$ABCC6^{-/-}$小鼠注射工程化以表达ENPP3-Fc蛋白的AAV颗粒。用常规饲料喂养野生型小鼠,用高磷酸盐Teklad饮食饲养$ABCC6^{-/-}$小鼠。

[0855] 载体(vector)注射:2周龄后,所有小鼠接受约1×10^{12}至1×10^{15}vg/kg的眶后注射或尾静脉注射,优选每只小鼠在PBS pH 7.4中1×10^{13}至1×10^{14}vg/kg。注射的载体(vector)是空的"无效的"(对照组)或携带NPP1或NPP3基因(研究组)。

[0856] 测定:如实施例3和4所述,对每个队列的肾脏组织学、PPi水平和血尿参数,如FGF-

23水平、维生素D、甲状旁腺激素(PTH)水平、血清/血尿素水平、血尿素氮(BUN)水平、血清/血液肌酸水平和血浆焦磷酸(PPi)水平)进行分析。

[0857] 结果:未治疗的ABCC6-/-j小鼠通常表现出体重降低和死亡率增加。相反,用表达ENPP1或ENPP3蛋白的AAV治疗的ABCC6-/-小鼠的体重有望增加,接近正常WT小鼠的体重范围。预期用空载体(vector)处理的ABCC6-/-小鼠在其心脏、主动脉和冠状动脉中显示钙化,并且在右心室的游离壁中显示心肌梗塞的组织学证据,显示冠状动脉、心脏、升主动脉和降主动脉的钙化,在冠状动脉钙化区域附近的心肌组织中显示心肌细胞坏死和心肌纤维化。相反,预期用表达ENPP1-Fc或ENPP3-Fc的载体(vector)处理的ABCC6-/-动物在组织学或尸检显微CT上显示不存在心脏、动脉或主动脉钙化。使用空载体(vector)治疗的$Enpp1^{asj/asj}$小鼠也显示出以肾髓质为中心的钙化,以及大量的、广泛的钙化,以髓质为中心,并延伸到肾皮质。相反,预期用基于病毒载体(vector)的ENPP1或ENPP3表达处理的$Enpp1^{asj/asj}$小鼠显示出小管腔和软组织脉管系统中肾矿物质沉积物的减少或缺乏,组织学类似于健康野生型小鼠的组织学。

[0858] 除了存活率、每日动物重量和终末组织学之外,通过尸检后高分辨率显微CT扫描对血管钙化、血浆PPi浓度成像评估治疗反应。WT或经治疗(表达ENPP1的载体(vector))的$ABCC6^{-/-}$通过显微CT预计都不会有任何血管钙化,相比之下,未治疗(空载体(vector))$ABCC6^{-/-}$队列的主动脉、冠状动脉和心脏预计可见明显的钙化。此外,预期治疗的(表达ENPP1的载体(vector))$ABCC6^{-/-}$动物的血清PPi浓度(5.2μM)升高至WT水平(4.4μM)并且显著高于未治疗的$ABCC6^{-/-}$水平(0.5μM)。

[0859] 与健康野生型小鼠(PP正常水平约为2-4μM;PTH约为10-65ng/L;FGF23中位数为13RU/ml,正常FGF23范围为5-210RU/ml;正常维生素D水平为20-50ng/mL)相比,未治疗的$ABCC6^{-/-}$鼠的血清无机磷(pi)显著升高,PTH和FGF23水平升高,1,25$(OH)_2$-维生素D水平下降,PPi水平降低(~0.5μM)。相反,预期治疗的$ABCC6^{-/-}$小鼠显示出PPi水平升高(~4-5μM),其预期高于在未治疗的$ABCC6^{-/-}$小鼠中发现的PPi水平(~0.5μM)。因此,普通技术人员可以通过观察一个或多个因素来确定基于载体(vector)的ENPP1或ENPP3治疗PXE的疗效,这些因素包括组织学分析显示的肾脏和冠状动脉软组织钙化减少(25%、或50%、或70%、或90%或100%)、血清PPi水平升高、维生素D水平正常化、FGF23水平降至正常范围、血液分析PTH水平正常化、存活率增加以及随着体重增加而观察到的尿尿素和肌酸增加所观察到的肾功能改善。

[0860] 人类受试对象的治疗:

[0861] 通过提供含pH 7.4下1X PBS中5×10^{11}至$5\times10^{15vg/kg}$的静脉注射来治疗患有PXE的人类患者,在一些实施方案中,能够递送和表达ENPP1或ENPP3的每个受试对象大约为在pH 7.4的1X PBS中提供大约1×10^{12}至1×10^{15}Vg/kg的静脉注射。通过如针对小鼠模型所讨论的周期性血液和尿液测试来监测上述一种或多种参数,观察PXE治疗成功。代替需要对肾脏切片或动脉组织染色的组织学分析,其在活患者中不可行,取而代之的是使用如实施例4中讨论的非侵入性可视化技术。

[0862] 具有可视化软组织钙化、心脏钙化、心肌梗死的技能的医生通过施用表达ENPP1或ENPP3的AAV病毒体对患有PXE的受试对象进行治疗。医生还可以使用递送ENPP1或ENPP3的构建体并在诱导型启动子控制下表达相应蛋白的病毒颗粒。因此,医师可选择基于症状改

善的速率和程度来控制剂量(所表达的ENPP1或ENPP3的量)。本领域的医学专业人员通过观察一个或多个阳性症状容易地推断成功的治疗和合适的剂量,如正常的维生素D水平(认为20ng/ml到50ng/mL对健康人来说是足够的。水平低于12ng/mL表示缺乏维生素D),血管样条纹的大小和/或数量消失或缩小,视网膜出血减少或没有,正常血尿素氮水平(健康成人的BUN水平为7-20mg/dL),体重增长,血清PPi水平增加(至少约4-5μm),动脉组织、结缔组织钙化减少(25%、或50%、或70%、或90%或100%减少)和/或通过无创技术如CT或超声扫描可视化的肾小管钙化减少。

[0863] 实施例7——使用表达人ENPP1或ENPP3的病毒载体(vector)治疗OPLL

[0864] 以下实施例提供表达人ENPP1或ENPP3的AAV,其预期有效治疗血管钙化和与PXE相关的症状。为了说明的目的在实施例中使用ENPP1-Fc和ENPP3-Fc融合体并且通过使用本发明的其他ENPP1或ENPP3融合体可以获得类似结果。

[0865] 根据实施例1制备表达ENPP1-Fc蛋白或ENPP3-Fc蛋白的AAV病毒体,并对足趾步行(Tip toe walking,ttw)小鼠施用(其是用于后纵韧带骨化的模型;(Okawa等人,1998,《自然遗传学》(Nature Genetics)19(3):271-3;Nakamura等人,1999,《人类遗传学》(Human Genetics)104(6):492-7)。用ENPP1和ENPP3治疗六组小鼠。

[0866] 对照队列:在该实验中,作为对照组的第一队列ENPP1 wt小鼠注射包括空载体(vector)的AAV颗粒,作为对照组的第二队列ttw小鼠注射包括空载体(vector)的AAV颗粒。

[0867] ENPP1处理的小鼠队列:第三队列ENPP1 ^{wt}小鼠注射工程化以表达ENPP1-Fc蛋白的AAV颗粒,第四队列ttw小鼠注射工程化以表达ENPP1-Fc蛋白的AAV颗粒。

[0868] ENPP3处理的小鼠队列:第五队列ENPP1 ^{wt}小鼠注射工程化以表达ENPP3-Fc蛋白的AAV颗粒,第六队列ttw小鼠注射工程化以表达ENPP3-Fc蛋白的AAV颗粒。用常规饲料喂养野生型小鼠,用高磷酸盐Teklad饮食饲养ttw小鼠。

[0869] 载体(vector)注射:2周龄后,所有小鼠接受约1×10^{12}至1×10^{15}vg/kg的眶后注射或尾静脉注射,优选每只小鼠在PBS pH 7.4中1×10^{13}至1×10^{14}vg/kg。注射的载体(vector)是空的"无效的"(对照组)或携带NPP1或NPP3基因(研究组)。

[0870] 测定:如实施例3和4所述,对每个队列的肾脏组织学、PPi水平和血尿参数,如FGF-23水平、维生素D、甲状旁腺激素(PTH)水平、血清/血尿素水平、血尿素氮(BUN)水平、血清/血液肌酸水平和血浆焦磷酸(PPi)水平)进行分析。

[0871] 结果:未治疗的ttw小鼠一般表现为体重减轻、脊柱增厚、嗜睡和死亡率增加。相反,用表达ENPP1或ENPP3蛋白的AAV治疗的ttw小鼠的体重有望增加,接近正常WT小鼠的体重范围,警觉性正常,脊柱厚度减少,接近野生型小鼠。预期用空载体(vector)处理的ttw小鼠在其心脏、主动脉和冠状动脉中显示钙化,并且在右心室的游离壁中显示心肌梗塞的组织学证据,显示冠状动脉、心脏、升主动脉和降主动脉的钙化,在冠状动脉钙化区域附近的心肌组织中显示心肌细胞坏死和心肌纤维化。相反,预期用表达ENPP1-Fc或ENPP3-Fc的载体(vector)处理的ttw动物在组织学或尸检显微CT上显示不存在心脏、动脉或主动脉钙化。使用空载体(vector)治疗的ttw小鼠也显示出以肾髓质为中心的钙化,以及大量的、广泛的钙化,以髓质为中心,并延伸到肾皮质。相反,预期用基于病毒载体(vector)的ENPP1或ENPP3表达处理的ttw小鼠显示出小管腔和软组织脉管系统中肾矿物质沉积物的减少或缺乏,脊柱钙化减少,组织学类似于健康野生型小鼠的组织学。

