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(54)发明名称

用于治疗同种异体移植物血管病、烟雾病、烟雾病综合征和内膜增殖的组合物和方法

(57)摘要

本公开提供了用于通过以下来治疗同种异体移植物血管病和烟雾病(MMD)和烟雾病综合征(MMS),治疗、抑制或预防受试者的不期望的内膜增殖的组合物和方法:施用外核苷酸焦磷酸酶磷酸二酯酶-1(ENPP1)药剂或外核苷酸焦磷酸酶磷酸二酯酶-3(ENPP3)。

CN 116322742 A

1.一种用于减少和/或预防具有同种异体移植物的受试者的同种异体移植物血管病的方法,所述方法包括向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此减少和/或预防所述受试者的同种异体移植物血管病。

2.一种用于减少和/或预防具有同种异体移植物的受试者的所述同种异体移植物的血管系统中血管平滑肌细胞增殖的进展的方法,所述方法包括向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此减少和/或预防所述受试者的所述同种异体移植物的所述血管系统中所述血管平滑肌细胞增殖的进展。

3.一种用于减少和/或预防具有实体器官同种异体移植物并且在所述器官同种异体移植物上经历外科手术的受试者的实体器官同种异体移植物中血管平滑肌细胞增殖的进展的方法,所述方法包括向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此减少和/或预防所述受试者的所述实体器官同种异体移植物中血管平滑肌细胞增殖的进展。

4.一种用于减少和/或预防具有实体器官同种异体移植物的受试者的实体器官同种异体移植物的血管系统中的狭窄或再狭窄的方法,所述方法包括向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此减少和/或预防所述实体器官同种异体移植物的所述血管系统中的狭窄或再狭窄。

5.一种用于延长具有实体器官同种异体移植物的受试者的实体器官同种异体移植物的存活期的方法,所述方法包括向所述受试者施用足量的ENPP1药剂或ENPP3药剂,所述量足以由此延长所述受试者的所述实体器官同种异体移植物的存活期。

6.一种用于抑制或预防具有实体器官同种异体移植物的受试者的实体器官同种异体移植物中的血管病的方法,所述方法包括向所述受试者施用足量的ENPP1药剂或ENPP3药剂,所述量足以抑制或预防所述实体器官同种异体移植物中的血管病。

7.根据权利要求1至6中任一项所述的方法,其中所述实体器官同种异体移植物是心脏同种异体移植物。

8.根据权利要求1至6中任一项所述的方法,其中所述实体器官同种异体移植物是肾同种异体移植物、肝同种异体移植物或肺同种异体移植物。

9.根据权利要求1至7中任一项所述的方法,其中所述受试者有风险患上心脏同种异体移植物血管病。

10.根据权利要求1至7中任一项所述的方法,其中所述受试者患有心脏同种异体移植物血管病。

11.一种用于抑制或预防具有血管同种异体移植物的受试者的同种异体移植的血管的血管病的方法,所述方法包括向受试者施用足量的ENPP1药剂或ENPP3药剂,所述量足以预防或抑制所述同种异体移植的血管的血管病。

12.一种用于抑制或预防具有血管同种异体移植物的受试者的同种异体移植的血管中血管平滑肌细胞增殖的方法,所述方法包括向所述受试者施用足量的ENPP1药剂或ENPP3药剂,所述量足以预防或抑制所述同种异体移植的血管中的血管平滑肌细胞增殖。

13.一种用于延长具有血管同种异体移植物的受试者的同种异体移植的血管的存活期的方法,所述方法包括向所述受试者施用足量的ENPP1药剂或ENPP3药剂,所述量足以由此延长所述同种异体移植的血管的存活期。

14.根据权利要求11至13中任一项所述的方法,其中所述同种异体移植的血管是同种

异体移植的动脉。

15.根据权利要求11至13中任一项所述的方法,其中所述同种异体移植的血管是同种异体移植的静脉。

16.根据权利要求1至15中任一项所述的方法,其中在移植所述实体器官或血管之前向所述受试者施用所述ENPP1药剂或所述ENPP3药剂。

17.根据权利要求1至15中任一项所述的方法,其中在移植所述实体器官或血管的同时向所述受试者施用所述ENPP1药剂或所述ENPP3药剂。

18.根据权利要求1至17中任一项所述的方法,其中在移植所述实体器官或血管之后向所述受试者施用所述ENPP1药剂或所述ENPP3药剂。

19.根据权利要求1至15中任一项所述的方法,其中在移植所述实体器官或血管之前、在移植所述实体器官或血管的同时和/或在移植所述实体器官或血管之后向所述受试者施用所述ENPP1药剂或所述ENPP3药剂。

20.根据权利要求1至19中任一项所述的方法,其进一步包括向所述受试者施用他汀(statin)、血管扩张剂、免疫抑制药物或抗凝剂。

21.根据权利要求1至20中任一项所述的方法,其中所述ENPP1药剂包括ENPP1多肽。

22.根据权利要求1至20中任一项所述的方法,其中所述ENPP1药剂包括编码ENPP1多肽的核酸。

23.根据权利要求1至20中任一项所述的方法,其中所述ENPP1药剂包括病毒载体,所述病毒载体包括编码ENPP1多肽的核酸。

24.根据权利要求21至23中任一项所述的方法,其中所述ENPP1多肽包括ENPP1的胞外结构域。

25.根据权利要求21至23中任一项所述的方法,其中所述ENPP1多肽包括ENPP1的催化结构域。

26.根据权利要求21至23中任一项所述的方法,其中所述ENPP1多肽包括SEQ ID NO:1的氨基酸99至925。

27.根据权利要求21至23中任一项所述的方法,其中所述ENPP1多肽包括异源蛋白。

28.根据权利要求27所述的方法,其中所述异源蛋白增加所述ENPP1多肽在哺乳动物体内的循环半衰期。

29.根据权利要求27或28所述的方法,其中所述异源蛋白为免疫球蛋白分子的Fc区。

30.根据权利要求29所述的方法,其中所述免疫球蛋白分子为IgG1分子。

31.根据权利要求27或28所述的方法,其中所述异源蛋白为白蛋白分子。

32.根据权利要求27至31中任一项所述的方法,其中所述异源蛋白处于所述ENPP1多肽的羧基末端。

33.根据权利要求27至32中任一项所述的方法,其中所述ENPP1药剂包括接头。

34.根据权利要求33所述的方法,其中所述接头将所述ENPP1多肽和所述异源蛋白分离。

35.根据权利要求33或34所述的方法,其中所述接头包括以下氨基酸序列:$(GGGGS)_n$,其中n为1至10的整数。

36.根据权利要求1至35中任一项所述的方法,其中所述ENPP1药剂皮下施用于所述受

试者。

37.根据权利要求1至35中任一项所述的方法,其中所述ENPP1药剂静脉内施用于所述受试者。

38.根据权利要求1至20中任一项所述的方法,其中所述ENPP3药剂包括ENPP3多肽。

39.根据权利要求1至20中任一项所述的方法,其中所述ENPP3药剂包括编码ENPP3多肽的核酸。

40.根据权利要求35至45中任一项所述的方法,其中所述ENPP3药剂包括病毒载体,所述病毒载体包括编码ENPP3多肽的核酸。

41.根据权利要求38至40中任一项所述的方法,其中所述ENPP3多肽包括ENPP3的胞外结构域。

42.根据权利要求38至40中任一项所述的方法,其中所述ENPP3多肽包括ENPP3的催化结构域。

43.根据权利要求38至40中任一项所述的方法,其中所述ENPP3多肽包括SEQ ID NO:7的氨基酸49至875。

44.根据权利要求38至40中任一项所述的方法,其中所述ENPP3多肽包括异源蛋白。

45.根据权利要求44所述的方法,其中所述异源蛋白增加所述ENPP3多肽在哺乳动物体内的循环半衰期。

46.根据权利要求44或45所述的方法,其中所述异源蛋白为免疫球蛋白分子的Fc区。

47.根据权利要求46所述的方法,其中所述免疫球蛋白分子为IgG1分子。

48.根据权利要求44或45所述的方法,其中所述异源蛋白为白蛋白分子。

49.根据权利要求44至42中任一项所述的方法,其中所述异源蛋白处于所述ENPP3多肽的羧基末端。

50.根据权利要求44至48中任一项所述的方法,其中所述ENPP3药剂包括接头。

51.根据权利要求50所述的方法,其中所述接头将所述ENPP3多肽和所述异源蛋白分离。

52.根据权利要求50或51所述的方法,其中所述接头包括以下氨基酸序列:$(GGGGS)_n$,其中n为1至10的整数。

53.根据权利要求38至52中任一项所述的方法,其中所述ENPP3药剂皮下施用于所述受试者。

54.根据权利要求38至52中任一项所述的方法,其中所述ENPP3药剂静脉内施用于所述受试者。

55.根据权利要求1至54中任一项所述的方法,其进一步包括向所述受试者施用补体抑制剂。

56.根据权利要求55所述的方法,其中所述补体抑制剂是C5抑制剂。

57.一种用于抑制或预防有风险患上烟雾病的受试者的脑血管闭塞的方法,所述方法包括:向所述受试者施用足量的ENPP1药剂或ENPP3药剂,所述量足以由此抑制或预防所述受试者的脑血管闭塞。

58.一种用于抑制或预防有风险患上烟雾病的受试者的不期望的血管平滑肌细胞增殖的方法,所述方法包括:向所述受试者施用足量的ENPP1药剂或ENPP3药剂,所述量足以由此

抑制或预防所述受试者的不期望的血管平滑肌细胞增殖。

59.一种用于治疗有风险患上烟雾病的受试者的方法,所述方法包括:向所述受试者施用足量的ENPP1药剂或ENPP3药剂,所述量足以由此治疗所述受试者。

60.一种用于抑制或预防患有烟雾病的受试者的脑血管闭塞的方法,所述方法包括:向所述受试者施用足量的ENPP1药剂或ENPP3药剂,所述量足以由此抑制或预防所述受试者的脑血管闭塞。

61.一种用于抑制或预防患有烟雾病的受试者的不期望的血管平滑肌细胞增殖的方法,所述方法包括:向所述受试者施用足量的ENPP1药剂或ENPP3药剂,所述量足以由此抑制或预防所述受试者的不期望的脑血管平滑肌细胞增殖。

62.一种用于治疗患有烟雾病的受试者的方法,所述方法包括:向所述受试者施用足量的ENPP1药剂或ENPP3药剂,所述量足以由此治疗所述受试者。

63.一种用于预防或改善受试者的与烟雾病相关的一种或多种症状的方法,所述方法包括:向所述受试者施用足量的ENPP1药剂或ENPP3药剂,所述量足以由此预防或改善所述受试者的一种或多种与烟雾病相关的症状。

64.一种用于抑制或预防预期接受或已经接受外科手术干预作为烟雾病的治疗的受试者的脑血管闭塞的方法,所述方法包括:向所述受试者施用足量的ENPP1药剂或ENPP3药剂,所述量足以由此抑制或预防所述受试者的脑血管闭塞。

65.一种用于抑制或预防预期接受或已经接受外科手术干预作为烟雾病的治疗的受试者的不期望的血管平滑肌细胞增殖的方法,所述方法包括:向所述受试者施用足量的ENPP1药剂或ENPP3药剂,所述量足以由此抑制或预防所述受试者的不期望的血管平滑肌细胞增殖。

66.根据权利要求57至65中任一项所述的方法,其中所述受试者携带RNF213R4810K突变。

67.根据权利要求57至65中任一项所述的方法,其中所述受试者具有烟雾病家族史。

68.根据权利要求62至67中任一项所述的方法,其中所述受试者经历脑中的狭窄、血栓形成、栓塞和/或出血。

69.根据权利要求66或67所述的方法,其中所述外科手术干预是血管旁路移植。

70.根据权利要求66或67所述的方法,其中所述外科手术干预是脑血运重建。

71.根据权利要求64至70中任一项所述的方法,其中在所述外科手术干预之前向所述受试者施用所述ENPP1药剂或所述ENPP3药剂。

72.根据权利要求64至71中任一项所述的方法,其中在所述外科手术干预的同时向所述受试者施用所述ENPP1药剂或所述ENPP3药剂。

73.根据权利要求64至72中任一项所述的方法,其中在所述外科手术干预之后向所述受试者施用所述ENPP1药剂或所述ENPP3药剂。

74.根据权利要求64至70中任一项所述的方法,其中在所述外科手术干预之前、在所述外科手术干预的同时和/或在所述外科手术干预的移植之后向所述受试者施用所述ENPP1药剂或所述ENPP3药剂。

75.根据权利要求57至74中任一项所述的方法,其进一步包括向所述受试者施用抗高血压药物和抗凝剂中的一种或两种。

76.根据权利要求57至75中任一项所述的方法,其中所述ENPP1药剂包括ENPP1多肽。

77.根据权利要求57至75中任一项所述的方法,其中所述ENPP1药剂包括编码ENPP1多肽的核酸。

78.根据权利要求57至75中任一项所述的方法,其中所述ENPP1药剂包括病毒载体,所述病毒载体包括编码ENPP1多肽的核酸。

79.根据权利要求76至78中任一项所述的方法,其中所述ENPP1多肽包括ENPP1的胞外结构域。

80.根据权利要求76至78中任一项所述的方法,其中所述ENPP1多肽包括ENPP1的催化结构域。

81.根据权利要求76至78中任一项所述的方法,其中所述ENPP1多肽包括SEQ ID NO:1的氨基酸99至925。

82.根据权利要求76至78中任一项所述的方法,其中所述ENPP1多肽包括异源蛋白。

83.根据权利要求82所述的方法,其中所述异源蛋白增加所述ENPP1多肽在哺乳动物体内的循环半衰期。

84.根据权利要求82或83所述的方法,其中所述异源蛋白为免疫球蛋白分子的Fc区。

85.根据权利要求84所述的方法,其中所述免疫球蛋白分子为IgG1分子。

86.根据权利要求82或83所述的方法,其中所述异源蛋白为白蛋白分子。

87.根据权利要求82至86中任一项所述的方法,其中所述异源蛋白处于所述ENPP1多肽的羧基末端。

88.根据权利要求82至87中任一项所述的方法,其中所述ENPP1药剂包括接头。

89.根据权利要求88所述的方法,其中所述接头将所述ENPP1多肽和所述异源蛋白分离。

90.根据权利要求88或89所述的方法,其中所述接头包括以下氨基酸序列:(GGGGS)n,其中n为1至10的整数。

91.根据权利要求57至90中任一项所述的方法,其中所述ENPP1药剂皮下施用于所述受试者。

92.根据权利要求57至90中任一项所述的方法,其中所述ENPP1药剂静脉内施用于所述受试者。

93.根据权利要求57至75中任一项所述的方法,其中所述ENPP3药剂包括ENPP3多肽。

94.根据权利要求57至75中任一项所述的方法,其中所述ENPP3药剂包括编码ENPP3多肽的核酸。

95.根据权利要求90至94中任一项所述的方法,其中所述ENPP3药剂包括病毒载体,所述病毒载体包括编码ENPP3多肽的核酸。

96.根据权利要求93至95中任一项所述的方法,其中所述ENPP3多肽包括ENPP3的胞外结构域。

97.根据权利要求93至95中任一项所述的方法,其中所述ENPP3多肽包括ENPP3的催化结构域。

98.根据权利要求93至95中任一项所述的方法,其中所述ENPP3多肽包括SEQ ID NO:7的氨基酸49至875。

99.根据权利要求93至95中任一项所述的方法,其中所述ENPP3多肽包括异源蛋白。

100.根据权利要求99所述的方法,其中所述异源蛋白增加所述ENPP3多肽在哺乳动物体内的循环半衰期。

101.根据权利要求99或100所述的方法,其中所述异源蛋白为免疫球蛋白分子的Fc区。

102.根据权利要求101所述的方法,其中所述免疫球蛋白分子为IgG1分子。

103.根据权利要求99或100所述的方法,其中所述异源蛋白为白蛋白分子。

104.根据权利要求99至103中任一项所述的方法,其中所述异源蛋白处于所述ENPP3多肽的羧基末端。

105.根据权利要求99至103中任一项所述的方法,其中所述ENPP3药剂包括接头。

106.根据权利要求105所述的方法,其中所述接头将所述ENPP3多肽和所述异源蛋白分离。

107.根据权利要求105或106所述的方法,其中所述接头包括以下氨基酸序列:(GGGGS)n,其中n为1至10的整数。

108.根据权利要求93至107中任一项所述的方法,其中所述ENPP3药剂皮下施用于所述受试者。

109.根据权利要求93至107中任一项所述的方法,其中所述ENPP3药剂静脉内施用于所述受试者。

110.一种用于减少和/或预防在外周血管上需要外科手术的受试者的所述外周血管中血管平滑肌细胞增殖的进展的方法,其中所述外科手术包括放置动静脉透析分流器,所述方法包括:向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此减少和/或预防所述受试者的所述外周血管的外科手术部位处所述外周血管中血管平滑肌细胞增殖的进展。

111.一种用于减少和/或预防在已放置动静脉透析分流器的部位处或周围的受试者的外周血管中血管平滑肌细胞增殖的进展的方法,所述方法包括:向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此减少和/或预防已放置所述动静脉透析分流器的部位处或周围的所述外周血管中血管平滑肌细胞增殖的进展。

112.根据权利要求110所述的方法,其中在所述外科手术或所述分流器放置之前、期间和/或之后施用所述药剂。

113.根据权利要求110至112中任一项所述的方法,其中所述受试者不患有ENPP1缺乏症。

114.根据权利要求110至113中任一项所述的方法,其中所述ENPP1药剂包括ENPP1多肽。

115.根据权利要求110至113中任一项所述的方法,其中所述ENPP1药剂包括编码ENPP1多肽的核酸。

116.根据权利要求110至113中任一项所述的方法,其中所述ENPP1药剂包括病毒载体,所述病毒载体包括编码ENPP1多肽的核酸。

117.根据权利要求114至116中任一项所述的方法,其中所述ENPP1多肽包括ENPP1的胞外结构域。

118.根据权利要求114至116中任一项所述的方法,其中所述ENPP1多肽包括ENPP1的催化结构域。

119.根据权利要求114至116中任一项所述的方法，其中所述ENPP1多肽包括SEQ ID NO:1的氨基酸99至925。

120.根据权利要求114至116中任一项所述的方法，其中所述ENPP1多肽包括异源蛋白。

121.根据权利要求120所述的方法，其中所述异源蛋白增加所述ENPP1多肽在哺乳动物体内的循环半衰期。

122.根据权利要求120或121所述的方法，其中所述异源蛋白为免疫球蛋白分子的Fc区。

123.根据权利要求122所述的方法，其中所述免疫球蛋白分子为IgG1分子。

124.根据权利要求120或121所述的方法，其中所述异源蛋白为白蛋白分子。

125.根据权利要求120至124中任一项所述的方法，其中所述异源蛋白处于所述ENPP1多肽的羧基末端。

126.根据权利要求114至125中任一项所述的方法，其中所述ENPP1药剂包括接头。

127.根据权利要求126所述的方法，其中所述接头将所述ENPP1多肽和所述异源蛋白分离。

128.根据权利要求126或127所述的方法，其中所述接头包括以下氨基酸序列：$(GGGGS)_n$，其中n为1至10的整数。

129.根据权利要求110至128中任一项所述的方法，其中所述ENPP1药剂皮下施用于所述受试者。

130.根据权利要求110至128中任一项所述的方法，其中所述ENPP1药剂静脉内施用于所述受试者。

131.根据权利要求110至113中任一项所述的方法，其中所述ENPP3药剂包括ENPP3多肽。

132.根据权利要求110至113中任一项所述的方法，其中所述ENPP3药剂包括编码ENPP3多肽的核酸。

133.根据权利要求110至113中任一项所述的方法，其中所述ENPP3药剂包括病毒载体，所述病毒载体包括编码ENPP3多肽的核酸。

134.根据权利要求131至133中任一项所述的方法，其中所述ENPP3多肽包括ENPP3的胞外结构域。

135.根据权利要求131至133中任一项所述的方法，其中所述ENPP3多肽包括ENPP3的催化结构域。

136.根据权利要求131至133中任一项所述的方法，其中所述ENPP3多肽包括SEQ ID NO:7的氨基酸49至875。

137.根据权利要求131至133中任一项所述的方法，其中所述ENPP3多肽包括异源蛋白。

138.根据权利要求137所述的方法，其中所述异源蛋白增加所述ENPP3多肽在哺乳动物体内的循环半衰期。

139.根据权利要求137或138所述的方法，其中所述异源蛋白为免疫球蛋白分子的Fc区。

140.根据权利要求139所述的方法，其中所述免疫球蛋白分子为IgG1分子。

141.根据权利要求137或138所述的方法，其中所述异源蛋白为白蛋白分子。

142.根据权利要求137至141中任一项所述的方法，其中所述异源蛋白处于所述ENPP3多肽的羧基末端。

143.根据权利要求110至113或131至142中任一项所述的方法，其中所述ENPP3药剂包括接头。

144.根据权利要求143所述的方法，其中所述接头将所述ENPP3多肽和所述异源蛋白分离。

145.根据权利要求143或144所述的方法，其中所述接头包括以下氨基酸序列：$(GGGGS)_n$，其中n为1至10的整数。

146.根据权利要求110至113或131至145中任一项所述的方法，其中所述ENPP3药剂皮下施用于所述受试者。

147.根据权利要求110至113或131至145中任一项所述的方法，其中所述ENPP3药剂静脉内施用于所述受试者。

148.根据权利要求110至147中任一项所述的方法，其中所述受试者：是吸烟者；患有高血压；胆固醇或甘油三酯水平升高；患有糖尿病；患有肾病；或肥胖。

149.根据权利要求110至148中任一项所述的方法，其进一步包括进行所述外科手术。

150.根据权利要求110至149中任一项所述的方法，其中所述外科手术和/或分流器放置进一步包括将透析导管引入到所述受试者体内。

151.根据权利要求110至150中任一项所述的方法，其中所述受试者正在接受或已经接受抗凝剂、抗生素和抗高血压药物中的一种或多种。

152.根据权利要求110至151中任一项所述的方法，其进一步包括向所述受试者施用抗凝剂、抗生素和抗高血压药物中的一种或多种。

153.根据权利要求110至152中任一项所述的方法，其进一步包括监测所述受试者的所述分流器的闭塞。

154.根据前述权利要求中任一项所述的方法，其中所述ENPP1药剂包括保留酶促活性的ENPP1变体。

155.根据前述权利要求中任一项所述的方法，其中所述ENPP3药剂包括保留酶促活性的ENPP3变体。

用于治疗同种异体移植物血管病、烟雾病、烟雾病综合征和内膜增殖的组合物和方法

[0001] 相关申请交叉引用

[0002] 本申请要求以下临时申请的优先权:于2020年7月2日提交的美国申请第63/047,793号、于2020年7月2日提交的美国申请第63/047,877号、于2020年7月2日提交的美国申请第63/047,865号申请和于2020年7月2日提交的美国申请第63/047,848号,其中每项申请的内容通过全文引用的方式并入本文。

技术领域

[0003] 本公开涉及治疗血管疾病的组合物和方法。

[0004] 序列表

[0005] 本申请含有已经以ASCII格式电子提交并且特此通过引用以其整体并入的序列表。创建于2021年7月2日的所述ASCII副本命名为4427-10502_sequence_ST25.txt并且大小为343.976字节。

背景技术

[0006] 肌内膜增殖或肌内膜增生是以血管壁的平滑肌细胞的异常增殖为特征的血管系统的复杂病理过程。增殖性平滑肌细胞迁移到内皮下区域并且形成增生性病变,所述增生性病变可能导致血管内腔狭窄和阻塞。

[0007] 心脏同种异体移植物血管病(CAV)是一种加速的纤维增生性病症,影响移植物的肌肉血管,并且是心脏移植术后发病率和死亡率的主要原因。CAV被认为是由免疫损伤和内皮细胞浸润介导的,导致血管平滑肌细胞增殖和随后的内腔狭窄。CAV的症状包含移植物心外膜和心肌内动脉两者的动脉内膜进行性增厚,通常由免疫介导的血管损伤驱动。在移植后三年内,所有心脏移植受体中至少约三分之一(严重程度不同)出现CAV。CAV通常以血管平滑肌细胞增殖、炎性免疫细胞聚集和脂质沉积为特征。CAV是一种进展缓慢的疾病,但由于移植物去神经,如急性移植物衰竭、心律失常、梗塞或心源性死亡等并发症通常可以在没有典型症状(如心绞痛)的情况下表现出来。

[0008] 类似的血管病发生在其它实体器官移植中,并且可能严重限制其长期存活。由于此类血管病很难治疗,并且可以影响同种异体移植物的几乎所有血管,因此其与同种异体移植物受体的显著发病率和死亡率有关,并且可能需要重复移植。因此,迫切需要有效的疗法来预防或减少实体器官同种异体移植物(如心脏异体移植物)中此类血管病的程度。

[0009] 烟雾病是一种闭塞性脑血管病症,于1957年在日本首次报道,其特征在于颈内动脉(ICA)的床突上段狭窄,并且在脑底部形成异常血管网络。烟雾病是通用术语,用于描述影响颅内颈内动脉的两种不同情况;烟雾病(MMD)是导致双侧动脉病的先天性疾病,在东亚和日本儿童和成人中更为突出,并且烟雾病综合征(MMS)是特发性疾病,通常见于20岁至40岁的白种人成年人。虽然MMS中没有已知的遗传组分,就像在MMD中一样,但其通常与如糖尿病、狼疮或类风湿性关节炎等自身免疫性病症相关。MMD和MMS的治疗选择涉及每日使用阿

司匹林(aspirin),改变生活方式以最大化脑灌注,以及外科手术直接或间接旁路以恢复血流。烟雾病主要影响女性(70%至85%)多于男性(15%至30%),其跨越多个种族,但在东亚人和白种人中最为普遍。烟雾病(MMD)在具有家族血统的儿童和成人中都是东亚人群体中的突出疾病。烟雾病综合征(MMS)在生命的第2个十年/第3个十年的白种人中非常突出,其为特发性,并且通常伴有合并症(自身免疫性疾病),临床文献通常无法区分患有MMD和MMS的患者。

[0010] 慢性血液透析是患有肾功能不良的患者的常见治疗方法。此类患者通常会进行外科手术程序,其中通常在其非惯用臂上形成人工动静脉瘘(AVF)。AVF为血液透析过程提供了持久的血管接入点。AVF的常见并发症是AVF或AVF位置处或附近的血管闭塞。例如,此类闭塞可能涉及血栓和内膜增生,并且如果不治疗,可能导致永久性神经损伤或患肢瘫痪(参见例如,Asif等人,(2006)《美国肾脏病学会临床杂志(Clin J Am Soc Nephrol.)》1:332-339;Nath等人,(2003)《美国病理学杂志(Am J Pathol.)》162:2079-90;以及Stolic(2013)《医学原理与实践(Med Pric Pract.)》22(3):220-228)。

发明内容

[0011] 一方面,本公开涉及一种用于减少和/或预防具有同种异体移植物的受试者的同种异体移植物血管病的方法,所述方法包括:向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此减少和/或预防所述受试者的同种异体移植物血管病。

[0012] 另一方面,本公开涉及一种用于预防或改善受试者的与烟雾病相关的一种或多种症状的方法,所述方法包括:向所述受试者施用足量的ENPP1药剂或ENPP3药剂,所述量足以由此预防或改善所述受试者的一种或多种与烟雾病相关的症状。

[0013] 另一方面,本公开涉及一种用于抑制或预防预期接受或已经接受外科手术干预作为烟雾病的治疗的受试者的脑血管闭塞的方法,所述方法包括:向所述受试者施用足量的ENPP1药剂或ENPP3药剂,所述量足以由此抑制或预防所述受试者的脑血管闭塞。

[0014] 另一方面,本公开涉及一种用于抑制或预防预期接受或已经接受外科手术干预作为烟雾病的治疗的受试者的不期望的血管平滑肌细胞增殖的方法,所述方法包括:向所述受试者施用足量的ENPP1药剂或ENPP3药剂,所述量足以由此抑制或预防所述受试者的不期望的血管平滑肌细胞增殖。

[0015] 另一方面,本公开还包含一种用于抑制或减缓受试者的I期铃木级(Suzuki grade)MMD向II期铃木级MMD的进展的方法,所述方法包括:向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此抑制和/或减缓所述受试者的I期MMD向II期MMD的进展。

[0016] 另一方面,本公开还包含一种用于抑制或减缓受试者的I期铃木级MMD向III期铃木级MMD的进展的方法,所述方法包括:向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此抑制和/或减缓所述受试者的I期MMD向III期MMD的进展。

[0017] 在又另一方面,本公开涉及一种用于抑制或预防具有发生烟雾病风险的受试者的脑血管闭塞的方法,所述方法包括:向所述受试者施用足量的ENPP1药剂或ENPP3药剂,所述量足以由此抑制或预防所述受试者的脑血管闭塞。

[0018] 在又另一方面,本公开涉及一种用于抑制或预防具有发生烟雾病风险的受试者的不期望的血管平滑肌细胞增殖的方法,所述方法包括:向所述受试者施用足量的ENPP1药剂

或ENPP3药剂,所述量足以由此抑制或预防所述受试者的不期望的血管平滑肌细胞增殖。

[0019] 在又另一方面,本公开还涉及一种用于治疗具有发生烟雾病风险的受试者的方法,所述方法包括:向所述受试者施用足量的ENPP1药剂或ENPP3药剂,所述量足以由此治疗所述受试者。