[0872] 除了存活率、每日动物重量和终末组织学之外,通过尸检后高分辨率显微CT扫描对血管钙化、血浆PPi浓度成像评估治疗反应。WT或经治疗(表达ENPP1的载体(vector))的ttw通过显微CT预计都不会有任何血管钙化,相比之下,未治疗(空载体(vector))ttw队列的主动脉、冠状动脉和心脏预计可见明显的钙化。此外,预期治疗的(表达ENPP1的载体(vector))ttw动物的血清PPi浓度(5.2μM)升高至WT水平(4.4μM)并且显著高于未治疗的ttw水平(0.5μM)。

[0873] 与健康野生型小鼠(PP正常水平约为2-4μM;PTH约为10-65ng/L;FGF23中位数为13RU/ml,正常FGF23范围为5-210RU/ml;正常维生素D水平为20-50ng/mL)相比,未治疗的ttw小鼠的血清无机磷(pi)显著升高,PTH和FGF23水平升高,1,25(OH)$_2$-维生素D水平下降,PPi水平降低(~0.5μM)。相反,预期治疗的ttw小鼠显示出PPi水平升高(~4-5μM),其预期高于在未治疗的ttw小鼠中发现的PPi水平(~0.5μM)。因此,普通技术人员可以通过观察一个或多个因素来确定基于载体(vector)的ENPP1或ENPP3治疗OPLL的疗效,这些因素包括组织学分析显示的肾脏和冠状动脉软组织钙化减少(25%、或50%、或70%、或90%或100%)、血清PPi水平升高、维生素D水平正常化、FGF23水平降至正常范围、血液分析PTH水平正常化、存活率增加以及随着体重增加而观察到的尿尿素和肌酸增加所观察到的肾功能改善。

[0874] 人类受试对象的治疗:

[0875] 通过提供含pH 7.4下1X PBS中5×10^{11}至$5\times10^{15vg/kg}$的静脉注射来治疗患有OPLL的人类患者,在一些实施方案中,能够递送和表达hENPP1或hENPP3的每个受试对象大约为在pH 7.4的1X PBS中提供大约1×10^{12}至1×10^{15}Vg/kg的静脉注射。通过如针对小鼠模型所讨论的周期性血液和尿液测试来监测上述一种或多种参数,观察OPLL治疗成功。代替需要对肾脏切片或动脉组织染色的组织学分析,其在活患者中不可行,取而代之的是使用如实施例4中讨论的非侵入性可视化技术。

[0876] 具有可视化软组织钙化、心脏钙化、心肌梗死的技能的医生通过施用表达hENPP1或hENPP3的AAV病毒体对患有OPLL的受试对象进行治疗。在一些实施方案中,医生使用递送hENPP1或hENPP3构建体并在诱导型启动子控制下表达相应蛋白的病毒颗粒。因此,医师可选择基于症状改善的速率和程度来控制剂量(所表达的hENPP1或hENPP3的量)。本领域的医学专业人员通过观察一个或多个阳性症状容易地推断成功的治疗和合适的剂量,如正常的维生素D水平(认为20ng/ml到50ng/mL对健康人来说是足够的。水平低于12ng/mL表示缺乏维生素D),正常血尿素氮水平(健康成人的BUN水平为7-20mg/dL),体重增长,血清PPi水平增加(至少约4-5μm),动脉组织钙化减少(25%、或50%、或70%、或90%或100%减少),脊柱厚度减少,疼痛感觉减轻,通过无创技术如CT、磁共振成像(MRI)或超声扫描可视化的椎管狭窄减少。

[0877] 实施例8——使用表达ENPP1或ENPP3的病毒载体(vector)治疗骨量减少和/或骨软化

[0878] 以下实施例提供表达ENPP1或ENPP3的AAV,其预期有效治疗与骨量减少和/或骨软化相关的症状。为了说明的目的在实施例中使用ENPP1-Fc和ENPP3-Fc并且通过使用本发明的其他ENPP1或ENPP3融合体可以获得类似结果。

[0879] 根据实施例1制备表达ENPP1-Fc蛋白或ENPP3-Fc蛋白的AAV病毒体,并将其施用于足趾步行(ttw)小鼠(其是骨关节炎的小鼠模型(Bertrand等人,2012,《风湿病年鉴》

(Annals Rheum.Diseases)71(7):1249-53))。用ENPP1和ENPP3治疗六组小鼠。使用ENPP1敲除小鼠(ENPP1^{KO})重复类似的实验,ENPP1敲除小鼠也用作骨量减少的模型。(Mackenzie等人,2012,《科学公共图书馆综合》(PloS one)7(2):e32177)除GACI外。

[0880] 对照队列:在该实验中,作为对照组的第一队列ENPP1 wt小鼠注射包括空载体(vector)的AAV颗粒,作为对照组的第二队列ttw(或ENPP1^{KO})小鼠注射包括空载体(vector)的AAV颗粒。

[0881] ENPP1处理的小鼠队列:第三队列ENPP1 ^{wt}小鼠注射工程化以表达ENPP1-Fc蛋白的AAV颗粒,第四队列ttw小鼠(或ENPP1^{KO})注射工程化以表达ENPP1-Fc蛋白的AAV颗粒。

[0882] ENPP3处理的小鼠队列:第五队列ENPP1 ^{wt}小鼠注射工程化以表达ENPP3-Fc蛋白的AAV颗粒,第六队列ttw(或ENPP1^{KO})小鼠注射工程化以表达ENPP3-Fc蛋白的AAV颗粒。用常规饲料喂养野生型小鼠,用高磷酸盐Teklad饮食饲养ttw(或ENPP1^{KO})小鼠。

[0883] 载体(vector)注射:2周龄后,所有小鼠接受约1×10^{12}至1×10^{15}vg/kg的眶后注射或尾静脉注射,优选每只小鼠在PBS pH 7.4中1×10^{13}至1×10^{14}vg/kg。注射的载体(vector)是空的"无效的"(对照组)或携带NPP1或NPP3基因(研究组)。

[0884] 测定:如实施例3和4所述,对每个队列的肾脏组织学、PPi水平和血尿参数,如FGF-23水平、维生素D、甲状旁腺激素(PTH)水平、血清/血尿素水平、血尿素氮(BUN)水平、血清/血液肌酸水平和血浆焦磷酸(PPi)水平)进行分析。

[0885] 组织学、组织形态测量和显微CT:按照实施例3中描述的方案进行骨分析。

[0886] 骨生物力学测试:按照实施例3中描述的方案进行骨分析。

[0887] 结果:未治疗的ttw(或ENPP1^{KO})小鼠与野生型相比通常表现出体重降低、嗜睡、皮质骨厚度和松质骨体积减少、软骨和韧带钙化、长骨如股骨和胫骨中的骨密度降低以及死亡率增加。相反,预期用表达ENPP1蛋白或ENPP3蛋白的AAV治疗的ttw(或ENPP1^{KO})小鼠显示体重增加,接近正常WT小鼠的体重范围,警觉性正常、骨矿物质密度增加、皮质骨厚度和松质骨体积改善、骨强度和骨延展性增加。预期用空载体(vector)处理的ttw(或ENPP1^{KO})小鼠在其心脏、主动脉和冠状动脉中显示钙化,并且在右心室的游离壁中显示心肌梗塞的组织学证据,显示冠状动脉、心脏、升主动脉和降主动脉的钙化,在冠状动脉钙化区域附近的心肌组织中显示心肌细胞坏死和心肌纤维化。相反,预期用表达ENPP1-Fc或ENPP3-Fc的载体(vector)处理的ttw(或ENPP1^{KO})动物在组织学或尸检显微CT上显示不存在心脏、动脉或主动脉钙化。使用空载体(vector)治疗的ttw(或ENPP1^{KO})小鼠也显示出以肾髓质为中心的钙化,以及大量的、广泛的钙化,以髓质为中心,并延伸到肾皮质。相反,预期用基于病毒载体(vector)的ENPP1或ENPP3表达处理的ttw(或ENPP1^{KO})小鼠显示出小管腔和软组织脉管系统中肾矿物质沉积物的减少或缺乏,脊柱钙化减少,组织学类似于健康野生型小鼠的组织学。

[0888] 除了存活率、每日动物重量和终末组织学之外,通过尸检后高分辨率显微CT扫描对血管钙化、血浆PPi浓度成像评估治疗反应。WT或经治疗(表达ENPP1的载体(vector))的ttw(或ENPP1^{KO})通过显微CT预计都不会有任何血管钙化,相比之下,未治疗(空载体(vector))ttw(或ENPP1^{KO})队列的主动脉、冠状动脉和心脏预计可见明显的钙化。此外,预期治疗的(表达ENPP1的载体(vector))ttw(或ENPP1^{KO})动物的血清PPi浓度(5.2μM)升高至WT水平(4.4μM)并且显著高于未治疗的ttw(或ENPP1^{KO})水平(0.5μM)。

[0889] 与健康野生型小鼠(PP正常水平约为2-4μM;PTH约为10-65ng/L;FGF23中位数为

13RU/ml,正常FGF23范围为5-210RU/ml;正常维生素D水平为20-50ng/mL)相比,未治疗的ttw(或$ENPP1^{KO}$)小鼠的血清无机磷(pi)显著升高,PTH和FGF23水平升高,1,25(OH)$_2$-维生素D水平下降,PPi水平降低(~0.5μM)。相反,预期治疗的ttw(或$ENPP1^{KO}$)小鼠显示出PPi水平升高(~4-5μM),其预期高于在未治疗的ttw(或$ENPP1^{KO}$)小鼠中发现的PPi水平(~0.5μM)。因此,普通技术人员可以通过观察一个或多个因素来确定基于载体(vector)的ENPP1或ENPP3治疗骨量减少、骨软化或骨关节炎的疗效,这些因素包括组织学分析显示的肾脏和冠状动脉软组织钙化减少(25%、或50%、或70%、或90%或100%)、血清PPi水平升高、维生素D水平正常化、FGF23水平降至正常范围、血液分析PTH水平正常化、长骨强度改善、骨密度增加、皮质骨厚度和松质骨体积改善、存活率增加以及随着体重增加而观察到的尿尿素和肌酸增加所观察到的肾功能改善。