[0020] 在又另一方面,本公开涉及一种用于抑制或预防患有烟雾病的受试者的脑血管闭塞的方法,所述方法包括:向所述受试者施用足量的ENPP1药剂或ENPP3药剂,所述量足以由此抑制或预防所述受试者的脑血管闭塞。本公开涉及一种用于抑制或预防患有烟雾病的受试者的不期望的血管平滑肌细胞增殖的方法,所述方法包括:向所述受试者施用足量的ENPP1药剂或ENPP3药剂,所述量足以由此抑制或预防所述受试者的不期望的脑血管平滑肌细胞增殖。

[0021] 在又另一方面,本公开涉及一种用于治疗患有烟雾病的受试者的方法,所述方法包括:向所述受试者施用足量的ENPP1药剂或ENPP3药剂,所述量足以由此治疗所述受试者。

[0022] 在又另一方面,本公开涉及一种用于治疗患有烟雾病的受试者的方法,所述方法包括:向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此治疗所述受试者的所述烟雾病。

[0023] 在又另一方面,本公开涉及一种用于治疗患有烟雾病综合征的受试者的方法,所述方法包括:向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此治疗所述受试者的所述烟雾病综合征。

[0024] 在又另一方面,本公开包含用于减少和/或预防受试者的脑动脉中血管平滑肌细胞增殖的进展的方法,所述方法包括:向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此减少和/或预防所述受试者的所述脑动脉中所述血管平滑肌细胞增殖的进展。在本文所描述的任何方法的一些实施例中,所述受试者具有I期、II期或III期、IV期铃木级MMD。

[0025] 在又另一方面,本公开还包含一种用于抑制或减缓受试者的I期铃木级MMD向II期铃木级MMD的进展的方法,所述方法包括:向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此抑制和/或减缓所述受试者的I期MMD向II期MMD的进展。

[0026] 另一方面,本公开的特征在于一种用于治疗患有烟雾病的受试者的方法,所述方法包括:向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此治疗所述受试者的所述外周动脉疾病。

[0027] 另一方面,本公开涉及一种用于治疗患有烟雾病综合征的受试者的方法,所述方法包括:向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此治疗所述受试者的所述烟雾病综合征。

[0028] 在又另一方面,本公开的特征在于一种用于减少和/或预防患有烟雾病的受试者的脑动脉中血管平滑肌细胞增殖的进展的方法,所述方法包括:向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此减少和/或者预防所述受试者的所述脑动脉中所述血管平滑肌细胞增殖的进展。

[0029] 本公开还涉及一种用于减少和/或预防在脑动脉上经历外科手术的受试者的所述脑动脉中血管平滑肌细胞增殖的进展的方法,所述方法包括:向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此减少和/或预防所述受试者的所述脑动脉的外科手术部位处所述脑动脉中血管平滑肌细胞增殖的进展。

[0030] 本公开还涉及一种用于减少和/或预防在脑动脉上经历外科手术的受试者的所述脑动脉中血管平滑肌细胞增殖的进展的方法,所述方法包括:向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此减少和/或预防所述受试者的所述脑动脉的外科手术部位处所述脑动脉中血管平滑肌细胞增殖的进展。

[0031] 另一方面,本公开的特征在于一种用于治疗患有烟雾病的受试者的方法,所述方法包括:向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此治疗所述受试者的所述外周动脉疾病。另一方面,本公开涉及一种用于治疗患有烟雾病综合征的受试者的方法,所述方法包括:向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此治疗所述受试者的所述烟雾病综合征。在又另一方面,本公开的特征在于一种用于减少和/或预防患有烟雾病的受试者的脑动脉中血管平滑肌细胞增殖的进展的方法,所述方法包括:向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此减少和/或者预防所述受试者的所述脑动脉中所述血管平滑肌细胞增殖的进展。

[0032] 另一方面,本公开还涉及一种用于减少和/或预防在已放置动静脉透析分流器的部位处或周围的受试者的外周血管中血管平滑肌细胞增殖的进展的方法,所述方法包括:向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此减少和/或预防已放置所述动静脉透析分流器的部位处或周围的所述外周血管中血管平滑肌细胞增殖的进展。

[0033] 一方面,本公开提供了一种用于减少和/或预防在外周血管上经历外科手术的受试者的所述外周血管中血管平滑肌细胞增殖的进展的方法,所述方法包括:向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此减少和/或预防所述受试者的所述外周血管的外科手术部位处所述外周血管中血管平滑肌细胞增殖的进展,其中所述外科手术包括放置动静脉透析分流器。

[0034] 另一方面,本公开涉及一种用于减少和/或预防在外周血管上需要外科手术的受试者的所述外周血管中血管平滑肌细胞增殖的进展的方法,其中所述外科手术包括放置动静脉透析分流器,所述方法包括:向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此减少和/或预防所述受试者的所述外周血管的外科手术部位处所述外周血管中血管平滑肌细胞增殖的进展。

[0035] 另一方面,本公开还包含一种用于减少和/或预防在外周血管中经历分流器放置的受试者的外周血管中血管平滑肌细胞增殖的进展的方法,所述方法包括:向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此减少和/或预防所述外周血管中血管平滑肌细胞增殖的进展。

[0036] 另一方面,本公开的特征在于一种用于减少和/或预防在外周血管中经历分流器放置的受试者的所述外周血管中的狭窄或再狭窄的方法,所述方法包括:向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此减少和/或预防所述外周血管中的狭窄或再狭窄。

[0037] 另一方面,本公开涉及一种用于减少和/或预防受试者的同种异体移植的血管的血管病的方法,所述方法包括:向受试者施用有效量的:(i)ENPP1药剂或ENPP3药剂以及(ii)补体抑制剂,由此减少和/或预防所述受试者的所述同种异体移植的血管的血管病。在一些实施例中,所述血管是动脉。在一些实施例中,所述血管是静脉。

[0038] 另一方面,本公开涉及一种用于减少和/或预防受试者的同种异体移植的血管的血管病的方法,所述方法包括:向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此减

少和/或者预防所述受试者的同种异体移植的血管的血管病。在一些实施例中，所述血管是动脉。在一些实施例中，所述血管是静脉。

[0039] 另一方面，本公开涉及一种用于减少和/或预防受试者的同种异体移植的血管的血管病的方法，所述方法包括：向所述受试者施用有效量的ENPP1药剂或ENPP3药剂，由此减少和/或者预防所述受试者的同种异体移植的血管的血管病。在一些实施例中，所述血管是动脉。在一些实施例中，所述血管是静脉。在一些实施例中，所述受试者已经接受或正在接受包括补体抑制剂的疗法。在一些实施例中，所述方法包括向所述受试者施用补体抑制剂。

[0040] 另一方面，本公开涉及一种用于减少和/或预防受试者的同种异体移植的血管中血管平滑肌细胞增殖的进展的方法，所述方法包括：向所述受试者施用有效量的：(i)ENPP1药剂或ENPP3药剂以及(ii)补体抑制剂，由此减少和/或预防所述受试者的同种异体移植的血管中血管平滑肌细胞增殖的进展。在一些实施例中，所述血管是动脉。在一些实施例中，所述血管是静脉。

[0041] 在另一方面，本公开涉及一种用于减少和/或预防具有同种异体移植物的受试者的同种异体移植物血管病(例如，心脏同种异体移植物血管病)的方法，所述方法包括：向所述受试者施用有效量的：(i)ENPP1药剂或ENPP3药剂以及(ii)补体抑制剂，由此减少和/或预防所述受试者的同种异体移植物血管病。

[0042] 另一方面，本公开涉及一种用于减少和/或预防受试者的同种异体移植的血管中血管平滑肌细胞增殖的进展方法，所述方法包括：向所述受试者施用有效量的ENPP1药剂或ENPP3药剂，由此减少和/或者预防所述受试者的同种异体移植的血管中血管平滑肌细胞增殖的进展。在一些实施例中，所述血管是动脉。在一些实施例中，所述血管是静脉。

[0043] 在又另一方面，本公开涉及一种用于减少和/或预防具有同种异体移植物，并且已经接受或正在接受包括补体抑制剂的疗法的受试者的同种异体移植物血管病(例如，心脏同种异体移植物血管病)的方法，所述方法包括：向所述受试者施用有效量的ENPP1药剂或ENPP3药剂，由此减少和/或预防所述受试者的同种异体移植物血管病。在一些实施例中，所述方法进一步包括向所述受试者施用所述补体抑制剂。

[0044] 另一方面，本公开涉及一种用于减少和/或预防具有同种异体移植物，并且已经接受或正在接受包括ENPP1药剂或ENPP3药剂的疗法的受试者的同种异体移植物血管病(例如，心脏同种异体移植物血管病)的方法，所述方法包括：向所述受试者施用有效量的补体抑制剂，由此减少和/或预防所述受试者的同种异体移植物血管病。在一些实施例中，所述方法进一步包括向所述受试者施用所述ENPP1药剂或ENPP3药剂。

[0045] 另一方面，本公开涉及一种用于减少和/或预防具有同种异体移植物的受试者的所述同种异体移植物的血管系统中血管平滑肌细胞增殖的进展的方法，所述方法包括向所述受试者施用有效量的：(i)ENPP1药剂或ENPP3药剂以及(ii)补体抑制剂，由此减少和/或预防所述受试者的所述同种异体移植物的所述血管系统中所述血管平滑肌细胞增殖的进展。

[0046] 另一方面，本公开涉及一种用于减少和/或预防具有同种异体移植物的受试者的所述同种异体移植物的血管系统中血管平滑肌细胞增殖的进展的方法，其中所述受试者已经接受或正在接受包括补体抑制剂的疗法，所述方法包括向所述受试者施用有效量的ENPP1药剂或ENPP3药剂，由此减少和/或预防所述受试者的所述同种异体移植物的所述血

管系统中所述血管平滑肌细胞增殖的进展。在一些实施例中，所述方法进一步包括向所述受试者施用所述补体抑制剂。

[0047] 另一方面，本公开涉及一种用于减少和/或预防具有同种异体移植物的受试者的所述同种异体移植物的血管系统中血管平滑肌细胞增殖的进展的方法，其中所述受试者已经接受或正在接受包括ENPP1药剂或ENPP3药剂的疗法，所述方法包括向所述受试者施用有效量的补体抑制剂，由此减少和/或预防所述受试者的所述同种异体移植物的所述血管系统中所述血管平滑肌细胞增殖的进展。在一些实施例中，所述方法进一步包括向所述受试者施用所述ENPP1药剂或ENPP3药剂。

[0048] 在又另一方面，本公开还涉及一种用于减少和/或预防在具有实体器官移植并且在所述器官移植上经历外科手术的受试者的实体器官移植中血管平滑肌细胞增殖的进展的方法，所述方法包括向所述受试者施用有效量的：(i)ENPP1药剂或ENPP3药剂以及(ii)补体抑制剂，由此减少和/或预防所述受试者的所述实体器官移植中血管平滑肌细胞增殖的进展。

[0049] 在又另一方面，本公开还特征在于一种用于延迟或预防或防范具有同种异体移植的血管的受试者的所述同种异体移植的血管失效的方法，所述方法包括：向所述受试者施用有效量的ENPP1药剂或ENPP3药剂，由此延迟、预防或提供针对所述受试者的所述同种异体移植的血管失效的防范。在一些实施例中，所述受试者已经接受或正在接受包括补体抑制剂的疗法。在一些实施例中，所述方法包括向所述受试者施用补体抑制剂。

[0050] 在又另一方面，本公开还特征在于一种用于延迟或预防或防范具有同种异体移植的血管的受试者的所述同种异体移植的血管失效的方法，所述方法包括：向所述受试者施用有效量的ENPP1药剂或ENPP3药剂，由此延迟、预防或提供针对所述受试者的所述同种异体移植的血管失效的防范。在一些实施例中，所述受试者已经接受或正在接受包括补体抑制剂的疗法。在一些实施例中，所述方法包括向所述受试者施用补体抑制剂。

[0051] 在又另一方面，本公开还特征在于一种用于延迟具有实体器官同种异体移植物的受试者的所述实体器官同种异体移植物失效的方法，所述方法包括：向所述受试者施用有效量的：(i)ENPP1药剂或ENPP3药剂，以及(ii)补体抑制剂，由此延迟所述受试者的实体器官同种异体移植物失效。在一些实施例中，所述同种异体移植物失效可以延迟至少两个月(例如，至少六个月、至少一年、至少两年、至少三年、至少五年、至少七年、至少10年或甚至超过10年)。

[0052] 在又另一方面，本公开还特征在于一种用于延迟具有同种异体移植的血管的受试者的所述同种异体移植的血管失效的方法，所述方法包括：向所述受试者施用有效量的：(i)ENPP1药剂或ENPP3药剂，以及(ii)补体抑制剂，由此延迟所述受试者的所述同种异体移植的血管失效。在一些实施例中，所述同种异体移植物失效可以延迟至少两个月(例如，至少六个月、至少一年、至少两年、至少三年、至少五年、至少七年、至少10年或甚至超过10年)。

[0053] 在又另一方面，本公开还特征在于一种用于延迟具有实体器官同种异体移植物的受试者的所述实体器官同种异体移植物失效的方法，所述方法包括：向所述受试者施用有效量的ENPP1药剂或ENPP3药剂，由此延迟所述受试者的实体器官移植物失效。在一些实施例中，所述同种异体移植物失效可以延迟至少两个月(例如，至少六个月、至少一年、至少两

年、至少三年、至少五年、至少七年、至少10年或甚至超过10年)。在一些实施例中,所述受试者已经接受或正在接受包括补体抑制剂的疗法。在一些实施例中,所述方法包括向所述受试者施用补体抑制剂。

[0054] 另一方面,本公开涉及一种用于减少和/或预防具有实体器官同种异体移植物的受试者的实体器官同种异体移植物的血管系统中的狭窄或再狭窄的方法,所述方法包括:向所述受试者施用有效量的:(i)ENPP1药剂或ENPP3药剂以及(ii)补体抑制剂,由此减少和/或预防所述实体器官同种异体移植物的所述血管系统中的狭窄或再狭窄。

[0055] 另一方面,本公开涉及一种用于减少和/或预防具有实体器官同种异体移植物的受试者的实体器官同种异体移植物的血管系统中的狭窄或再狭窄的方法,所述方法包括:向所述受试者施用有效量的ENPP1药剂或ENPP3药剂以及补体抑制剂,由此减少和/或预防所述实体器官同种异体移植物的所述血管系统中的狭窄或再狭窄。在一些实施例中,所述受试者已经接受或正在接受包括补体抑制剂的疗法。在一些实施例中,所述方法包括向所述受试者施用补体抑制剂。

[0056] 在又另一方面,本公开还特征在于一种用于延迟或预防或作为针对具有实体器官同种异体移植物的受试者的所述实体器官同种异体移植物排斥的防范的方法,所述方法包括:向所述受试者施用有效量的:(i)ENPP1药剂或ENPP3药剂,以及(ii)补体抑制剂,由此延迟或预防所述受试者的实体器官同种异体移植物排斥。