[0890] 人类受试对象的治疗:

[0891] 通过提供含pH 7.4下1X PBS中5×10^{11}至$5\times10^{15vg/kg}$的静脉注射来治疗患有骨量减少、骨软化或骨关节炎的人类患者,在一些实施方案中,能够递送和表达hENPP1或hENPP3的每个受试对象大约为在pH 7.4的1X PBS中提供大约1×10^{12}至1×10^{15}Vg/kg的静脉注射。通过如针对小鼠模型所讨论的周期性骨强度、骨密度血液和尿液测试来监测上述一种或多种参数,观察骨量减少、骨软化或骨关节炎治疗成功。代替需要对肾脏切片或动脉组织染色的组织学分析,其在活患者中不可行,取而代之的是使用如实施例4中讨论的非侵入性可视化技术。

[0892] 类似地,使用双能量x射线吸收测定法(DXA)或外周双能量x射线吸收测定法(pDXA)或定量超声(QUS)或外周定量计算机断层成像术(pQCT)对患者进行周期性骨密度测量。从这些方法之一获得的骨密度得分提供了治疗后获得的状况和进展的指标。-1.0或更高的T值被认为是正常骨密度,-1.0和-2.5之间的T值表明存在骨量减少,而-2.5或更低的T值表明存在骨质疏松。预期在用本发明的ENPP1或ENPP3治疗的患者中T值逐渐改善。

[0893] 具有可视化软组织钙化、心脏钙化、骨密度观察技能的医生通过表达hENPP1或hENPP3的AAV病毒体给药治疗患有骨量减少或骨关节炎的受试对象。在一些实施方案中,医生使用递送hENPP1或hENPP3构建体并在诱导型启动子控制下表达相应蛋白的病毒颗粒。因此,医师可选择基于症状改善的速率和程度来控制剂量(所表达的hENPP1或hENPP3的量)。本领域的医学专业人员通过观察一个或多个阳性症状容易地推断成功的治疗和合适的剂量,如正常的维生素D水平(认为20ng/ml到50ng/mL对健康人来说是足够的。水平低于12ng/mL表示缺乏维生素D),正常骨密度(T值≥-1),正常血尿素氮水平(健康成人的BUN水平为7-20mg/dL),体重增长,血清PPi水平增加(至少约4-5μm),动脉组织钙化减少(25%、或50%、或70%、或90%或100%减少),通过无创技术如CT、磁共振成像(MRI)或超声扫描可视化的骨强度改善。

[0894] 实施例9——使用表达ENPP1或ENPP3的病毒载体(vector)治疗ADHR-2或ARHR-2和/或XLH

[0895] 以下实施例提供表达ENPP1或ENPP3的AAV,其预期有效治疗与ADHR-2或ARHR-2或XLH相关的症状。为了说明的目的在实施例中使用ENPP1-Fc和ENPP3-Fc并且通过使用本发明的其他ENPP1或ENPP3融合体可以获得类似结果。

[0896] 根据实施例1制备表达ENPP1-Fc蛋白或ENPP3-Fc蛋白的AAV病毒体,并将其施用至

X连锁低磷酸血症(XLH)的HYP小鼠模型;(Liang等人,2009,《国际钙化组织》(Calcif.Tissue Int.)85(3):235-46)。用ENPP1和ENPP3治疗六组小鼠。使用ENPP1年龄强化的关节小鼠()重复类似的实验,ENPP1年龄强化的关节小鼠也用作ARHR-2的模型。(《美国人类遗传学》(Am J Hum Genet.)2010Feb 12;86(2):273-278.)除了GACI之外。

[0897] 对照队列:在该实验中,作为对照组的第一队列ENPP1 wt小鼠注射包括空载体(vector)的AAV颗粒,作为对照组的第二队列HYP(或$ENPP1^{asj/asj}$)小鼠注射包括空载体(vector)的AAV颗粒。

[0898] ENPP1处理的小鼠队列:第三队列$ENPP1^{wt}$小鼠注射工程化以表达ENPP1-Fc蛋白的AAV颗粒,第四队列HYP(或$ENPP1^{asj/asj}$)小鼠注射工程化以表达ENPP1-Fc蛋白的AAV颗粒。

[0899] ENPP3处理的小鼠队列:第五队列$ENPP1^{wt}$小鼠注射工程化以表达ENPP3-Fc蛋白的AAV颗粒,第六队列HYP(或$ENPP1^{asj/asj}$)小鼠注射工程化以表达ENPP3-Fc蛋白的AAV颗粒。用常规饲料喂养野生型小鼠,用高磷酸盐Teklad饮食饲养HYP(或$ENPP1^{asj/asj}$)小鼠。

[0900] 载体(vector)注射:2周龄后,所有小鼠接受约1×10^{12}至1×10^{15}vg/kg的眶后注射或尾静脉注射,优选每只小鼠在PBS pH 7.4中1×10^{13}至1×10^{14}vg/kg。注射的载体(vector)是空的"无效的"(对照组)或携带NPP1或NPP3基因(研究组)。

[0901] 测定:如实施例3和4所述,对每个队列的肾脏组织学、PPi水平和血尿参数,如FGF-23水平、维生素D、甲状旁腺激素(PTH)水平、血清/血尿素水平、血尿素氮(BUN)水平、血清/血液肌酸水平和血浆焦磷酸(PPi)水平)进行分析。

[0902] 组织学、组织形态测量和显微CT:按照实施例3中描述的方案进行骨分析。

[0903] 骨生物力学测试:按照实施例3中描述的方案进行骨分析。

[0904] 结果:未治疗的HYP(或$ENPP1^{asj/asj}$)小鼠与野生型相比通常表现出体重降低、嗜睡、皮质骨厚度和松质骨体积减少、软骨和韧带钙化、长骨如股骨和胫骨中的骨密度降低以及死亡率增加。相反,预期用表达ENPP1蛋白或ENPP3蛋白的AAV治疗的HYP(或$ENPP1^{asj/asj}$)小鼠显示体重增加,接近正常WT小鼠的体重范围,警觉性正常、骨矿物质密度增加、皮质骨厚度和松质骨体积改善、骨强度和骨延展性增加。预期用空载体(vector)处理的HYP(或$ENPP1^{asj/asj}$)小鼠在其心脏、主动脉和冠状动脉中显示钙化,并且在右心室的游离壁中显示心肌梗塞的组织学证据,显示冠状动脉、心脏、升主动脉和降主动脉的钙化,在冠状动脉钙化区域附近的心肌组织中显示心肌细胞坏死和心肌纤维化。相反,预期用表达ENPP1-Fc或ENPP3-Fc的载体(vector)处理的HYP(或$ENPP1^{asj/asj}$)小鼠在组织学或尸检显微CT上显示不存在心脏、动脉或主动脉钙化。使用空载体(vector)治疗的HYP(或$ENPP1^{asj/asj}$)小鼠也显示出以肾髓质为中心的钙化,以及大量的、广泛的钙化,以髓质为中心,并延伸到肾皮质。相反,预期用基于病毒载体(vector)的ENPP1或ENPP3表达处理的HYP(或$ENPP1^{asj/asj}$)小鼠显示出小管腔和软组织脉管系统中肾矿物质沉积物的减少或缺乏,脊柱钙化减少,组织学类似于健康野生型小鼠的组织学。

[0905] 除了存活率、每日动物重量和终末组织学之外,通过尸检后高分辨率显微CT扫描对血管钙化、血浆PPi浓度成像评估治疗反应。WT或经治疗(表达ENPP1的载体(vector))的HYP(或$ENPP1^{asj/asj}$)小鼠通过显微CT预计都不会有任何血管钙化,相比之下,未治疗(空载体(vector))HYP(或$ENPP1^{asj/asj}$)队列的主动脉、冠状动脉和心脏预计可见明显的钙化。此外,预期治疗的(表达ENPP1的载体(vector))HYP(或$ENPP1^{asj/asj}$)小鼠的血清PPi浓度(5.2μ

M)升高至WT水平(4.4μM)并且显著高于未治疗的HYP(或ENPP1$^{asj/asj}$)水平(0.5μM)。

[0906] 与健康野生型小鼠(PP正常水平约为2-4μM;PTH约为10-65ng/L;FGF23中位数为13RU/ml,正常FGF23范围为5-210RU/ml;正常维生素D水平为20-50ng/mL)相比,未治疗的HYP(或ENPP1$^{asj/asj}$)小鼠的血清无机磷(pi)显著升高,PTH和FGF23水平升高,1,25(OH)$_2$-维生素D水平下降,PPi水平降低(~0.5μM)。相反,预期治疗的HYP(或ENPP1$^{asj/asj}$)小鼠显示出PPi水平升高(~4-5μM),其预期高于在未治疗的HYP(或ENPP1$^{asj/asj}$)小鼠中发现的PPi水平(~0.5μM)。因此,普通技术人员可以通过观察一个或多个因素来确定基于载体(vector)的ENPP1或ENPP3治疗ADHR-2或ARHR-2或XLH的疗效,这些因素包括组织学分析显示的肾脏和冠状动脉软组织钙化减少(25%、或50%、或70%、或90%或100%)、血清PPi水平升高、维生素D水平正常化、FGF23水平降至正常范围、血液分析PTH水平正常化、长骨强度改善、骨密度增加、皮质骨厚度和松质骨体积改善、存活率增加以及随着体重增加而观察到的尿尿素和肌酸增加所观察到的肾功能改善。

[0907] 人类受试对象的治疗:

[0908] 通过提供含pH 7.4下1X PBS中5×10^{11}至$5\times10^{15vg/kg}$的静脉注射来治疗患有ADHR-2或ARHR-2或XLH的人类患者,在一些实施方案中,能够递送和表达hENPP1或hENPP3的每个受试对象大约为在pH 7.4的1X PBS中提供大约1×10^{12}至1×10^{15}Vg/kg的静脉注射。通过如针对小鼠模型所讨论的周期性骨强度、骨密度血液和尿液测试来监测上述一种或多种参数,观察ADHR-2或ARHR-2或XLH治疗成功。代替需要对肾脏切片或动脉组织染色的组织学分析,其在活患者中不可行,取而代之的是使用如实施例4中讨论的非侵入性可视化技术。

[0909] 类似地,使用双能量x射线吸收测定法(DXA)或外周双能量x射线吸收测定法(pDXA)或定量超声(QUS)或外周定量计算机断层成像术(pQCT)对患者进行周期性骨密度测量。从这些方法之一获得的骨密度得分提供了治疗后获得的状况和进展的指标。-1.0或更高的T值被认为是正常骨密度,-1.0和-2.5之间的T值表明存在骨量减少,而-2.5或更低的T值表明存在骨质疏松。预期在用本发明的ENPP1或ENPP3治疗的患者中T值逐渐改善。

[0910] 具有可视化软组织钙化、心脏钙化、骨密度观察技能的医生通过施用表达hENPP1或hENPP3的AAV病毒体给药治疗患有ADHR-2或ARHR-2或XLH的受试对象。在一些实施方案中,医生使用递送hENPP1或hENPP3构建体并在诱导型启动子控制下表达相应蛋白的病毒颗粒。因此,医师可选择基于症状改善的速率和程度来控制剂量(所表达的hENPP1或hENPP3的量)。本领域的医学专业人员通过观察一个或多个阳性症状容易地推断成功的治疗和合适的剂量,如正常的维生素D水平(认为20ng/ml到50ng/mL对健康人来说是足够的。水平低于12ng/mL表示缺乏维生素D),正常骨密度(T值≥-1),正常血尿素氮水平(健康成人的BUN水平为7-20mg/dL),体重增长,血清PPi水平增加(至少约4-5μm),动脉组织钙化减少(25%、或50%、或70%、或90%或100%减少),通过无创技术如CT、磁共振成像(MRI)或超声扫描可视化的骨强度改善。

[0911] 实施例10——病毒给药后模型小鼠中血浆PPi水平、ENPP1浓度和活性水平的分析。

[0912] 本实验使用三个队列的正常小鼠。每个队列包括五只成年小鼠。将第一队列用作“对照组”,并将盐水溶液注射至对照组。第二队列用作“低剂量组”,低剂量组注射浓度为$1e^{13}$ vg/kg的AAV载体(vector)。第三队列使用“高剂量组”,高剂量组注射浓度为$1e^{14}$ vg/

kg的AAV载体(vector)。图4示意性地示出了从AAV构建体产生病毒颗粒并将包括ENPP1融合蛋白的重组AAV病毒颗粒注射到正常小鼠中的过程。所有组的小鼠在注射后第7天、第28天和第56天取血,以收集血浆和血清。

[0913] 将血液收集到肝素处理的管中。分离血浆,通过Nanosep 30kDa Omega离心过滤器(Pall,OD030C35)过滤除去血小板。将样本在最高速度(~20kg)下在4℃下离心20min。收集流过物并置于干冰上以极速冰冻样本。将样本储存在-80℃下用于以后的测定。

[0914] $$\text{比活度（pmol/min/μg）} = \frac{\text{调整后的}V_{max}^{*}\text{（OD/min）} \times \text{转换系数}^{**}\text{（pmol/OD）}}{\text{酶量（μg）}}$$

[0915] *对底物空白进行调整

[0916] **使用校准标准品4-硝基苯酚(Sigma-Aldrich,货号241326)衍生

[0917] 采集的样本首先进行检测以用比色底物对硝基苯基胸苷5′-单磷酸(Sigma)测定ENPP1活性水平。将血浆样本与1mg/ml对硝基苯基胸苷5′-单磷酸在1％Triton,200mM Tris,pH 8.0缓冲液中孵育1小时。1小时后加入100mM NaOH终止反应,在405nm测定吸光度。通过下列R&D系统公开的测定方案测定重组人ENPP-1的比活性;货号:6136-WN。

[0918] ENPP1活性测定的结果在图5中,并且它们显示注射后ENPP1活性存在剂量依赖性增加。使用正常小鼠血浆作为参比标准来标准化ENPP1活性水平,并使用单向ANOVA进行统计分析。图5显示与对照组相比,低剂量组的ENPP1活性水平较高。同样,与低剂量组和对照组相比,高剂量组ENPP1活性水平较高。在低剂量组和高剂量组中,在高剂量组中从第7天至第56天的血浆样本中ENPP1活性是稳定的,但在低剂量组中从第28天至第56天的ENPP1活性有轻微降低。

[0919] 然后使用来自Sigma的ENPP1多克隆抗体(SAB1400199)的夹心ELISA测定法测定样本以确定ENPP1的浓度。96孔澄清平底聚苯乙烯高结合微孔板(Corning号9018)、BSA(Sigma#7906)、10×杜尔贝克磷酸盐缓冲盐水(DPBS)(Quality Biological号119-068-101)、吐温-20(Sigma货号P2287)、抗ENPP1、小鼠产生的抗体(Sigma-Aldrich货号SAB1400199)、Sure Blue TMB微孔过氧化物酶底物(1-组分)(KPLProd#52-00-01)、2N硫酸(BDH产品#BDH7500-1)、级纯水(MilliQ Water)、C57BL/6小鼠血浆NaHep混合性别(BioIVT货号MSE01PLNHPNN)、小鼠血清(BIO IVT elevating Science货号MSE01SRMPNN)用于ELISA检测。

[0920] ENPP1-Fc蛋白的标准曲线通过按照本领域已知的标准方法产生。制备2mg/ml-30ng.ml的ENPP1-Fc蛋白的简单连续稀释液。首先将该96孔板用1μg/1mL过夜包被溶液包被,该过夜包被溶液包括在1XPBS中的ENPP1捕获抗体。然后将孔用含5％BSA的PBS孵育1小时,然后用后封闭溶液洗涤。将ENPP1稀释样本加入到包被的96孔板中并孵育1.5小时。孵育后,将孔用300μl的0.05T％PBST洗涤4次。然后将洗涤的孔用100μL/孔的检测HRP抗体缀合物处理并孵育1小时。与HRP抗体缀合物孵育后,将孔用300μl的0.05T％PBST洗涤4次。然后将洗涤的孔用每孔100μl的TMB微孔过氧化物酶底物处理并在黑暗中孵育30min。然后将这些孔用300μl的0.05T％PBST洗涤4次并且使用2N硫酸终止反应。使用酶标仪在450nm波长下读取孔的吸光度。使用吸光度读数和ENPP1连续稀释样本的相应浓度产生标准曲线。

[0921] 然后在病毒注射后7、28和56天,使用从对照、低剂量和高剂量组中获得的血浆样本重复该测定。将各血浆样本中产生的吸光度与ENPP1-Fc的标准曲线相关联,以测定血浆

样本中ENPP1-Fc的浓度。ENPP1浓度测定的结果显示在图6中,并且它们显示在病毒载体(vector)注射后ENPP1浓度的剂量依赖性增加。使用正常小鼠血浆作为参比标准来标准化ENPP1浓度水平,并使用单向ANOVA进行统计分析。图6显示与对照组相比,低剂量组的ENPP1浓度较高。同样,与低剂量组和对照组相比,高剂量组ENPP1活性水平较高。在低剂量组和高剂量组中,在高剂量组中从第7天至第56天的样本中ENPP1水平是稳定的,但在低剂量组中从第28天至第56天的ENPP1水平有轻微降低。

[0922] 还使用硫酸化酶测定来测定样本以确定血浆PPi的浓度。使用ATP硫酸化酶(NEB-M0394L,批号:10028529)、腺苷5'-磷酸硫酸(APS;Santa Cruz;sc-214506),PPi:100uM储备液,HEPES pH 7.4缓冲液(波士顿生物制品(Boston Bioproducts)BB2076),1M硫酸镁($MgSO_4$)溶液,1M氯化钙($CaCl_2$)溶液,BactiterGlo(Promega G8231),平板(Costar 3915,黑色平底)和平板读数器(Molecular DevicesSpectramax I3x)进行PPi-硫酸化酶测定。使用连续稀释在水中制备PPi标准品(0.125-4μM)。在过量的腺苷5'磷酸硫酸(APS)存在下,通过ATP硫酸化酶将PPi标准品和过滤的血浆样本中的PPi转化成ATP。将样本(15μl)用5μl的混合物处理,该混合物含有8mM $CaCl_2$、2mM MgSO4、40mM HEPES pH7.4、80uM APS(Santa Cruz,sc-214506)和0.1U/ml的ATP硫酸化酶(NEB-M0394L)。将混合物在37℃孵育40min,之后通过在90℃孵育10min使ATP硫酸化酶失活。通过将20μl处理的样本或标准品与20μl的BactiterGlo试剂混合,使用BactiterGlo(Promega G8231)测定产生的ATP。随后在酶标仪中测定生物发光,并且根据标准曲线,随后测定每个样本中产生的PPi的量。