[0057] 在又另一方面,本公开还特征在于一种用于延迟或预防或作为具有实体器官同种异体移植物的受试者的所述实体器官同种异体移植物排斥的防范的方法,其中所述受试者正在接受或已经接受包括ENPP1药剂或ENPP3药剂的疗法,所述方法包括:向所述受试者施用有效量的补体抑制剂,由此延迟或预防所述受试者的实体器官同种异体移植物排斥。在一些实施例中,所述方法还可以包含向所述受试者施用所述ENPP1药剂或ENPP3药剂。

[0058] 在又另一方面,本公开还特征在于一种用于延迟或预防或作为具有同种异体移植的血管的受试者的所述同种异体移植的血管的排斥的防范的方法,所述方法包括:向所述受试者施用有效量的:(i)ENPP1药剂或ENPP3药剂,以及(ii)补体抑制剂,由此延迟或预防所述受试者的所述血管的排斥。在一些实施例中,所述血管是动脉。在一些实施例中,所述血管是静脉。

[0059] 在又另一方面,本公开还特征在于一种用于延迟或预防或作为具有同种异体移植的血管的受试者的所述同种异体移植的血管的排斥的防范的方法,其中所述受试者正在接受或已经接受包括ENPP1药剂或ENPP3药剂的疗法,所述方法包括:向所述受试者施用有效量的补体抑制剂,由此延迟或预防所述受试者的所述同种异体移植的血管的排斥。在一些实施例中,所述方法还可以包含向所述受试者施用所述ENPP1药剂或ENPP3药剂。在一些实施例中,所述血管是动脉。在一些实施例中,所述血管是静脉。

[0060] 另一方面,本公开涉及一种用于减少和/或预防具有同种异体移植物的受试者的所述同种异体移植物的血管系统中血管平滑肌细胞增殖的进展的方法,所述方法包括向所述受试者施用有效量的ENPP1药剂,由此减少和/或预防所述受试者的所述同种异体移植物的所述血管系统中所述血管平滑肌细胞增殖的进展。

[0061] 另一方面,本公开涉及一种用于减少和/或预防具有实体器官同种异体移植物的受试者的实体器官同种异体移植物的血管系统中的狭窄或再狭窄的方法,所述方法包括:

向所述受试者施用有效量的ENPP1药剂或ENPP3药剂，由此减少和/或预防所述实体器官同种异体移植物中的狭窄或再狭窄。

[0062] 另一方面，本公开涉及一种用于延长具有实体器官同种异体移植物的受试者的实体器官同种异体移植物的存活期的方法，所述方法包括向所述受试者施用足量的ENPP1药剂或ENPP3药剂，所述量足以由此延长所述受试者的所述实体器官同种异体移植物的存活期。

[0063] 另一方面，本公开涉及一种用于抑制或预防具有实体器官同种异体移植物的受试者的实体器官同种异体移植物中的血管病的方法，所述方法包括向所述受试者施用足量的ENPP1药剂或ENPP3药剂，所述量足以抑制或预防所述实体器官同种异体移植物中的血管病。

[0064] 另一方面，本公开涉及一种用于抑制或预防具有血管同种异体移植物的受试者的同种异体移植的血管的血管病的方法，所述方法包括向受试者施用足量的ENPP1药剂或ENPP3药剂，所述量足以预防或抑制所述同种异体移植的血管的血管病。

[0065] 另一方面，本公开涉及一种用于抑制或预防具有血管同种异体移植物的受试者的同种异体移植的血管中血管平滑肌细胞增殖的方法，所述方法包括向所述受试者施用足量的ENPP1药剂或ENPP3药剂，所述量足以预防或抑制所述同种异体移植的血管中的血管平滑肌细胞增殖。

[0066] 另一方面，本公开涉及一种用于延长具有血管同种异体移植物的受试者的同种异体移植的血管的存活期的方法，所述方法包括向所述受试者施用足量的ENPP1药剂或ENPP3药剂，所述量足以由此延长所述同种异体移植的血管的存活期。

[0067] 另一方面，本公开还涉及一种用于减少和/或预防在具有实体器官移植并且在所述器官移植上经历外科手术的受试者的实体器官移植中血管平滑肌细胞增殖的进展的方法，所述方法包括向所述受试者施用有效量的ENPP1药剂，由此减少和/或预防所述受试者的所述实体器官移植中血管平滑肌细胞增殖的进展。

[0068] 另一方面，本公开还特征在于一种用于预防或防范具有实体器官同种异体移植物的受试者的所述实体器官同种异体移植物失效的方法，所述方法包括：向所述受试者施用有效量的ENPP1药剂或ENPP3药剂，由此预防或提供针对所述受试者的实体器官移植物失效的防范。

[0069] 另一方面，本公开还特征在于一种用于延迟具有实体器官同种异体移植物的受试者的所述实体器官同种异体移植物失效的方法，所述方法包括：向所述受试者施用有效量的ENPP1药剂或ENPP3药剂，由此延迟所述受试者的实体器官移植物失效。在一些实施例中，所述同种异体移植物失效可以延迟至少两个月(例如，至少六个月、至少一年、至少两年、至少三年、至少五年、至少七年、至少10年或甚至超过10年)。

[0070] 另一方面，本公开涉及一种用于减少和/或预防受试者的同种异体移植的血管的血管病的方法，所述方法包括：向受试者施用有效量的：(i)ENPP1药剂或ENPP3药剂以及(ii)补体抑制剂，由此减少和/或预防所述受试者的所述同种异体移植的血管的血管病。在一些实施例中，所述血管是动脉。在一些实施例中，所述血管是静脉。

[0071] 另一方面，本公开涉及一种用于减少和/或预防受试者的同种异体移植的血管的血管病的方法，所述方法包括：向所述受试者施用有效量的ENPP1药剂或ENPP3药剂，由此减

少和/或者预防所述受试者的同种异体移植的血管的血管病。在一些实施例中，所述血管是动脉。在一些实施例中，所述血管是静脉。

[0072] 另一方面，本公开涉及一种用于减少和/或预防受试者的同种异体移植的血管的血管病的方法，所述方法包括：向所述受试者施用有效量的ENPP1药剂或ENPP3药剂，由此减少和/或者预防所述受试者的同种异体移植的血管的血管病。在一些实施例中，所述血管是动脉。在一些实施例中，所述血管是静脉。在一些实施例中，所述受试者已经接受或正在接受包括补体抑制剂的疗法。在一些实施例中，所述方法包括向所述受试者施用补体抑制剂。

[0073] 另一方面，本公开涉及一种用于减少和/或预防受试者的同种异体移植的血管中血管平滑肌细胞增殖的进展方法，所述方法包括：向所述受试者施用有效量的ENPP1药剂或ENPP3药剂，由此减少和/或者预防所述受试者的同种异体移植的血管中血管平滑肌细胞增殖的进展。在一些实施例中，所述血管是动脉。在一些实施例中，所述血管是静脉。在一些实施例中，所述受试者已经接受或正在接受包括补体抑制剂的疗法。在一些实施例中，所述方法包括向所述受试者施用补体抑制剂。

[0074] 在另一方面，本公开涉及一种用于减少和/或预防具有同种异体移植物的受试者的同种异体移植物血管病(例如，心脏同种异体移植物血管病)的方法，所述方法包括：向所述受试者施用有效量的：(i)ENPP1药剂或ENPP3药剂以及(ii)补体抑制剂，由此减少和/或预防所述受试者的同种异体移植物血管病。

[0075] 在又另一方面，本公开涉及一种用于减少和/或预防具有同种异体移植物，并且已经接受或正在接受包括补体抑制剂的疗法的受试者的同种异体移植物血管病(例如，心脏同种异体移植物血管病)的方法，所述方法包括：向所述受试者施用有效量的ENPP1药剂或ENPP3药剂，由此减少和/或预防所述受试者的同种异体移植物血管病。在一些实施例中，所述方法进一步包括向所述受试者施用所述补体抑制剂。

[0076] 在本文所述的任何方法的一些实施例中，在所述外科手术之前、期间和/或之后施用所述药剂。

[0077] 在本文所述的任何方法的一些实施例中，在分流器放置之前、期间和/或之后施用所述药剂。

[0078] 在本文所述的任何方法的一些实施例中，其中外科手术和/或分流器放置进一步包括将透析导管引入到所述受试者体内。

[0079] 在一些实施例中，本文所述的任何方法可以包括向所述受试者施用抗凝剂、抗生素和抗高血压药物中的一种或多种。

[0080] 在一些实施例中，本文所述的任何方法可以包括监测所述受试者的所述分流器的闭塞，如血栓形成。

[0081] 在一些实施例中，本文所述的任何方法进一步包含向所述患者施用一种或多种免疫抑制剂。

[0082] 在本文所述的方法中的任何方法的一些实施例中，所述ENPP1药剂包括保留酶促活性的ENPP1变体。

[0083] 在本文所述的方法中的任何方法的一些实施例中，所述ENPP3药剂包括保留酶促活性的ENPP3变体。

[0084] 在本文所述的任何方法的一些实施例中，所述受试者是正在接受或已经接受抗凝

剂、抗生素和抗高血压药物中的一种或多种的受试者。

[0085] 在本文所述的任何方法的一些实施例中，所述受试者已经接受和/或正在接受与所述实体器官同种异体移植物移植结合的免疫抑制疗法，如一种或多种免疫抑制剂。

[0086] 在本文所述的任何方法的一些实施例中，所述受试者已经接受和/或正在接受与所述实体器官同种异体移植物移植结合的他汀(statin)药物、血管扩张剂、抗凝剂(例如，阿司匹林)和免疫抑制剂中的一种或多种。

[0087] 在一些实施例中，本文所述的任何方法进一步包含向所述患者施用他汀药物、血管扩张剂、抗凝剂(例如，阿司匹林)和免疫抑制剂中的一种或多种。

[0088] 在一些实施例中，本文所述的任何方法进一步包含对所述实体器官同种异体移植物进行血运重建外科手术。

[0089] 在本文所述的任何方法的一些实施例中，所述受试者预期在所述实体器官同种异体移植物上经历，已经经历或正在经历血运重建外科手术。

[0090] 在一些实施例中，所述血运重建外科手术包括血管成形术、旁路移植和/或支架放置。

[0091] 在本文所述的任何方法的一些实施例中，在所述外科手术之前、期间和/或之后施用所述药剂。

[0092] 在本文所述的任何方法的一些实施例中，所述外科手术包括球囊血管成形术和/或放置支架。

[0093] 在一些实施例中，本文所述的方法进一步包括进行所述外科手术。

[0094] 在本文所述的方法中的任何方法的一些实施例中，所述ENPP1药剂包括ENPP1多肽。

[0095] 在本文所述的方法中的任何方法的一些实施例中，所述ENPP1药剂包括编码ENPP1多肽的核酸。

[0096] 在本文所述的方法中的任何方法的一些实施例中，所述ENPP1药剂包括病毒载体，所述病毒载体包括编码ENPP1多肽的核酸。

[0097] 在本文所述的方法中的任何方法的一些实施例中，所述ENPP1多肽包括ENPP1的胞外结构域。

[0098] 在本文所述的方法中的任何方法的一些实施例中，所述ENPP1多肽包括ENPP1的催化结构域。

[0099] 在本文所述的方法中的任何方法的一些实施例中，所述ENPP1多肽包括SEQ ID NO:1的氨基酸99至925。

[0100] 在本文所述的方法中的任何方法的一些实施例中，所述ENPP1多肽包括异源蛋白。

[0101] 在本文所述的方法中的任何方法的一些实施例中，所述异源蛋白增加所述ENPP1多肽在哺乳动物体内的循环半衰期。

[0102] 在本文所述的方法中的任何方法的一些实施例中，所述异源蛋白为免疫球蛋白分子的Fc区。

[0103] 在本文所述的方法中的任何方法的一些实施例中，所述免疫球蛋白分子为IgG1分子。

[0104] 在本文所述的方法中的任何方法的一些实施例中，所述异源蛋白为白蛋白分子。

[0105] 在本文所述的方法中的任何方法的一些实施例中,所述异源蛋白处于所述ENPP1多肽的羧基末端。

[0106] 在本文所述的方法中的任何方法的一些实施例中,ENPP1药剂包括接头。

[0107] 在本文所述的方法中的任何方法的一些实施例中,所述接头将所述ENPP1多肽和所述异源蛋白分离。

[0108] 在本文所述的方法中的任何方法的一些实施例中,所述接头包括以下氨基酸序列:$(GGGGS)_n$,其中n为1至10的整数。

[0109] 在本文所述的方法中的任何方法的一些实施例中,所述ENPP1药剂皮下施用于所述受试者。

[0110] 在本文所述的方法中的任何方法的一些实施例中,所述ENPP1药剂静脉内施用于所述受试者。

[0111] 在本文所述的任何方法的一些实施例中,所述受试者:是吸烟者;患有高血压;胆固醇或甘油三酯水平升高;患有糖尿病;患有肾病;或肥胖。

[0112] 在本文所述的任何方法的一些实施例中,所述受试者具有I期、II期或III期铃木级MMD。另一方面,本公开的特征在于一种用于抑制或减缓受试者的I期铃木级MMD外周动脉疾病向III期铃木级MMD的进展的方法,所述方法包括:向所述受试者施用有效量的ENPP3药剂,由此抑制和/或减缓所述受试者的I期铃木级MMD向III期铃木级MMD的进展。

[0113] 另一方面,本公开的特征在于一种用于减少和/或预防在脑动脉上需要外科手术的受试者的所述脑动脉中血管平滑肌细胞增殖的进展的方法,其中所述受试者患有烟雾病,所述方法包括:向所述受试者施用有效量的ENPP1药剂或ENPP3药剂,由此减少和/或预防所述受试者的所述脑动脉的外科手术部位处所述脑动脉中血管平滑肌细胞增殖的进展。

[0114] 在本文所述的任何方法的一些实施例中,所述脑动脉是颈外动脉(ECA)、颈内动脉(ICA)、脑中动脉(MCA)和脑前动脉(ACA)中的一种或多种。

[0115] 在本文所述的任何方法的一些实施例中,在支架放置之前、期间和/或之后施用所述ENPP3药剂。

[0116] 在本文所述的任何方法的一些实施例中,所述实体器官同种异体移植物是心脏同种异体移植物。

[0117] 在本文所述的任何方法的一些实施例中,所述实体器官同种异体移植物是肺同种异体移植物、肝同种异体移植物或肾同种异体移植物。

[0118] 在本文所述的任何方法的一些实施例中,所述补体抑制剂是补体组分C5抑制剂,如抗C5抗体,例如,依库丽单抗(eculizumab)或雷夫利珠单抗-cwvz(ravulizumab-cwvz)。

[0119] 在一些实施例中,所述补体抑制剂是补体组分C1(包含C1s和C1q)、C2、C3、C4、C5、C6、C7、C8和/或C9的抑制剂,如与此类补体组分中的任一种结合并抑制其功能的抗体。