[0923] 血浆PPi测定的结果显示在图7中。结果显示病毒载体(vector)注射后血浆PPi剂量依赖性增加。使用正常小鼠血浆作为参考标准以标准化血浆PPi浓度水平,并使用单向ANOVA进行统计分析。图7显示与对照组相比,低剂量组中血浆PPi浓度稍高。同样,与低剂量组和对照组相比,高剂量组血浆PPi浓度较高。在低剂量组和高剂量组中,在高剂量组中从第7天至第56天的血浆样本中ENPP1水平是稳定的,但观察到在低剂量组中从第28天至第56天的ENPP1水平有轻微降低。

[0924] 在相关实验中,5-6周龄的C57/Bl雄性小鼠以1e14 vg/kg静脉内施用单剂量的AAV病毒载体(vector)或载体(vehicle)对照(不含AAV载体(vector))。给动物施用GK1.5(40μg/小鼠,在病毒载体(vector)或载体(vehicle)给药前一天,然后在此后每七天给药25μg/小鼠,直到完成研究)。将AAV病毒载体(vector)工程化以表达ENPP1和IgG Fc的融合蛋白,其类似于实施例10中描述的多肽,除了融合蛋白的ENPP1部分和IgG Fc部分通过以下接头氨基酸序列:GGGGS连接。施用AAV病毒载体(vector)的小鼠在大约40天的时间内表现出比仅仅载体(vehicle)对照更高水平的ENPP1酶活性。

[0925] 实施例11——病毒给药后112天模型小鼠中ENPP1浓度和活性水平的分析。

[0926] 本实验使用三个队列的正常小鼠。每个队列包括五只成年小鼠。将第一队列用作"对照组",并将盐水溶液注射至对照组。第二队列用作"低剂量组",低剂量组注射浓度为$1e^{13}$vg/kg的AAV载体(vector)。第三队列使用"高剂量组",高剂量组注射浓度为$1e^{14}$vg/kg的AAV载体(vector)。图4示意性地示出了从AAV构建体产生病毒颗粒并将包括ENPP1融合蛋白的重组AAV病毒颗粒注射到正常小鼠中的过程。所有组的小鼠在注射后第7天、第28天、第56天和第112天取血,以收集血浆和血清。

[0927] 将血液收集到肝素处理的管中。将样本在最高速度(-20kg)下在4℃下离心20min。

收集流过物并置于干冰上以极速冰冻样本。将样本储存在-80℃下用于以后的测定。

[0928] 如实施例10所描述,采集的样本首先进行检测以用比色底物对硝基苯基胸苷5′-单磷酸(Sigma)测定ENPP1活性水平。ENPP1活性测定的结果在图9中,并且它们显示注射后ENPP1活性存在剂量依赖性增加。使用正常小鼠血浆作为参比标准来标准化ENPP1活性水平,并使用单向ANOVA进行统计分析。图9显示与对照组相比,低剂量组的ENPP1活性水平较高。同样,与低剂量组和对照组相比,高剂量组ENPP1活性水平较高。

[0929] 按照实施例10中所教导的方案,然后使用来自Sigma的ENPP1多克隆抗体(SAB1400199)的夹心ELISA测定法测定样本以确定ENPP1的浓度。然后在病毒注射后7、28、56和112天,使用从对照、低剂量和高剂量组中获得的血浆样本重复该测定。将各血浆样本中产生的吸光度与ENPP1-Fc的标准曲线相关联,以测定血浆样本中ENPP1-Fc的浓度。

[0930] ENPP1浓度测定的结果显示在图8中,并且它们显示在病毒载体(vector)注射后ENPP1浓度的剂量依赖性增加。使用正常小鼠血浆作为参比标准来标准化ENPP1浓度水平,并使用单向ANOVA进行统计分析。图8显示与对照组相比,低剂量组的ENPP1浓度较高。同样,与低剂量组和对照组相比,高剂量组ENPP1水平较高。

[0931] 其它实施方案

[0932] 从前面的描述中,显然可以对本文所述的本发明进行改变和修饰以将其用于各种用途和条件,包括在具有不同启动子或增强子或本领域已知的不同细胞类型的不同病毒载体(vector)中,使用不同的信号序列来表达ENPP1或ENPP3或其组合的功能性变体,用于治疗以病理性钙化或骨化的存在为特征的任何疾病的在根据本发明的范围内。

[0933] 在本文中对变量的任何定义中的元素列表的引用包括将该变量定义为任何单个元素或所列元素的组合(或子组合)。本文对实施方案的列举包括作为任何单个实施方案或与任何其他实施方案或其部分组合的实施方案。

[0934] 本说明书中提及的所有出版物和专利申请指示本发明所属领域技术人员的水平。所有出版物和专利申请均以引用的方式并入本文中,其程度如同每一单独出版物或专利申请具体且单独地指示以引用的方式并入一样。

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[0002] <110> 依诺兹梅制药公司

[0003] S•江格斯

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[0011] <151> 2019-03-21

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[0013] <151> 2019-07-22

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[1507] Val Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys

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785 790 795 800
Glu Arg Phe Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu
805 810 815
Thr Gly Leu Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile
820 825 830
Leu Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile
835 840 845

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

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[1557] 245 250 255
[1558] His Ser Tyr Tyr Thr Leu Ile Asp Leu Ser Pro Val Ala Ala Ile Leu
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[1803] 675 680 685
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[4695] Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys Asn Ile Thr His Gly
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[4705] Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr Lys His Leu Ala Asn
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[4707] Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val Val Leu Thr Ser Cys
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[4709] Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro Gly Trp Leu Asp Val
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[4714] 865 870 875 880
[4715] Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr Gly Leu Asp Phe Tyr
[4716] 885 890 895
[4717] Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu Gln Leu Lys Thr Tyr
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[4719] Leu Pro Thr Phe Glu Thr Thr Ile Gly Gly Gly Ser Gly Gly Gly Gly
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[4721] Ser Gly Gly Gly Gly Ser Met Lys Trp Val Thr Phe Leu Leu Leu Leu
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[4723] Phe Val Ser Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg Glu Ala
[4724] 945 950 955 960
[4725] His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His
[4726] 965 970 975
[4727] Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys
[4728] 980 985 990
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[4740] 1070 1075 1080
[4741] Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly His Tyr Leu His
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[4743] Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
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[4750] 1145 1150 1155
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[4785] Ile Leu Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser
[4786] 1415 1420 1425
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[4788] 1430 1435 1440
[4789] Pro Cys Phe Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys
[4790] 1445 1450 1455
[4791] Glu Phe Lys Ala Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr
[4792] 1460 1465 1470
[4793] Leu Pro Glu Lys Glu Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala
[4794] 1475 1480 1485
[4795] Glu Leu Val Lys His Lys Pro Lys Ala Thr Ala Glu Gln Leu Lys
[4796] 1490 1495 1500
[4797] Thr Val Met Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys Cys Lys
[4798] 1505 1510 1515
[4799] Ala Ala Asp Lys Asp Thr Cys Phe Ser Thr Glu Gly Pro Asn Leu
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[4814] Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala Ser
[4815] 35 40 45
[4816] Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala
[4817] 50 55 60
[4818] Arg Ala Arg Thr Ala Lys Asp Pro Asn Thr Tyr Lys Ile Ile Ser Leu
[4819] 65 70 75 80
[4820] Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly
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[4850] 165 170 175
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[4853] Leu Leu Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys
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[4858] 225 230 235 240
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[4860] 245 250 255
[4861] Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr Lys
[4862] 260 265 270
[4863] Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly Asp
[4864] 275 280 285
[4865] Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met Cys
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[4867] Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys Cys Asp Lys
[4868] 305 310 315 320
[4869] Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val Glu His Asp Thr
[4870] 325 330 335
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[4872] 340 345 350
[4873] Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Thr
[4874] 355 360 365
[4875] Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Asp Tyr Ser Val Ser Leu
[4876] 370 375 380
[4877] Leu Leu Arg Leu Ala Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys Cys
[4878] 385 390 395 400
[4879] Ala Glu Ala Asn Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu Phe
[4880] 405 410 415
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[4882] 420 425 430
[4883] Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val
[4884] 435 440 445
[4885] Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu
[4886] 450 455 460
[4887] Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu Pro
[4888] 465 470 475 480
[4889] Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile Leu
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[4891] Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His Val
[4892] 500 505 510
[4893] Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe Ser
[4894] 515 520 525
[4895] Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys Ala Glu
[4896] 530 535 540
[4897] Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu Lys Glu Lys
[4898] 545 550 555 560
[4899] Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val Lys His Lys Pro
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[4905] Thr Glu Gly Pro Asn Leu Val Thr Arg Cys Lys Asp Ala Leu Ala
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[4918] Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
[4919] 35 40 45
[4920] Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
[4921] 50 55 60
[4922] His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
[4923] 65 70 75 80
[4924] Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
[4925] 85 90 95
[4926] Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
[4927] 100 105 110
[4928] Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
[4929] 115 120 125
[4930] Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
[4931] 130 135 140
[4932] Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
[4933] 145 150 155 160
[4934] Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
[4935] 165 170 175
[4936] Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
[4937] 180 185 190
[4938] Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
[4939] 195 200 205
[4940] His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
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[4943] 225
[4944] <210> 35
[4945] <211> 618
[4946] <212> PRT
[4947] <213> 人工序列(Artificial Sequence)
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[4954] 20 25 30
[4955] His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu

[4956] 35 40 45
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[4958] 50 55 60
[4959] Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp
[4960] 65 70 75 80
[4961] Glu Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
[4962] 85 90 95
[4963] Lys Leu Cys Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala
[4964] 100 105 110
[4965] Asp Cys Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
[4966] 115 120 125
[4967] His Lys Asp Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala
[4968] 130 135 140
[4969] Glu Ala Met Cys Thr Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly
[4970] 145 150 155 160
[4971] His Tyr Leu His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
[4972] 165 170 175
[4973] Glu Leu Leu Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys
[4974] 180 185 190
[4975] Cys Ala Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly
[4976] 195 200 205
[4977] Val Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys
[4978] 210 215 220
[4979] Ser Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
[4980] 225 230 235 240
[4981] Ala Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr
[4982] 245 250 255
[4983] Lys Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly
[4984] 260 265 270
[4985] Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met
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[4993] Gln Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
[4994] 340 345 350
[4995] Thr Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Asp Tyr Ser Val Ser
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[5003] Asp Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu
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[5005] Val Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val
[5006] 435 440 445
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[5008] 450 455 460
[5009] Pro Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile
[5010] 465 470 475 480
[5011] Leu Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His
[5012] 485 490 495
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[6310] 1 5 10 15
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[6312] <211> 14
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[7050] Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu Glu Leu
[7051] 770 775 780
[7052] Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile Thr Gly
[7053] 785 790 795 800
[7054] Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile Leu Lys
[7055] 805 810 815

[7056] Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp Leu Ile Asn Asp
[7057] 820 825 830
[7058] Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
[7059] 835 840 845
[7060] Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
[7061] 850 855 860
[7062] Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
[7063] 865 870 875 880
[7064] Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
[7065] 885 890 895
[7066] Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
[7067] 900 905 910
[7068] Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
[7069] 915 920 925
[7070] Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
[7071] 930 935 940
[7072] Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
[7073] 945 950 955 960
[7074] Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
[7075] 965 970 975
[7076] Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
[7077] 980 985 990
[7078] Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
[7079] 995 1000 1005
[7080] Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
[7081] 1010 1015 1020
[7082] Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
[7083] 1025 1030 1035
[7084] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
[7085] 1040 1045 1050
[7086] Leu Ser Pro Gly Lys
[7087] 1055

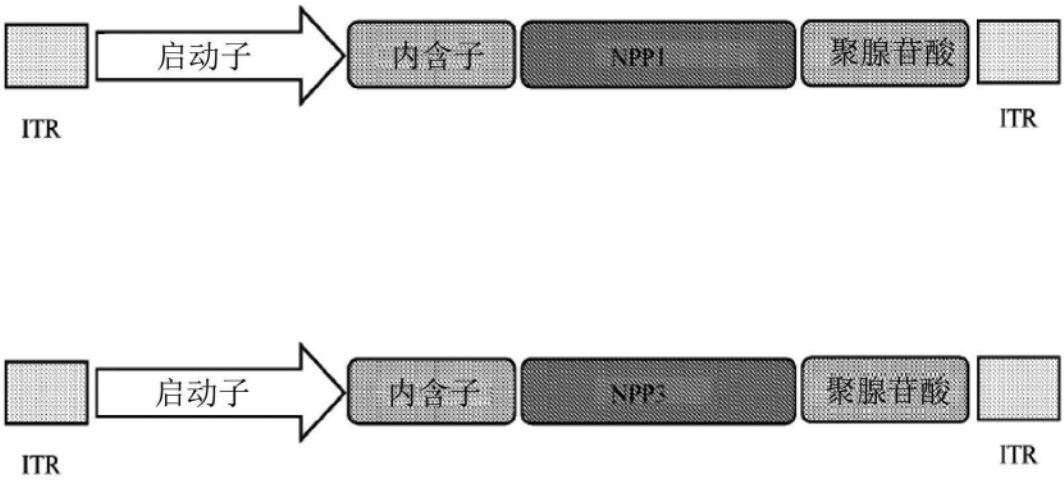

图1——表达载体(vector)的示意图

信号序列	滴度（mg/L）
天青杀素信号序列	731
NPP2信号序列	127
NPP7信号序列	136

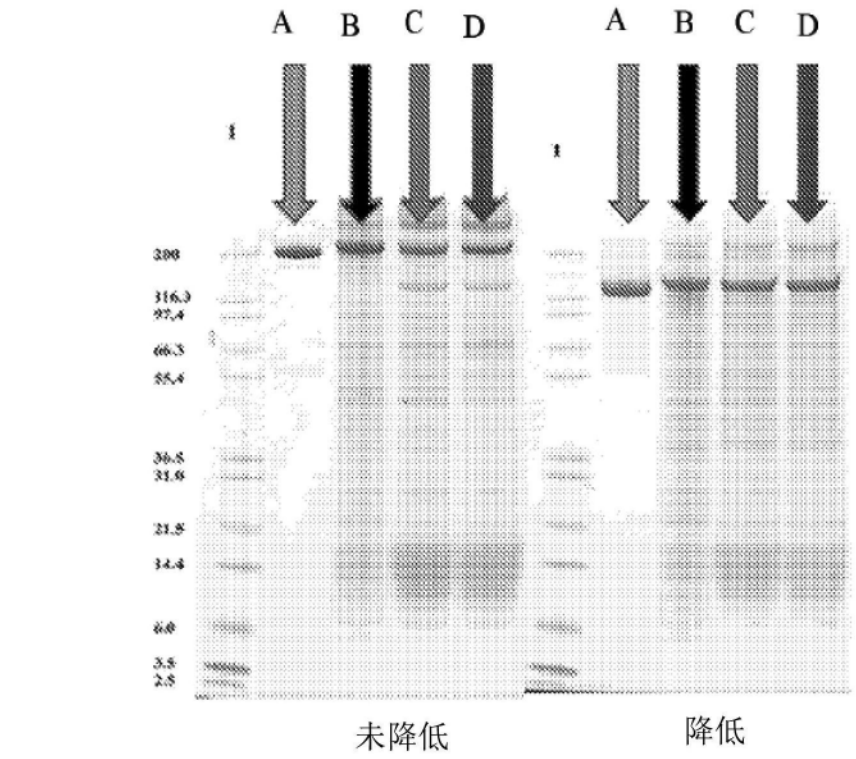

图2——不同信号序列的比较

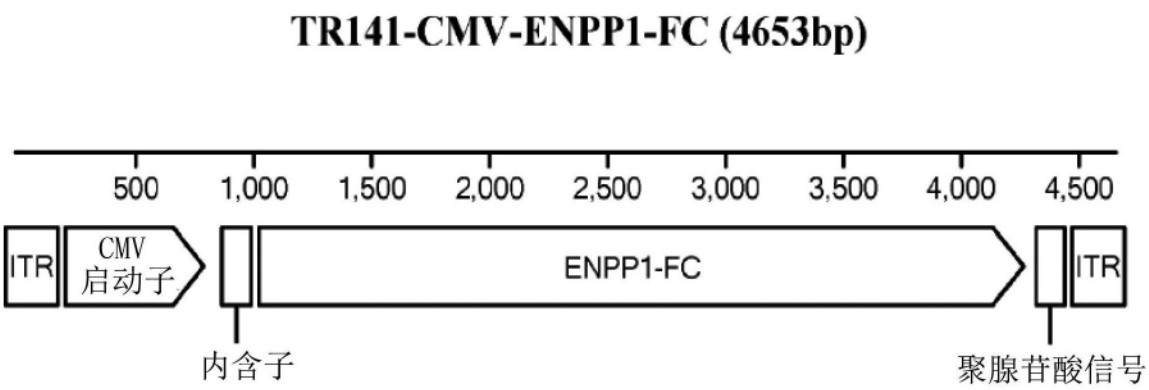

图3——ENPP1-FC的质粒图谱

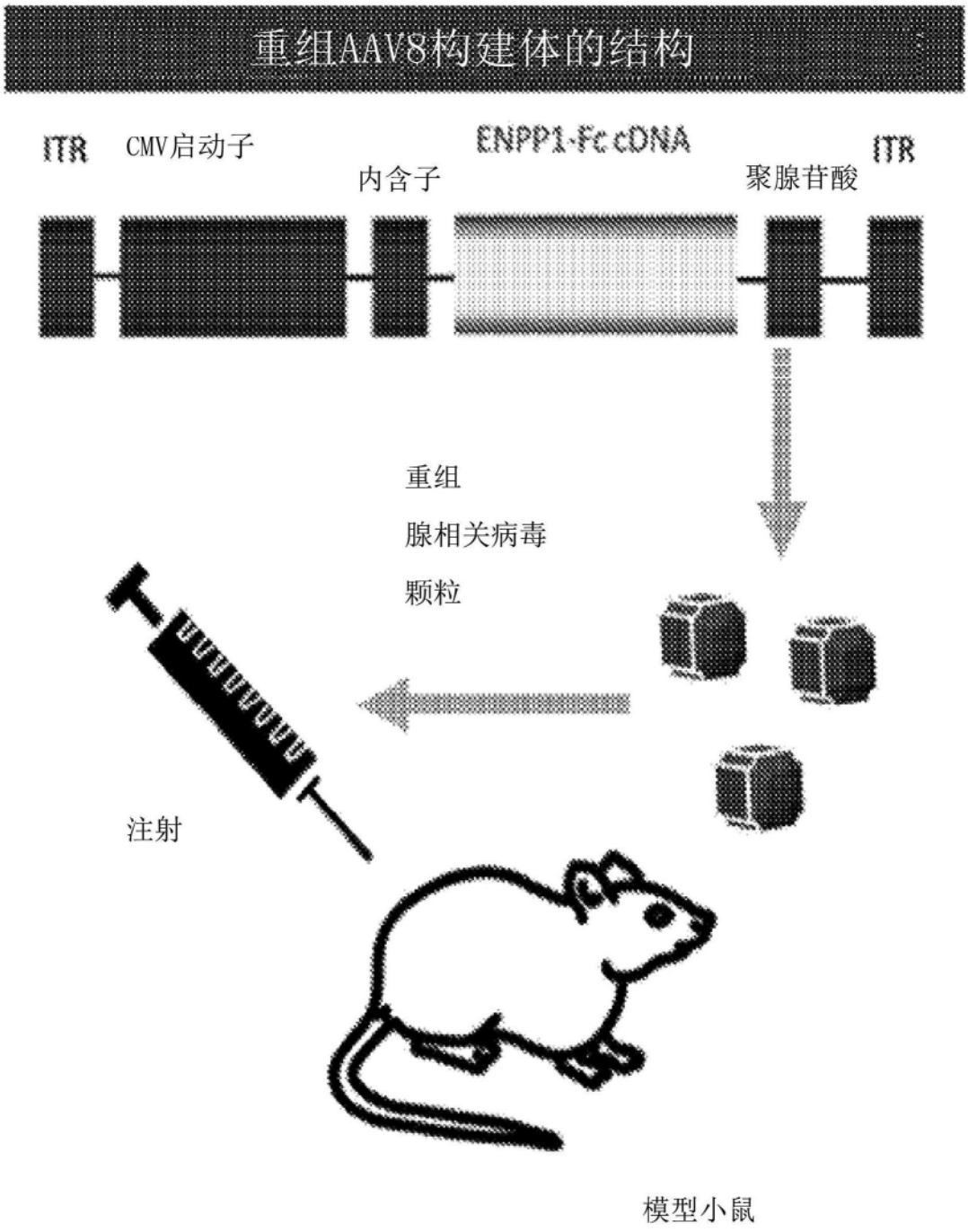
重组AAV8构建体的结构
ITR
CMV启动子
内含子
ENPP1-Fc cDNA
聚腺苷酸
ITR
重组
腺相关病毒
颗粒
注射
模型小鼠