[0120] 在一些实施例中,所述补体抑制剂是康普他汀(compstatin)或其类似物。

[0121] 在一些实施例中,所述补体抑制剂是C5a抑制剂、C5aR抑制剂、C3抑制剂、因子D抑制剂、因子B抑制剂、C4抑制剂、C1q抑制剂、C1s抑制剂或其任何组合。

[0122] 在本文所述的任何方法的一些实施例中,所述补体抑制剂是凝集素途径抑制剂,如抗MASP2抗体(例如,OMS721)。

[0123] 另一方面,本公开涉及一种用于减少和/或预防具有实体器官同种异体移植物的

受试者的实体器官同种异体移植物的血管系统中的狭窄或再狭窄的方法,所述方法包括:向所述受试者施用有效量的ENPP1药剂,由此减少和/或预防所述实体器官同种异体移植物的所述血管系统中的狭窄或再狭窄。

[0124] 另一方面,本公开涉及一种用于减少和/或预防患有同种异体移植物血管病的受试者的同种异体移植物血管病的方法,所述方法包括向所述受试者施用有效量的ENPP3药剂,由此治疗所述受试者的所述同种异体移植物血管病。

[0125] 另一方面,本公开涉及一种用于减少和/或预防具有同种异体移植物的受试者的所述同种异体移植物的血管系统中血管平滑肌细胞增殖的进展的方法,所述方法包括向所述受试者施用有效量的ENPP3药剂,由此减少和/或预防所述受试者的所述同种异体移植物的所述血管系统中所述血管平滑肌细胞增殖的进展。

[0126] 另一方面,本公开还涉及一种用于减少和/或预防在具有实体器官移植并且在所述器官移植上经历外科手术的受试者的实体器官移植中血管平滑肌细胞增殖的进展的方法,所述方法包括向所述受试者施用有效量的ENPP3药剂,由此减少和/或预防所述受试者的所述实体器官移植中血管平滑肌细胞增殖的进展。

[0127] 在本文所述的任何方法的一些实施例中,在所述外科手术之前、期间和/或之后施用所述药剂。

[0128] 在本文所述的任何方法的一些实施例中,所述外科手术包括球囊血管成形术和/或放置支架。

[0129] 在本文所述的任何方法的一些实施例中,所述受试者不患有ENPP1缺乏症。

[0130] 在本文所述的方法中的任何方法的一些实施例中,所述ENPP3药剂包括ENPP3多肽。

[0131] 在本文描述的任何方法的一些实施例中,ENPP3药剂包括编码ENPP3多肽的核酸。

[0132] 在本文所述的方法中的任何方法的一些实施例中,所述ENPP3药剂包括病毒载体,所述病毒载体包括编码ENPP3多肽的核酸。

[0133] 在本文所述的方法中的任何方法的一些实施例中,所述ENPP3多肽包括ENPP3的胞外结构域。

[0134] 在本文所述的方法中的任何方法的一些实施例中,所述ENPP3多肽包括ENPP3的催化结构域。

[0135] 在本文所述的方法中的任何方法的一些实施例中,所述ENPP3多肽包括SEQ ID NO:.7的氨基酸49至875

[0136] 在本文所述的方法中的任何方法的一些实施例中,所述ENPP3多肽包括异源蛋白。

[0137] 在本文所述的方法中的任何方法的一些实施例中,所述异源蛋白增加所述ENPP3多肽在哺乳动物体内的循环半衰期。

[0138] 在本文所述的方法中的任何方法的一些实施例中,所述异源蛋白为免疫球蛋白分子的Fc区。

[0139] 在本文所述的方法中的任何方法的一些实施例中,所述免疫球蛋白分子为IgG1分子。

[0140] 在本文所述的方法中的任何方法的一些实施例中,所述异源蛋白为白蛋白分子。

[0141] 在本文所述的方法中的任何方法的一些实施例中,所述异源蛋白处于所述ENPP3

多肽的羧基末端。

[0142] 在本文所述的方法中的任何方法的一些实施例中,所述ENPP3药剂包括接头。

[0143] 在本文所述的方法中的任何方法的一些实施例中,所述接头将所述ENPP3多肽和所述异源蛋白分离。

[0144] 在本文所述的方法中的任何方法的一些实施例中,所述接头包括以下氨基酸序列:(GGGGS)n,其中n为1至10的整数。

[0145] 在本文所述的方法中的任何方法的一些实施例中,所述ENPP3药剂皮下施用于所述受试者。

[0146] 在本文所述的方法中的任何方法的一些实施例中,所述ENPP3药剂静脉内施用于所述受试者。

[0147] 在本文所述的任何方法的一些实施例中,所述受试者:是吸烟者;患有高血压;胆固醇或甘油三酯水平升高;患有糖尿病;患有肾病;或肥胖。在本文所述的任何方法的一些实施例中,所述受试者患有脑动脉闭塞。

[0148] 另一方面,本公开涉及一种用于减少和/或预防具有实体器官同种异体移植物的受试者的实体器官同种异体移植物的血管系统中的狭窄或再狭窄的方法,所述方法包括:向所述受试者施用有效量的ENPP3药剂,由此减少和/或预防所述实体器官同种异体移植物中的狭窄或再狭窄。

[0149] 根据以下详细描述和权利要求书,本公开的其它特征和优点将显而易见。

附图说明

[0150] 图1示出了移植前后对照和实验小鼠的预防性治疗方案的示意图。实验小鼠在主动脉移植前7天通过每天皮下注射以10mg/kg体重的示例性剂量用ENPP1-Fc治疗。向对照队列注射含有pH 7.4的tris缓冲盐水的媒剂。然后在移植后28天解剖所有小鼠,并且小鼠大约10周龄。

[0151] 图2示出了小鼠心脏移植的示意图。其还示出了移植的主动脉5μm切片的形态测量结果。计算每个切片的中层面积、内膜面积和内膜/中层比率(I/M比率)。

[0152] 图3示出了猪异位心脏移植模型的示意图。3(A)示出了在使用冷心脏停搏液(Plegisol)实现心脏停止后采集供体心脏。3(B)示出了移植物维持在冰盐水浆中,并且通过形成房室间隔缺损和解除二尖瓣功能来准备植入,以最小化左心室萎缩和腔内血栓形成。3(C)示出了受体的下腔静脉(IVC)和肾下主动脉被分离。3(D)示出了通过将供体肺动脉与受体的IVC和供体升主动脉与受体的腹主动脉吻合来植入移植物心脏。通过使用(E)心电图(ECG)和(F)超声心动图(UCG)监测移植物功能。箭头表示异位心脏同种异体移植物引起的电尖峰。(Hsu等人,《移植(Transplantation.)》2018年12月;102(12):2002-2011)。

[0153] 图4是支架植入后第14天和第42天通过血管造影术拍摄的代表性深动脉图像的一系列照片。两幅对照图像展示了由于第42天的内膜增殖而导致的深动脉相对于第14天的血管形态的变窄。相比之下,在用ENPP1-Fc治疗的动物中,在第14天与第42天之间,观察到深动脉形态几乎没有明显变化。血管内支架的上边界和下边界在每张照片中由矩形标识。

[0154] 图5是支架植入后第14天和第42天通过光学相干断层扫描(OCT)拍摄的代表性深动脉图像的一系列照片。两幅对照图像展示了相对于第14天的血管形态,第42天的深动脉

内膜明显增厚。相比之下，在用ENPP1-Fc治疗的动物中，在第14天与第42天之间观察到很少可见的内膜增厚。第42天的照片突出显示了狭窄的程度。

[0155] 图6是条形图，描绘了用ENPP1-Fc(治疗)或给定媒剂对照(对照)治疗的猪在第14天和第42天的深动脉狭窄面积百分比，如通过OCT测量的。

[0156] 图7示出了脑外科手术诱导MMD前后对照和实验小鼠的预防性治疗方案的示意图。实验小鼠在外科手术前7天通过每天皮下注射以10mg/kg体重的示例性剂量用ENPP1-Fc治疗。向对照队列注射含有pH 7.4的tris缓冲盐水的媒剂。然后在移植后28天解剖所有小鼠，并且小鼠大约10周龄。

[0157] 图8示出了通过颈内动脉狭窄建立MMD模型的过程。8A)示出了外科手术程序期间小鼠的方向。头部(牙齿)、前爪和尾部受到约束，并且在颈部中线(红色虚线)处形成切口。白框表示后面的图像区域。8B)示出了暴露气管、胸锁乳突(SCM)肌和二腹(PBD)肌的后腹部的颈部区域的开口。8C)示出了缝合线(S1-2)的放置，所述缝合线牵开SCM和PBD以暴露颈总动脉、颈内动脉和颈外动脉(CCA、ICA、ECA)。8D)示出了枕动脉(OA)、迷走神经(VN)和ICA的识别。8E)示出了OA的缝合线结扎，并且虚线示出切口以更好地暴露ICA。8F)示出了切开的OA，ICA暴露并使用6±0缝合线隔离。8G)示出了ICA上的微线圈放置在ECA深处(如H中所看到的)。(Roberts等人，颈内动脉狭窄：一种治疗烟雾病综合征的新型外科手术模型(Internal carotid artery stenosis:A novel surgical model for moyamoya syndrome，《公共科学图书馆·综合(PLoS One.)》2018;13(1):e0191312)。

[0158] 图9是血液透析血液从受试者的手臂(含有透析分流器)流入导管，经过压力监测器、血液泵和肝素泵(预防凝血)的图。血液在进入透析器或过滤器之前流过另一个压力监测器。过滤的血液继续经过静脉压监测器、空气阱和空气检测器以及空气检测器夹，并且返回受试者的手臂。

[0159] 图10是位于受试者右上胸部区域100中的可植入分流器2的视图。可植入透析分流器2也可以植入身体的其它区域，只要其被植入到中等大小的动脉附近合理处，其通常介于6mm与8mm之间，用于可植入透析分流器2。可植入透析分流器优选地包括以单个结构彼此连接的动脉端口4和静脉端口6。在其它实施例中，端口4、6可以是单独的结构，所述单独的结构可以包含允许其彼此连接的特征。动脉移植物12通常延伸穿过动脉端口4，而静脉移植物18从静脉端口6延伸。在植入过程期间，动脉移植物12优选地在其每一端连接到动脉26的侧壁，而静脉移植物18的端部连接到静脉34。在其它实施例中，动脉移植物12可以通过一对端对端吻合连接到动脉26。另外，静脉移植物18可以采取静脉导管的形式，所述静脉导管插入静脉34中，使得其可以进入中心静脉系统。可以通过用动脉导管102穿刺动脉端口4和用静脉导管104穿刺静脉端口来进行透析。动脉导管102和静脉导管104中的每一个都连接到透析机。

具体实施方式

[0160] 定义

[0161] 除非另外定义，否则本文使用的所有技术术语和科学术语具有与本公开所属领域的普通技术人员通常所理解的含义相同的含义。尽管在本公开的实践或测试中可以使用类似于或等同于本文所描述的那些方法和材料的任何方法和材料，但是描述了优选方法和材

料。

[0162] 为了清楚起见，“NPP1”和“ENPP1”是指相同蛋白质并且可在本文中互换使用。如本文所使用的，术语“ENPP1蛋白”或“ENPP1多肽”是指由ENPP1基因编码的能够切割ATP以产生PPi并且还减少软组织中的异位钙化的外核苷酸焦磷酸酯酶/磷酸二酯酶-1蛋白。

[0163] ENPP1蛋白为II型跨膜糖蛋白并切割多种底物，所述底物包含核苷酸和核苷酸糖的磷酸二酯键以及核苷酸和核苷酸糖的焦磷酸酯键。ENPP1蛋白具有跨膜结构域和可溶性胞外结构域。胞外结构域被进一步细分为生长素介质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Braddock等人的PCT申请公开第WO 2014/126965号中详细描述，所述申请专利通过引用以其整体并入本文。

[0164] 如本文所使用的，ENPP1多肽涵盖表现出ENPP1酶促活性的多肽、保留ENPP1酶促活性的ENPP1变体、ENPP1或ENPP1变体的包含表现出ENPP1酶促活性的缺失变体的片段。ENPP1酶促活性是指ENPP1多肽将三磷酸腺苷(ATP)切割成血浆焦磷酸酯(PPi)的能力，如下文所指出的。

[0165] 如本文所用的，ENPP3多肽涵盖表现出ATP切割酶促活性的多肽、保留ATP切割酶促活性的ENPP3突变体、包含表现出ATP切割酶促活性的缺失变体的ENPP3片段或ENPP3变体。ATP切割酶促活性是指ENPP3多肽将三磷酸腺苷(ATP)切割成血浆焦磷酸酯(PPi)的能力，如下文所指出的。

[0166] ENPP1多肽和ENPP3多肽、其突变体或突变体片段的一些实例先前已在Braddock等人的国际PCT申请公开第WO/2014/126965号、Braddock等人的第WO/2016/187408号、Braddock等人的第WO/2017/087936号和Braddock等人的第WO2018/027024号中描述，所述文献中的全部内容通过引用以其整体并入本文。

[0167] 关于ENPP1多肽或ENPP3多肽的“酶促活性”被定义为将ATP水解活性处理成AMP和PPi和/或将AP3a水解处理成ADP和AMP。NPP1和NPP3易于将ATP水解成AMP和PPi。NPP1的稳态米氏酶促常数(the steady-state Michaelis-Menten enzymatic constant)是使用ATP作为底物确定的。NPP1可以通过对酶促反应的HPLC分析表现为切割ATP，并且底物和反应产物的身份是通过使用ATP、AMP和ADP标准品确认的。在酶促产物AMP累积的情况下，ATP底物在存在NPP1的情况下随时间的推移而降解。使用各种浓度的ATP底物，在存在ATP的情况下得到了NPP1的初始速率速度，并且数据拟合到曲线中以得到酶促速率常数。在生理pH下，NPP1的动力学速率常数为Km＝144μM并且$kcat_t$＝7.8s^{-1}。

[0168] 如本文所使用的，术语“ENPP1前体蛋白”是指其信号肽序列位于ENPP1 N末端处的ENPP1。在蛋白水解时，从ENPP1切割信号序列以提供ENPP1蛋白。可用于本公开内的信号肽序列包含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。

[0169] 如本文所使用的，术语“ENPP3前体蛋白”是指其信号肽序列位于ENPP3 N末端处的ENPP3。在蛋白水解时，从ENPP3切割信号序列以提供ENPP3蛋白。可用于本公开内的信号肽序列包含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。

[0170] 如本文所使用的，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，也被称为阳离子抗菌蛋白CAP37或肝素结合蛋白(HBP)为人体内由AZU1基因编码

的蛋白质。编码天青杀素信号肽的核苷酸序列MTRLTVLALLAGLLASSRA(SEQ ID NO:42)与NPP1基因或NPP3基因的核苷酸序列融合,所述核苷酸序列在被编码时产生ENPP1前体蛋白或ENPP3前体蛋白。(用于开发高表达CHO细胞系的经优化的信号肽(Optimized signal peptides for the development of high expressing CHO cell lines),Kober等人,《生物技术和生物工程化(Biotechnol Bioeng.)》2013年4月;110(4):1164-73)。