图4——给药的示意图

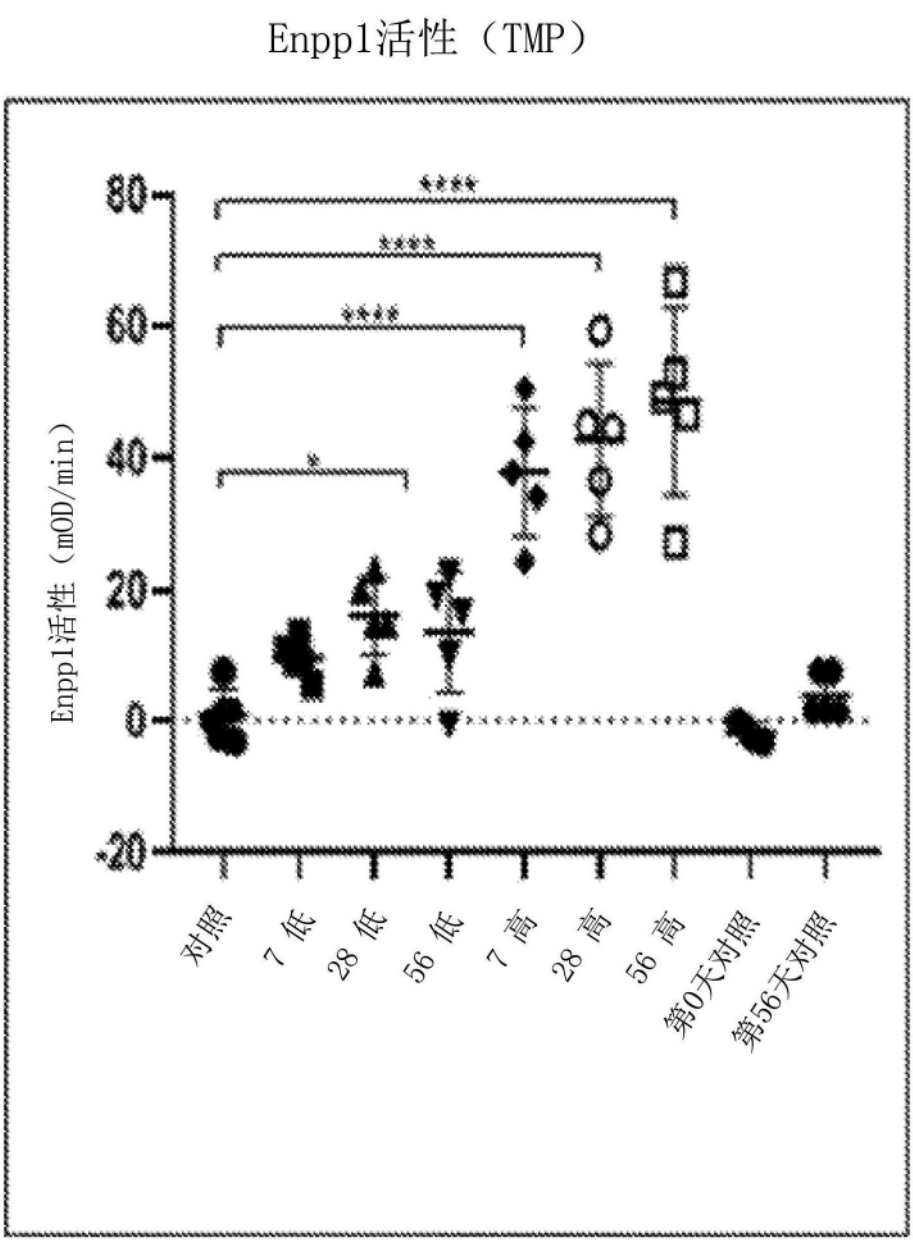

图5——病毒载体(vector)给药后ENPP1活性剂量依赖性增加

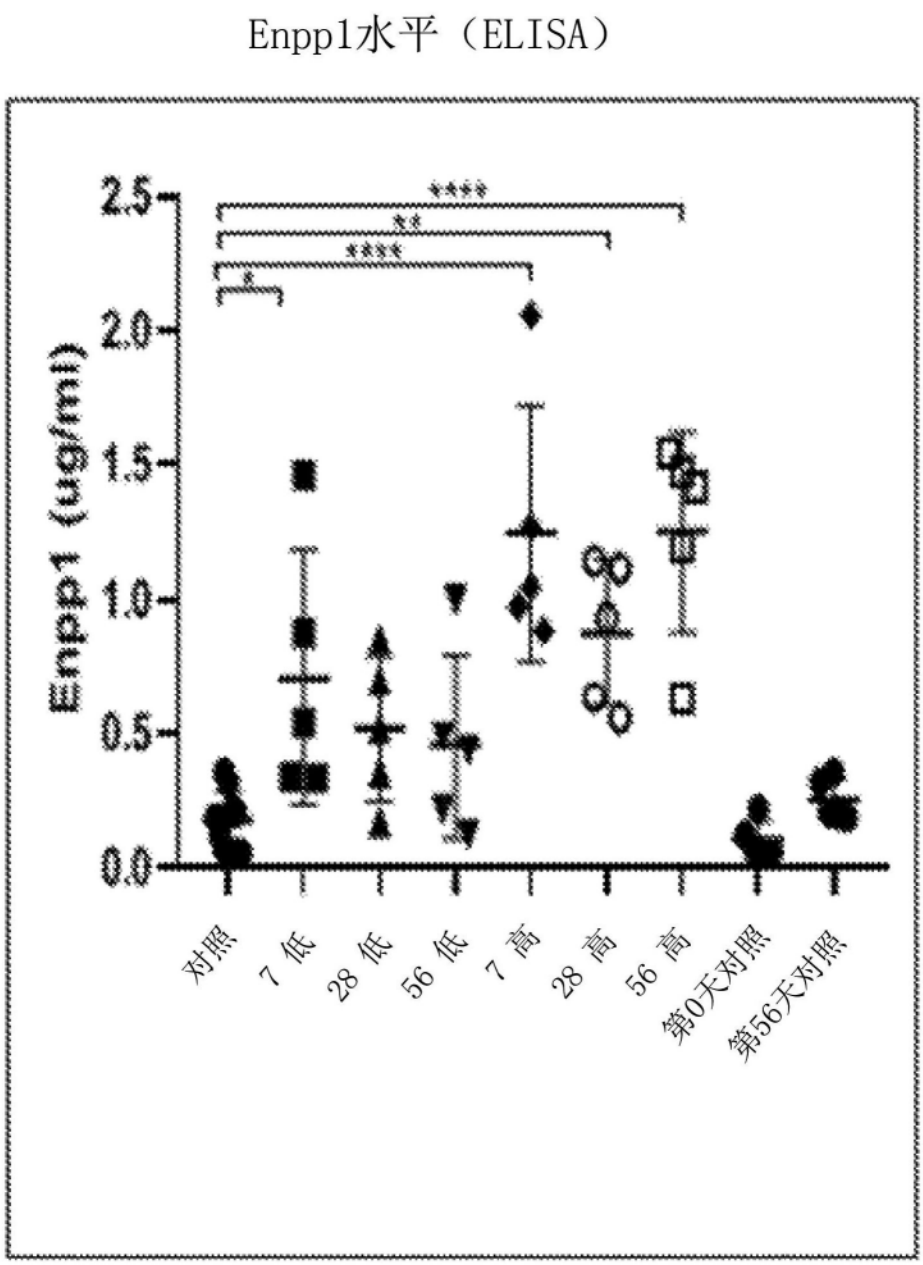

图6——病毒载体(vector)给药后ENPP1浓度剂量依赖性增加

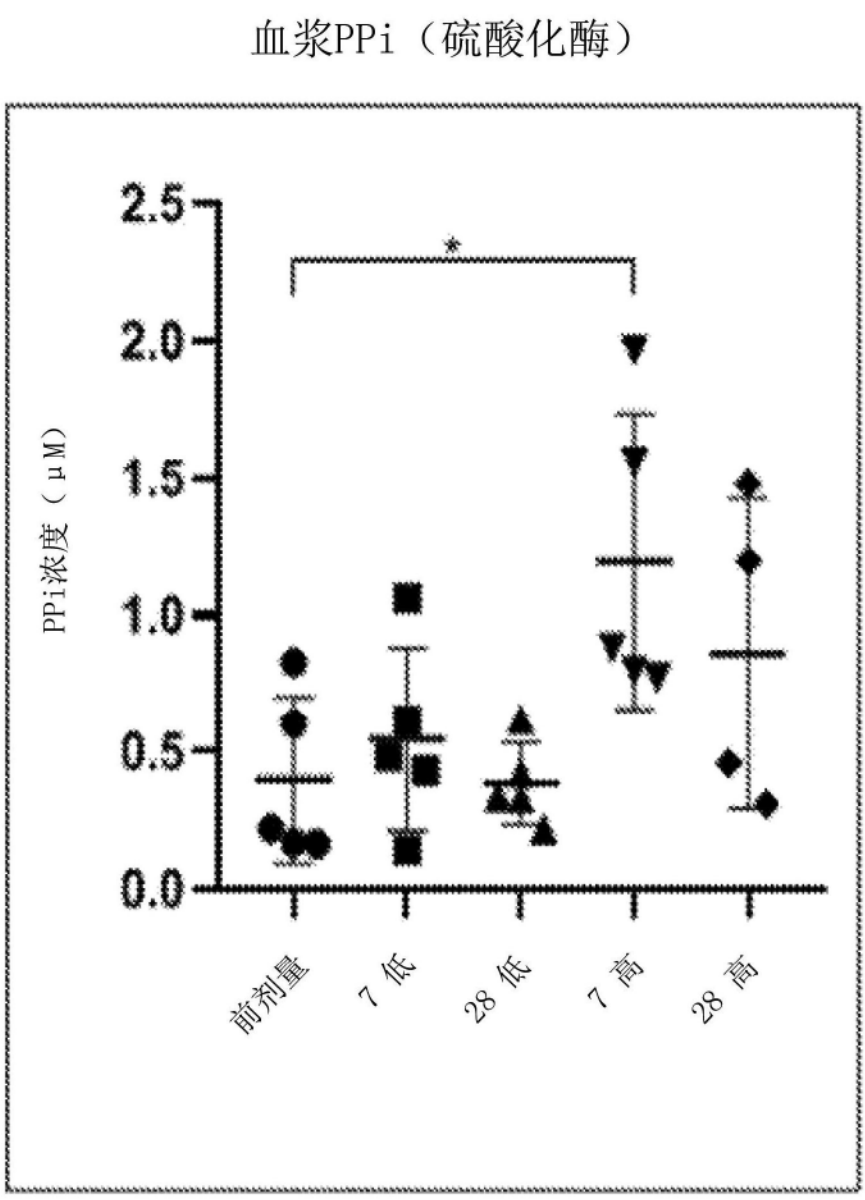