[0171] 如本文所使用的,术语“ENPP1-Fc构建体”是指与IgG分子(优选地,人IgG)的FcR结合结构域重组融合和/或化学缀合(包含共价缀合和非共价缀合两者)的ENPP1(例如,ENPP1的胞外结构域)。在某些实施例中,ENPP1的C末端与FcR结合结构域的N末端融合或缀合。

[0172] 如本文所用,术语“ENPP3-Fc构建体”是指与IgG分子(优选地,人IgG)的FcR结合结构域重组融合和/或化学缀合(包含共价缀合和非共价缀合两者)的ENPP3。在某些实施例中,ENPP1的C末端与FcR结合结构域的N末端融合或缀合。

[0173] 如本文所用,术语“Fc”是指人IgG(免疫球蛋白)Fc结构域。设想了IgG的亚型,如IgG1、IgG2、IgG3和IgG4用作Fc结构域。“Fc区或Fc多肽”是IgG分子的与通过IgG分子的木瓜蛋白酶消化获得的可结晶片段相关的部分。Fc区包括IgG分子的通过二硫键连接的两个重链的一半的C末端。所述Fc区不具有抗原结合活性但含有碳水化物部分和用于互补的结合位点以及Fc受体,包含FcRn受体。Fc片段含有整个第二恒定结构域CH2(根据Kabat编号系统,人IgG1的残基231-340)和第三恒定结构域CH3(残基341-447)。术语“IgG铰链-Fc区”或“铰链-Fc片段”是指IgG分子的由Fc区(残基231-447)和铰链区(残基216-230)组成的从Fc区的N末端延伸的区。术语“恒定结构域”是指免疫球蛋白分子的相对于所述免疫球蛋白的含有抗原结合位点的其它部分,即可变区,具有更保守的氨基酸序列的部分。恒定结构域含有重链的CH1结构域、CH2结构域和CH3结构域以及轻链的CHL结构域。

[0174] 如本文所用,术语“功能等效变体”如本文所用涉及与ENPP1或ENPP3的序列(以上定义的)基本上同源并且分别保留ENPP1或ENPP3的酶促活性和生物活性的多肽。用于确定变体是否保留天然ENPP1或ENPP3的生物活性的方法是技术人员广泛已知的并且包含所述应用的实验部分中使用的测定中的任何测定。具体地,ENPP1或ENPP3的通过病毒载体递送的功能等效变体涵盖在本公开中。

[0175] ENPP1或ENPP3的功能等效变体为分别与天然ENPP1或ENPP3同源的多肽。表达“基本上同源”涉及所述蛋白质序列相对于以上所述的ENPP1或ENPP3序列的同一性程度分别为至少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%时并且仍保持野生型ENPP1或ENPP3蛋白相对于ATP切割的至少50%、55%、60%、70%、80%或90%活性的蛋白质序列。

[0176] 两种多肽之间的同一性程度是使用本领域的技术人员广泛已知的计算机算法和方法确定的。两种氨基酸序列之间的同一性优选地是通过使用BLASTP算法(《BLAST手册(BLAST Manual)》,Altschul,S.等人,马里兰州贝塞斯达的美国国立卫生院美国国家医学图书馆美国国家生物技术信息中心(NCBI NLM NIH Bethesda,Md.)20894,Altschul,S.等人,《分子生物学杂志(J.Mol.Biol.)》215:403-410(1990))确定的,但还可以使用其它类似算法。使用了BLAST和BLAST 2.0以及本文所述参数来确定序列同一性百分比。用于进行BLAST分析的软件可通过美国国家生物技术信息中心公开获得。

[0177] ENPP1或ENPP3功能等效变体可以通过替代多核苷酸内考虑要用于分别产生ENPP1

或ENPP3的宿主细胞中的密码子偏爱性的核苷酸来获得。此“密码子优化”可以通过计算机算法确定,所述计算机算法并入了密码子频率表,如由威斯康辛州麦迪逊遗传学计算机组(enetics Computer Group,Madison,Wis)的威斯康辛大学包版本9.0提供的针对密码子偏爱性的“Human high.cod”。ENPP1多肽或ENPP3多肽的变体预期保留野生型ENPP1或ENPP3蛋白相对于ATP切割的至少50%、55%、60%、70%、80%或90%活性。

[0178] 如本文所用,术语“ENPP1片段”是指ENPP1蛋白的片段或一部分或全长NPP1的活性子序列,其至少具有以蛋白质形式或以编码蛋白质的核酸形式施用的ENPP1催化结构域。

[0179] 如本文所用,术语“ENPP1药剂”是指至少包括能够通过切割腺苷三磷酸(ATP)产生血浆焦磷酸酯(Ppi)的催化结构域的ENPP1多肽或融合蛋白或ENPP1片段或编码至少包括能够通过酶促切割ATP产生PPi的催化结构域的ENPP1融合蛋白或ENPP1片段的多核苷酸,如cDNA或RNA,或含有编码所述多肽或融合蛋白或片段的多核苷酸的载体,如病毒载体。

[0180] 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。野生型基因是群体中最常观察到的基因,并且因此被任意设计为人NPP1或NPP3基因的“正常”或“野生型”形式。相比之下,术语“功能等效的”是指相比于野生型基因或基因产物时在序列和/或功能性质方面展示出修饰(即,更改的特性)的NPP1或NPP3基因或基因产物。天然存在的突变体可以被分离;这些突变体是通过与野生型基因或基因产物相比时其具有更改的特性(包含更改的核酸序列)这一事实鉴定的。

[0181] 当提及如量、持续时间等可测量的值时,如本文所用的“约”意味着涵盖与指定值的+20%或+10%,更优选地+5%,甚至更优选地+1%,以及仍更优选地+0.1%的变化,因为此类变化适合于执行所公开的方法。

[0182] 如本文定义的,术语“部分”是指可以与ENPP1蛋白或ENPP3多肽共价或非共价连接并且能够赋予其所连接的蛋白质期望性质的化学组分或生物分子。例如,术语部分可以指骨靶向肽,如聚天冬氨酸或聚谷氨酸(具有4-20个保守asp或glu残基)或延长ENPP1多肽或ENPP3多肽的半衰期的分子。部分的一些其它实例包含Fc、白蛋白、转铁蛋白、聚乙二醇(PEG)、同氨基酸聚合物(HAP)、脯氨酸-丙氨酸-丝氨酸聚合物(PAS)、弹性蛋白样肽(ELP)和明胶样蛋白(GLK)。

[0183] 如本文所定义的,术语“受试者”、“个体”或“患者”是指哺乳动物,优选是指在NPP1基因中不具有功能缺失突变的人,如导致病理性钙化和病理性骨化疾病的功能缺失突变,如婴儿全身性动脉钙化(GACI),常染色体隐性低磷佝偻病2型(ARHR2)、婴儿特发性动脉钙化(IIAC)、后纵韧带骨化(OPLL)、低磷血症佝偻病、骨关节炎、动脉粥样硬化斑块钙化、遗传性和非遗传性骨关节炎、强直性脊柱炎,随年龄增长而发生的动脉硬化、终末期肾病和早衰引起的钙过敏症。此类患者将具有正常水平的血清NPP1,这是指在健康受试者中维持正常水平的血浆焦磷酸酯(PPi)所需的NPP1的量。PPi的正常水平对应于2μM至3μM。

[0184] 如本文所使用的,术语“血浆焦磷酸酯(PPi)水平”是指动物的血浆中存在的焦磷酸酯的量。在某些实施例中,动物包含大鼠、小鼠、猫、狗、人、牛和马。存在若干种用于测量PPi的方式,其中之一是通过使用具有修饰的尿甘-二磷酸葡萄糖(UDPG)焦磷酸化酶(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)进行的酶促测定。

[0185] 通常,健康人类受试者的血浆PPi水平的范围为约1μm至约3μM,在一些情况下介于

1-2μm之间。患有ENPP1表达缺陷的受试者倾向于表现出低ppi水平,所述水平的范围比正常水平低至少10%、比正常水平低至少20%、比正常水平低至少30%、比正常水平低至少40%、比正常水平低至少50%、比正常水平低至少60%、比正常水平低至少70%、比正常水平低至少80%以及其组合。在患有婴儿全身性动脉钙化(GACI)的患者中,发现ppi水平低于1μm,并且在一些情况下低于检测水平。在患有弹性纤维假黄瘤(PXE)的患者中,ppi水平低于0.5μm。(《动脉粥样硬化、血栓形成和血管生物学(Arterioscler Thromb Vasc Biol.)》2014年9月;34(9):1985-9;Braddock等人,《自然通讯(Nat Commun)》.2015;6:10006)。

[0186] 如本文所使用的,术语"PPi"是指无机焦磷酸酯。

[0187] "低水平的PPi"是指受试者的血浆焦磷酸酯(PPi)水平至少比正常水平的2%至5%低0.1%至0.99%的情况。健康人受试者血浆PPi的正常水平为1.8μM至2.6μM。+/-0.1μM(《关节炎和风湿症(Arthritis and Rheumatism)》,第22卷,第8期(1979年8月))

[0188] 如本文所用,术语"非外科手术组织损伤"是指在创伤事件期间持续到组织或血管的损伤,包含但不限于涉及使用钝力或如刀等尖锐物体的肢体冲突、如从高处跌落的机械损伤、由于重机械造成的工作场所损伤或如车祸等车辆损伤。

[0189] 如本文所用,术语"心肌梗塞"是指由于动脉的内壁中斑块的形成而发生,从而导致到心脏的血流减少并且由于缺乏氧气供应而损伤心肌的对心肌的永久损伤。MI的症状包含从左臂延续到颈部的胸部疼痛、呼吸短促、出汗、恶心、呕吐、心脏跳动异常、焦虑、疲劳、无力、应激、抑郁和其它因素。

[0190] 如本文所使用的,术语"烟雾病"或"烟雾病综合征"是指脑动脉的狭窄闭塞性疾病,涉及平滑肌细胞增殖伴有内膜增生,导致韦利斯氏环(circle of Willis)周围的动脉狭窄和闭塞。其涉及在皮层下区域形成类似"烟雾"("烟雾病")的新血管。MMD发生在儿童和成人中,有两个高峰——在5岁至10岁左右,第二个高峰出现在生命的第三个十年与第五个十年之间。常见症状包含头痛或头晕、四肢或身体一侧无力或瘫痪、言语问题——无法说话或回忆单词,感觉或认知障碍、不自主运动、癫痫发作或意识丧失、视力问题、中风和脑出血。80%的MMD病例是RNF213和或R4810K突变的携带者。MMD和MMS的治疗选择涉及每日使用阿司匹林,改变生活方式以最大化脑灌注,以及外科手术直接或间接旁路以恢复血流。

[0191] 对最终MMD的诊断标准进行了修订,以包含双侧和单侧颈动脉末端狭窄(ICA)伴有脑基底血管网络异常的患者。患者群体分级的铃木系统已经用于MMD。MMD的最终诊断需要在单侧病例中进行导管血管造影术,而双侧病例可以通过导管血管造影术或磁共振成像/血管造影术(MRI/MRA)快速诊断。

[0192] 如本文所使用的,短语"脑血管闭塞"是指脑中血管的暂时或永久阻塞。血管狭窄(狭窄)、血栓形成(clot formation或thrombosis)、阻塞(栓塞)或血管破裂(出血)可能导致血流受限。缺乏足够的血流(缺血)会影响脑组织,并且可能导致中风。

[0193] 如本文所使用的,术语"铃木分类系统"是指由铃木等人开发的分类系统(Suzuki J,Takaku A.脑血管"烟雾病",表现为脑基底异常网状血管的疾病(Cerebrovascular″moyamoya″disease.Disease showing abnormal net-like vessels in base of brain.)《神经病学档案(Arch Neurol.)》1969;20(3):288±99.)。此分类系统将患者的临床表现分为四个期。绝大多数患者将进展通过铃木期的部分或全部,尽管进展可能以不同的速率发生,并且儿童的进展似乎比青少年或成人更快。所述系统仅基于常规血管造影术,并且如下

表所示。

[0194]

级别	症状
I 期	颈动脉分叉变窄；颈内动脉（ICA）分叉变窄
II 期	烟雾病开始；脑前动脉（ACA）、脑中动脉（MCA）扩张并且 ICA 分叉变窄伴有烟雾病变化
III 期	烟雾病强化，ICA 分叉的烟雾病变化进一步增加，并且 ACA 和 MCA 变窄
IV 期	烟雾病最大化，烟雾病变化随着 ICA 的闭塞变化和薄弱 ACA 和 MCA 而减少
V 期	烟雾病减少，随着 ICA、ACA 和 MCA 的闭塞，烟雾病变化进一步减少
VI 期	烟雾病消失，ICA 基本上随着脑从颈外动脉（ECA）供应而消失

[0195] 如本文所使用的，术语“颈内动脉(ICA)”是指位于颈部内侧并向脑和眼睛供应血液的动脉。

[0196] 如本文所使用的，术语“颈外动脉(ECA)”是指头部和颈部的主要动脉。其起源于颈总动脉(当其分裂成颈外动脉和颈内动脉时)。ECA为面部、头皮、颅骨和脑膜供应血液。如本文所使用的，术语“脑前动脉(ACA)”是指脑上的一条动脉，所述动脉向额叶和上内侧顶叶的大部分中线部分供应含氧血液。一对脑前动脉起源于颈内动脉，并且韦利斯氏环的一部分。

[0197] 如本文所使用的，术语“脑中动脉(MCA)”是指向脑供血的三大成对动脉之一。MCA起源于颈内动脉，并且继续进入外侧沟，然后在其中分支并延伸到外侧脑皮层的许多部位。其还向前颞叶和岛叶皮质供血。

[0198] 如本文所使用的，术语“常规血管造影术”是指血管造影术或动脉造影术，其是一种医学成像技术，用于可视化身体血管和器官的内部或内腔，特别关注动脉、静脉和心室。传统上，这是通过将不透射线的造影剂注射到血管中并使用基于X射线的技术(如荧光透视)进行成像来实现的。

[0199] 如本文所使用的，术语“导管血管造影术”是指一种医疗程序，其中导管、x射线成像引导和造影剂注射用于检查身体关键区域(如脑或心脏)的血管是否存在异常，如动脉瘤和动脉粥样硬化(斑块)等疾病。

[0200] 如本文所使用的，术语“磁共振血管造影(MRA)”是指一种医疗过程，其中磁共振成像扫描仪用于借助于使用静脉注射针施用的造影剂来可视化如脑、肺和心脏等关键区域的血管中的阻塞。其是诊断血管中阻塞或闭塞的非侵入性方法。

[0201] 如本文所用，术语“需要外科手术的受试者”是指没有ENPP1缺乏且患有外周动脉(如股动脉、股腘动脉或胫腓动脉)动脉闭塞的患者。

[0202] 如本文所用，术语“外科手术部位”是指由于血管创伤或意外创伤而在其上发生组织损伤的动脉的区。

[0203] 如本文所用，术语“脑钙化”(BC)是指其中钙和其它矿物质在血管壁和组织实质中沉积发生从而导致神经元死亡和胶质增生的非特异性神经病理学。脑钙化通常与各种慢性和急性脑病症相关，包含唐氏综合征(Down's syndrome)、路易体病(Lewy body disease)、

阿尔茨海默氏病(Alzheimer's disease)、帕金森氏病(Parkinson's disease)、血管性痴呆、脑肿瘤和各种内分泌病状。心脏组织的钙化是指钙沉积物(可能包含其它矿物质)在心脏组织,如主动脉组织和冠状组织中累积。

[0204] 如本文中关于透析分流器的使用所使用的,狭窄减缓并减少了通过AV瘘的血流,导致透析治疗质量、穿刺后出血的延长或瘘疼痛的问题。狭窄也可以导致通道堵塞或结块。

[0205] 如本文所用,术语"手术刀切口"是指在外科手术程序期间使用如手术刀等尖锐物体在组织中进行的切口。切口是在身体组织中进行以使下面的组织、骨或器官暴露使得可以进行外科手术程序的切口。

[0206] 如本文所用,术语"外科手术部位"是指由于血管创伤或意外创伤而在其上发生组织损伤的动脉的区。

[0207] 术语"动静脉分流器"或"AV分流器"或简称"分流器"是指植入的装置,所述装置包含连接动脉和静脉的导管。分流器连接动脉和静脉插管,并且为有效的血液透析提供比正常体积更大的血液流量。分流器可以位于身体的任何部位,并且最常位于手臂、腿部或右锁骨下方的胸部区域。

[0208] 如本文所使用的,术语"涂覆的分流器"是指能够缓慢洗脱治疗化合物或多肽(如ENPP1或ENPP3)以减少外科手术部位处血管平滑肌细胞增殖量的分流器,通常用于去除动脉阻塞。

[0209] 如本文所使用的,术语"血液透析"是指补偿肾功能异常所需的治疗,其中废物和水从血液中过滤出来,并且过滤的清洁血液返回身体。血液透析有助于控制血压,并且平衡受试者血液中的重要矿物质,如钾、钠和钙。

[0210] 如本文所使用的,术语"瘘"是指中空或管状器官与体表之间,或两个中空或管状器官之间的异常或手术形成的通道。

[0211] 术语"支架"是指放置在血管、管道或导管内的管状支架,用于帮助愈合或缓解阻塞。

[0212] 术语"血管"是指通过组织和器官运送血液的管状结构;静脉、动脉或毛细血管。

[0213] 如本文所使用的,术语"补体抑制剂"是指阻止或减少补体级联的激活和/或传播的分子(例如,蛋白质(如抗体)、小分子或肽),所述补体级联导致形成C3a或通过C3a受体的信号传导,C5a或通过C5a受体的信号传导或末端补体的形成。补体抑制剂在本领域中是众所周知的,并在例如以下中进行了描述:Zipfel等人,(2019)《免疫学前沿(Front Immunol)》10:2166。还参见例如,美国专利第5,679,345号,所述美国专利的公开内容通过全文引用的方式并入。

[0214] 如本文所用,术语"改变"、"缺乏"、"变化"或"突变"是指细胞中的基因中影响其所编码的多肽的功能、活性、表达(转录或翻译)或构象的突变,包含错义突变和无义突变、插入、缺失、移码和提前终止。

[0215] 如本文所定义的,短语"中层面积"是动脉的外部弹性膜与内部弹性膜之间的面积。

[0216] 如本文所定义的,短语"内膜区域(intimal area)"和所述内膜面积是动脉的所述内部弹性膜与内腔之间的区域/面积。

[0217] 如本文所定义的,短语"外部弹性膜"是指紧挨着动脉的血管中层的平滑肌外部的

弹性结缔组织的层。

[0218] 如本文所定义的，短语“内部弹性膜”是指形成血管的血管内膜的最外部部分的弹性组织的层。

[0219] 如本文所定义的，短语“内腔”是指血管的内部，如血流通过其发生的动脉、静脉或毛细管中的中心空间。

[0220] 如本文所定义的，短语“血管病”是指血管系统的疾病。“血管系统”是指身体或器官(如实体器官移植或身体部分)中的血管排列。“血管”是指受试者体内的动脉、小动脉、毛细血管和静脉中的一种或多种，或受试者的实体器官同种异体移植物。“血管炎”是指静脉、动脉、毛细血管或淋巴管的炎症。“血管化移植物”是指受体血管系统与移植物中的血管连接后的移植物。

[0221] 如本文所定义的，短语“心脏同种异体移植物血管病(CAV)”是指同种异体移植物或实体器官移植(如心脏)的血管并发症，其中供应移植的心脏的血管逐渐变窄并限制其血流，随后导致心肌损伤或猝死。CAV的诊断是通过定期随访和监测移植的器官(如心脏)的早期疾病迹象。这涉及包含冠状动脉血管造影术和血管内超声在内的侵入性诊断，以及包含多巴酚丁胺负荷超声心动图、正电子发射断层扫描、计算机断层血管造影术(CT血管造影术)在内的非侵入性调查，以及各种生物标志物的水平，如C-反应性蛋白、血清脑钠肽、肌钙蛋白和血清microRNA 628-5p。

[0222] 如本文所定义的，“同种异体移植物”是指将器官或组织从供体移植到同种异体的受体。同种异体移植物涉及许多人体器官和组织移植物，包含来自尸体、活体亲属和活体无关供体的器官和组织。

[0223] 如本文所定义的，“实体器官同种异体移植物”是指实体器官的同种异体移植物。“实体器官”是一种内部器官，具有牢固的组织一致性，并且既不是中空的(如胃肠道器官)，也不是液体(如血液)。实体器官包含但不限于肾、肝、角膜、肠、心脏、肺和胰腺。

[0224] 如本文所定义的，术语“移植物排斥”或“移植排斥”是指其中移植的器官或组织被受体的免疫系统排斥的情况，这会破坏同种异体移植物，并且通过移植的组织血管的纤维化导致移植的器官长期丧失功能。

[0225] 如本文所定义的，短语“延长同种异体移植物的存活期”是指防止受体免疫系统对移植的供体器官或组织的排斥，并且提高移植的器官的寿命。相对于无治疗的同种异体移植物的存活期，同种异体移植物的存活期可以延长至少12个月、18个月、2年、3年、4年、5年、8年、10年或更长。

[0226] 如本文所定义的，短语“心脏同种异体移植物”是指涉及供体心脏移植到受体或一个或多个供体动脉或静脉移植到受体心脏的实体器官移植。心脏同种异体移植物中的移植物排斥通常通过进行心肌内活检来诊断。

[0227] 如本文所定义的，短语“肾同种异体移植物”是指涉及供体肾移植到受体或一个或多个供体动脉或静脉移植到受体肾的实体器官移植。肾同种异体移植物中的移植物排斥通常通过监测尿蛋白水平来诊断，如总蛋白与肌酐比率、白蛋白与肌酐比率、血清肌酐水平和肾小球滤过率。

[0228] 如本文所定义的，短语“肝同种异体移植物”是指涉及供体肝移植到受体或一个或多个供体动脉或静脉移植到受体肝的实体器官移植。肝同种异体移植物中的移植物排斥通

过监测转氨酶、胆红素和碱性磷酸酶水平来诊断。

[0229] 如本文所定义的，短语“肺同种异体移植物”是指涉及供体肺移植到受体或一个或多个供体动脉或静脉移植到受体肺的实体器官移植。肺同种异体移植物中的移植物排斥通过支气管镜检查、经支气管活检和肺功能测试来诊断。

[0230] 如本文所定义的，短语“同种异体移植的血管”或“同种异体移植的血管系统”是指将一个或多个供体血管(如动脉、静脉、毛细血管和/或小动脉)移植到受体的体内。

[0231] 如本文所定义的，短语“同种异体移植的动脉”是指将一条或多条供体动脉移植到受体的体内。

[0232] 如本文所定义的，短语“同种异体移植的静脉”是指将一条或多条供体静脉移植到受体的体内。

[0233] 如本文所定义的，短语“心肌内活检”是指经皮获得少量心肌组织用于诊断、治疗和研究目的的程序。其主要用于(1)跟踪移植心脏的心肌排斥；(2)诊断特定的炎性、浸润性或家族性心肌病症；以及(3)对未知心肌肿块进行采样。

[0234] 如本文所定义的，短语“经支气管肺活检”是指通过内镜引导的钳子从肺中获得的活检，这有助于评估沿着支气管血管束和中央肺区分布的移植中的病变。

[0235] 如本文所定义的，短语“外科手术”是指涉及血管介入的侵入性医疗程序，所述血管介入通过手术刀切口或射频消融或冷冻消融或激光消融产生组织损伤。

[0236] 如本文所定义的，短语“组织损伤”是指增殖或增殖开始和最终引起动脉壁增厚的血管平滑肌的迁移以及在如搭支架或血管成形术等经皮血管介入之后引起再狭窄的动脉内腔空间减小。

[0237] 如本文所定义的，短语“NPP1缺乏的”或“ENPP1缺乏症”是指相对于NPP1蛋白的正常血清水平或NPP1的正常活性，NPP1蛋白的量或NPP1活性减少，其中此类减少导致病理性钙化和/或病理性骨化的疾病或病症。此类病理性疾病包含但不限于GACI和ARHR2。如本文所使用的，ENPP1缺乏症不是指NPP1蛋白和/或NPP1活性的少量减少，这不会导致病理性钙化和/或病理性骨化的疾病或病症。

[0238] 如本文所定义的，短语“再狭窄”是指狭窄再发生。狭窄是指使血管变窄，从而导致血流受限。再狭窄通常涉及动脉或其它大血管已变窄、接受了用于清除阻塞的治疗并且随后变得再次变窄。再狭窄通常通过使用超声X射线断层扫描(CT)、核成像、光学成像或对比度增强图像或免疫组织化学检测中的一种或多种检测。如本文所定义的，短语“肌内膜增殖”是指血管平滑肌细胞增殖，所述增殖发生在个体的动脉壁的血管内膜处。

[0239] 如本文所用，短语“减少或预防肌内膜增殖”是指可溶性NPP1能够在施用时降低组织损伤部位处的增殖血管平滑肌细胞水平，由此减少动脉壁的增厚并且防止动脉再狭窄的发生或降低动脉再狭窄的水平。

[0240] 如本文所用，术语“治疗(treatment)”或“治疗(treating)”被定义为向患有疾病或病症、疾病或病症的症状或可能患上疾病或病症的受试者施涂或施用可溶性NPP1(单独的或与另一种药剂组合)或向来自患者的单独组织或细胞系施涂或施用治疗剂(例如，用于诊断或体外应用)，目的是治愈、愈合、缓和、缓解、改变、补救、减轻、改善或影响疾病或病症、疾病或病症的症状或患上疾病或病症的可能。此类治疗可以基于从药物基因组学领域获得的知识具体定制或修改。

[0241] 如本文所用,术语“预防(prevent)”或“预防(prevention)”或“减少(reduce)”意指疾病或疾病未发展(如果未发生疾病或病症的话)或疾病或病症未进一步发展(如果疾病或病症已经发展的话)。还考虑了其能够预防与病症或疾病相关的病症中的一些或全部。

[0242] 如本文所用,术语“有效量”是指相比于尚未接受此量的对应受试者,足以改善病状、病症、疾病或使病状、病症或疾病进展或推进减少的药剂(例如NPP1融合多肽或NPP3融合多肽)的量。有效量还可以治疗、愈合、预防或改善病状、疾病或病症。所述术语在其范围内还包含有效增强正常生理功能的量。如本文所用,术语“多肽”是指由氨基酸残基、相关天然存在的结构变体和通过肽键连接的其合成非天然存在的类似物构成的聚合物。

[0243] 如本文所用,术语“分离的”意指改变或从自然状态中去除。例如,天然存在于活体动物体内的核酸或多肽不是“分离的”,但与其天然状态的共存材料部分或完全分离的相同核酸或多肽是“分离的”。分离的核酸或蛋白质可以以基本上纯化形式存在,或者可以存在于非天然环境,例如宿主细胞中。

[0244] 如本文所用,“基本上纯化”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其通常在其天然存在状态下所缔合的其它组分分离的多肽。非限制性实施例包含95%纯度、99%纯度、99.5%纯度、99.9%纯度和100%纯度。

[0245] 如本文所用,术语“寡核苷酸”或“多核苷酸”是长度的范围为至少2个,在某些实施例中,至少8个、15个或25个核苷酸,但可以为高达50个、100个、1000个或5000个核苷酸长的核酸或与多核苷酸特异性杂交的化合物。

[0246] 如本文所用,术语“药物组合物”或“组合物”是指可用于本公开内的至少一种化合物与药学上可接受的载体的混合物。药物组合物促进化合物施用于患者。本领域中存在施用化合物的多种技术,包含但不限于皮下、静脉内、口服、气溶胶、吸入、直肠、阴道、透皮、鼻内、颊下、舌下、肠胃外、鞘内、胃内、眼部、肺和局部施用。

[0247] 如本文所用,术语“药学上可接受的”是指不消除化合物的生物活性或性质并且相对无毒的材料,如载体或稀释剂,即,材料可以施用于个体,不会引起不期望的生物学效应或以有害方式与其所含有的组合物的组分中的任何组分,例如磷酸盐缓冲盐水(PBS)相互作用

[0248] 如本文所用,术语“病理性钙化”是指钙盐在身体的血管、软组织、分泌和排泄通道中异常沉积,从而导致其硬化。病理性钙化存在两种类型,即营养不良性钙化和转移性钙化,所述营养不良性钙化出现在垂死组织和死亡组织中,所述转移性钙化使细胞外钙水平升高(高钙血症),超过细胞和组织的稳态能力。钙化可以涉及细胞以及细胞外基质组分,如基底膜中的胶原和动脉细胞壁中的弹性纤维。易于钙化的组织的一些实例包含:胃粘膜-胃、肾和肺、角膜、心瓣、全身动脉和肺静脉的内上皮衬里。

[0249] 如本文所用,术语“病理性骨化”是指其中骨在骨系统以外的组织中和在结缔组织中产生,通常未表现出骨原性质的病理性病状。骨化根据受影响的组织或器官的性质被分类为三种类型,软骨内骨化是出现在软骨中并代替软骨的骨化。膜内骨化是出现在结缔组织中并代替结缔组织的骨的骨化。化生性骨化,即骨物质在通常软体结构中发育;也被称为异养骨化。

[0250] 如本文所用,“钙化减少”是通过使用如X射线、显微CT和MRI等非侵入性方法观察到的。钙化减少还是通过使用无线电成像与99mTc-焦磷酸酯(99mPYP)摄取推断的。小鼠体