图7——病毒载体(vector)给药后血浆焦磷酸盐(PPi)水平剂量依赖性增加

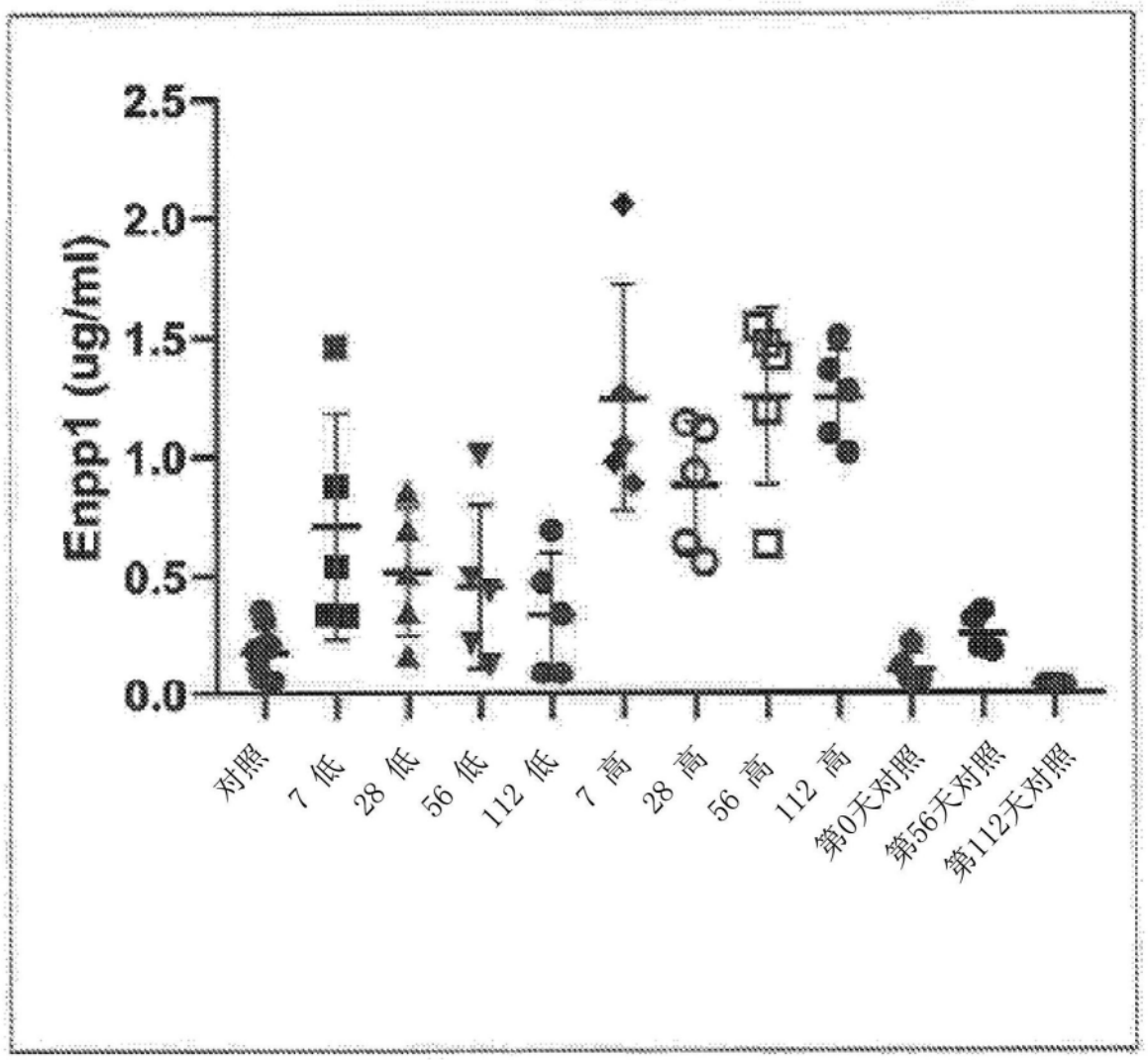

图8——病毒载体(vector)给药后ENPP1持续表达多达112天

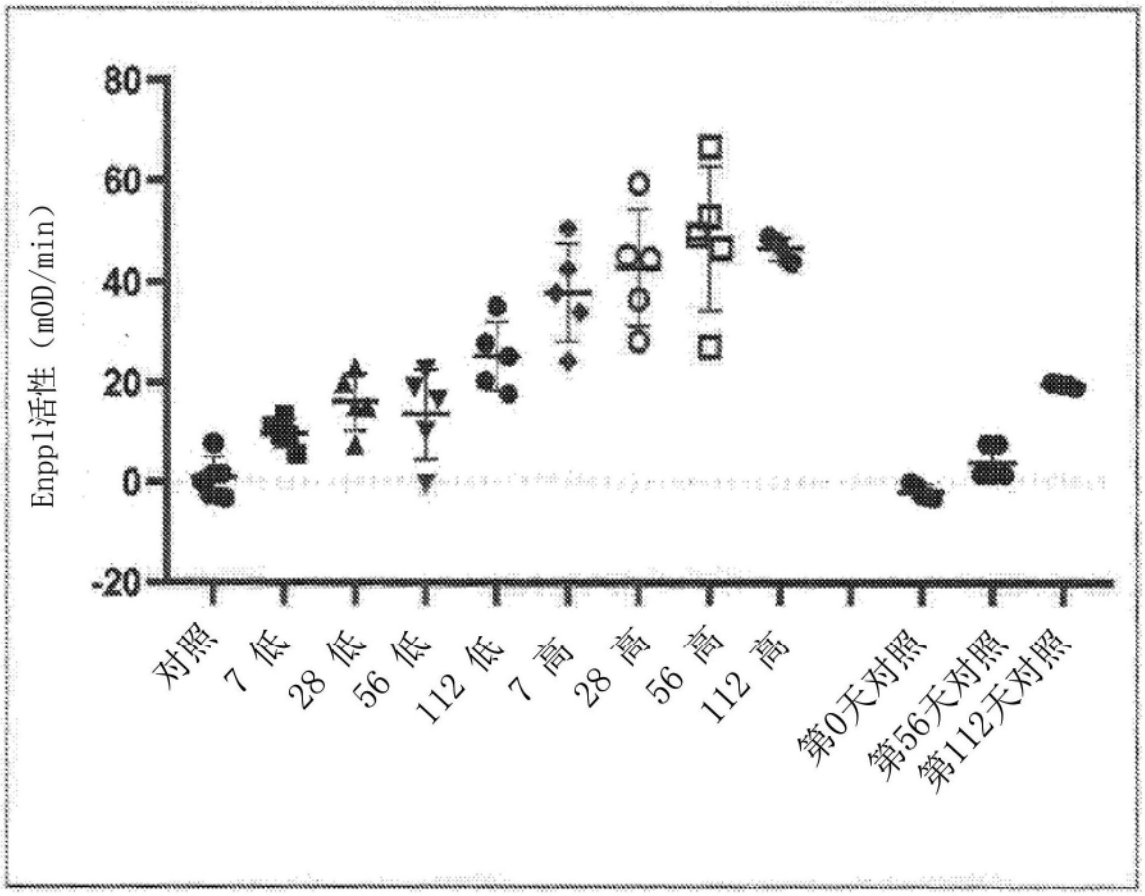

图9——病毒载体(vector)给药后ENPP1活性剂量依赖性增加