内钙化的存在是通过事后剖析通过显微计算机断层(CT)扫描和使用如苏木精和伊红(H&E)以及阿里扎林红等染料通过由以下确立的以下方案从心脏、主动脉和肾提取的组织学切片评估的:Braddock等人,(《自然通信(Nature Communications)》第6卷,论文编号:10006(2015))。

[0251] 如本文所用,术语“异位钙化”是指特征在于钙盐在组织中的病理性沉积或软组织中的骨生长的病状。

[0252] 如本文所用,术语“软组织的异位钙化”是指不适当的生物矿化,其通常由发生在软组织中的导致软组织的硬化丧失的磷酸钙、羟基磷灰石、草酸钙和磷酸八钙构成。“动脉钙化”是指发生在动脉和心瓣中导致动脉硬化和或变窄的异位钙化。动脉中的钙化与动脉粥样硬化斑块负荷和心肌梗塞风险增加、外周血管疾病中的缺血性发作增加以及血管成形术后的解剖风险增加相关。

[0253] 如本文所用,术语“静脉钙化”是指发生在静脉中降低静脉的弹性并限制血流,然后可能导致血压和冠状动脉缺损增加的异位

[0254] 如本文所用,术语“血管钙化”是指矿物质在血管系统中的病理性沉积。其具有多种形式,包含内膜钙化和中层钙化,但也可能存在于心脏的瓣中。血管钙化与动脉粥样硬化、糖尿病、某些遗传性病状和肾病,尤其是CKD相关。患有血管钙化的患者发生不良心血管事件的风险较高。血管钙化影响各种各样的患者。特发性婴儿动脉钙化是新生儿的动脉钙化的一种罕见形式的血管钙化。

[0255] 术语“腺相关病毒载体”、“AAV载体”、“腺相关病毒”、“AAV病毒”、“AAV病毒体”、“AAV病毒颗粒”和“AAV颗粒”如本文互换使用的是指由至少一个AAV衣壳蛋白(优选地通过特定AAV血清型的衣壳蛋白中的所有衣壳蛋白)和包壳重组病毒基因组构成的病毒颗粒。所述颗粒包括重组病毒基因组和转录调节区,所述重组病毒基因组具有包括编码人ENPP1或人ENPP3或其功能等效变体的序列的异源多核苷酸,所述转录调节区至少包括侧接有AAV反向末端重复序列的启动子。所述颗粒通常被称为“AAV载体颗粒”或“AAV载体”。

[0256] 如本文所用,术语“载体”意指能够转运其所连接的另一种核酸的核酸分子。在一些实施例中,载体是质粒,即另外的DNA区段可以连接到其中的环状双链DNA环。在一些实施例中,载体是病毒载体,其中另外的核苷酸序列可以连接到病毒基因组中。在一些实施例中,载体能够在其所引入的宿主细胞(例如,具有复制的细菌起源的细菌载体和外皮哺乳动物载体)中自主复制。在其它实施例中,载体(例如,非游离型哺乳动物载体)在引入到宿主细胞中时整合到宿主细胞的基因组中,并且由此与宿主基因组一起复制。此外,某些载体(表达载体)能够引导其操作性地连接的基因的表达。

[0257] 如本文所用,术语“重组宿主细胞”(或简称为“宿主细胞”)如本文所用意指外源性核酸和/或重组载体已引入到其中的细胞。应当理解,“重组宿主细胞”和“宿主细胞”不仅意指特定受试者细胞,而且还意指此类细胞的后代。因为某些修饰可能由于突变或环境影响而在后续世代中发生,所以此类后代实际上可能会与亲本细胞不相同,但仍包含在如本文所使用的术语“宿主细胞”的范围内。

[0258] 如本文所用,术语“重组病毒基因组”是指其中至少一个外来表达盒多核苷酸插入到天然存在的AAV基因组中的AAV基因组。根据本公开的AAV的基因组通常包括顺式作用5’和3’反向末端重复序列(ITR)和表达盒。

[0259] 如本文所用,术语“表达盒”是指重组或合成产生具有允许靶细胞中的特定核酸进行转录的一系列指定核酸元件的核酸构建体。根据本公开的AAV载体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操作性地连接的转录调节区。

[0260] 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。根据本公开的转录调节区包含启动子和任选地增强子。

[0261] 如本文所用,术语“启动子”是指起到控制一种或多种多核苷酸的转录的作用,位于多核苷酸序列上游,并且通过DNA依赖性RNA聚合酶的结合位点、转录起始位点和包含但不限于转录因子结合位点、阻遏子和活化剂蛋白结合位点的任何其它DNA序列以及本领域已知用于直接或间接起作用来调节来自启动子的转录的量的任何其它核苷酸序列的存在进行结构鉴定的核酸片段。任何种类的启动子均可以用于本公开中,包含诱导型启动子、组成型启动子和组织特异性启动子。

[0262] 如本文所用,术语“增强子”是指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。在另一实施例中,增强子是肝脏特异性增强子,更优选地是肝控制区增强子(HCR)。

[0263] 如本文所用,术语“操作性地连接”是指启动子序列相对于所关注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,则其与编码序列可操作地连接)。通常,操作性地连接的启动子与所关注序列邻接。然而,增强子不必与所关注序列邻接来控制其表达。在另一实施例中,启动子和编码ENPP1或ENPP3或其功能等效变体的核苷酸序列。

[0264] 术语“有效量”是指编码ENPP1或ENPP3的用于提供期望生物学结果的无毒但充足量的病毒载体。所述结果可以是疾病的体征、症状或病因减少和/或缓解,或生物体系的任何其它期望的更改。

[0265] 如本文所用,术语“Cap蛋白”是指具有天然AAV Cap蛋白(例如VP1、VP2、VP3)的至少一种功能活性的多肽。Cap蛋白的功能活性的实例包含能够诱导衣壳的形成、促进单链DNA的累积、促进AAV DNA包装到衣壳内(即衣壳化)、与细胞受体结合并且促进病毒体进入到宿主细胞中。原则上,任何Cap蛋白都可以在本公开的上下文中使用。

[0266] 如本文所用,术语“衣壳”是指其中病毒基因组被包装的结构。衣壳由由蛋白质制成的几个寡聚结构亚基组成。例如,AAV具有通过三种衣壳蛋白的相互作用形成的二十面体衣壳:VP1、VP2和VP3。

[0267] 如本文所用,术语“Rep蛋白”是指具有天然AAV Rep蛋白(例如,Rep 40、52、68、78)的至少一种功能活性的多肽。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,包含通过识别促进DNA复制、DNA复制的AAV起源的结合和基因巧合以及DNA解旋酶促活性。

[0268] 如本文所用,术语“腺相关病毒ITR”或“AAV ITR”是指存在于腺相关病毒的基因组的DNA链的两端处的反向末端重复序列。ITR序列是有效扩增AAV基因组所必需的。这些序列的另一个性质是其能够形成发夹。此特性有助于其自引发,所述自引发允许第二DNA链进行引发酶非依赖性合成。用于修饰这些ITR序列的程序是本领域已知的(Brown T,“基因克隆(Gene Cloning)”,英国伦敦的查普曼&霍尔出版社(Chapman&Hall,London,GB),1995;Watson R等人,“重组DNA(Recombinant DNA)”,第2版美国纽约州纽约的科学美国人出版社

(Scientific American Books,New York,N.Y.,US),1992;Alberts B等人,“细胞分子生物学(Molecular Biology of the Cell)”,美国纽约州纽约的兰登书屋出版公司(Garland Publishing Inc.),2008;Innis M等人编辑,“PCR方案:方法和应用指南(PCR Protocols.A Guide to Methods and Applications)”,美国加利福尼亚州圣地亚哥的学术出版社公司(Academic Press Inc.,San Diego,Calif.,US),1990;以及Schleef M,Ed.,“用于疗法和接种的质粒(Plasmid for Therapy and Vaccination)”,德国魏因海姆的威利-VCH突出出版公司(Wiley-VCH Verlag GmbH,Weinheim,Del.),2001)。

[0269] 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为在下游基因对其有特异性的组织中比在任何其它组织中活性程度高得多的基因。在这种情况下,在除了启动子对其有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。

[0270] 如本文所用,术语“诱导型启动子”是指例如通过应用化学诱导剂在生理上或发育上进行调节的启动子。例如,所述诱导型启动子可以是四环素(tetracycline)诱导型启动子、米非司酮(mifepristone,RU-486)诱导型启动子等。

[0271] 如本文所用,术语“组成型启动子”是指在很少考虑或不考虑细胞环境条件的情况下在生物体的所有细胞中或在大多数发育阶段期间其活性保持在相对恒定的水平下的启动子。在另一实施例中,转录调节区允许ENPP1组成型表达。组成型启动子的实例包含但不限于逆转录病毒劳斯氏肉瘤病毒(retroviral Rous sarcoma virus,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)。

[0272] 如本文所用,术语“多腺苷酸化信号”涉及介导聚腺嘌呤拉伸与mRNA的3’末端连接的核酸序列。合适的多腺苷酸化信号包含但不限于SV40早期多腺苷酸化信号、SV40晚期多腺苷酸化信号、HSV胸苷激酶多腺苷酸化信号、鱼精蛋白基因多腺苷酸化信号、腺病毒5EIb多腺苷酸化信号、牛生长激素多腺苷酸化信号、人变体生长激素多腺苷酸化信号等。

[0273] 如本文所用,术语“信号肽”是指在蛋白质翻译期间在所关注初生蛋白的氨基末端处结合的氨基酸残基(长度范围为10-30个残基)的序列。信号肽被信号识别颗粒(SRP)识别并且在转运后在内质网处被信号肽酶切割。(Lodish等人,2000,《分子细胞生物学(Molecular Cell Biology)》,第4版)。

[0274] 如本文所用,术语“免疫应答”或“免疫反应”是指宿主对入侵性(感染性)致病生物体中的抗原的免疫系统或者是指外来蛋白的引入或表达。免疫应答通常是体液的和局部的;由B细胞产生的抗体与抗原-抗体复合物中的抗原组合以灭活或中和抗原。通常在人蛋白被注射到小鼠模型系统中时观察到免疫应答。通常,通过在引入外来抗原之前注射免疫抑制剂来使小鼠模型系统成为免疫耐受性的,以确保更好的活力。

[0275] 如本文所用,器官,术语“免疫抑制”是使用免疫抑制剂药物促进对如外来蛋白等外来抗原、器官移植、骨髓和组织移植的免疫耐受性来有意降低对宿主免疫系统的激活或功效。免疫抑制剂药物的非限制性实例包含抗CD4(GK1.5)抗体、环磷酰胺、硫唑嘌呤(依木兰(Imuran))、吗替麦考酚酯(山喜多(Cellcept))、环孢霉素(新山地明(Neoral)、山地明(Sandmmunice)、金格福(Ggraf))、甲氨蝶呤(雷马特曲(Rheumatrex))、来氟米特(爱若华

(Arava))、环磷酰胺(癌得散(Cytoxan))和氯霉素(氯氨布西(Leukeran))。

[0276] 范围:在整个本公开中,本公开的各个方面可以范围格式呈现。应当理解,采用范围格式的描述仅仅是为了方便和简洁起见,并且不应该被解释为是对本公开的范围的固定限制。因此,对范围的描述应被视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,对范围,如1至6的描述应被视为已经具体公开了子范围,如1至3、1至4、1至5、2至4、2至6、3至6等,以及所述范围内的个别数字,例如,1、2、2.7、3、4、5、5.3和6。无论范围的宽度如何,这都适用。

[0277] 治疗方法

[0278] 本公开涉及施用ENPP1药剂或ENPP3药剂以治疗PAD,所述施用包含向受试者施用sNPP1多肽和sNPP3多肽以及其融合蛋白,并且涉及施用编码此类多肽的核酸。此类多肽的序列包含但不限于以下。

[0279] 序列

[0280] SEQ ID NO:1-ENPP1氨基酸序列-野生型

[0281]

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

```
Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu Ser
His
                260                 265                 270
Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala Ser
Phe
            275                 280                 285
Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys Gly
Glu
        290                 295                 300
Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly Thr
Phe
305                 310                 315
320
Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro Asp
Ile
                    325                 330                 335
Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Leu
Ala
                340                 345                 350
Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His Phe
Tyr
            355                 360                 365
Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr Gly
Pro
        370                 375                 380
Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly Met
Val
385                 390                 395
400
Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg Cys
Leu
                    405                 410                 415
Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser Cys
Lys
                420                 425                 430
Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn Ile
Lys
            435                 440                 445
Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val Pro
Asp
        450                 455                 460
Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu Ser
Cys
465                 470                 475
480
Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe Leu
Pro
                    485                 490                 495
Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu Thr
Phe
                500                 505                 510
Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu Arg
Lys
            515                 520                 525
Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser Asn
Met
```

[0282]

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

[0283]

Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp Ile Leu
675 680 685
Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser Phe Ser
690 695 700
Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile Pro Leu
705 710 715 720
Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val Ser
725 730 735
Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser Gly Ile
740 745 750
Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln Ser
755 760 765
Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys Tyr
770 775 780
Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val Phe Asp
785 790 795 800
Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln Lys
805 810 815

```
      Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe
Phe
                  820                 825                 830
      Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His
Cys
            835                 840                 845
      Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp
Asn
        850                 855                 860
      Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu
Glu
      865                 870                 875
880
      Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile
Thr
                  885                 890                 895
      Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile
Leu
                  900                 905                 910
      Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp
            915                 920                 925
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[0284]

[0285] SEQ ID No:2-天青杀素-ENPP1-FC

[0286]

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MTRLTVLALLAGLLASSRA**APSCAKEVKSCKGRCFERTFGNCRCDAACVELGNCCLDYQETCIEPE
HIWTCNKFRCGEKRLTRSLCACSDDCKDKGDCCINYSSVCQGEKSWVEEPCESINEPQCPAGFETPPT
LLFSLDGFRAEYLHTWGGLLPVISKLKKCGTYTKNMRPVYPTKTFPNHYSIVTGLYPESHGIIDNKMY
DPKMNASFSLKSKEKFNPEWYKGEPIWVTAKYQGLKSGTFFWPGSDVEINGIFPDIYKMYNGSVPFEE
RILAVLQWLQLPKDERPHFYTLYLEEPDSSGHSYGPVSSEVIKALQRVDGMVGMLMDGLKELNLHRCL
NLILISDHGMEQGSCKKYIYLNKYLGDVKNIKVIYGPAARLRPSDVPDKYYSFNYEGIARNLSCREPN
QHFKPYLKHFLPKRLHFAKSDRIEPLTFYLDPQWQLALNPSERKYCGSGFHGSDNVFSNMQALFVGYG
PGFKHGIEADTFENIEVYNLMCDLLNLTPAPNNGTHGSLNHLLKNPVYTPKHPKEVHPLVQCPFTRNP
RDNLGCSCNPSILPIEDFQTQFNLTVAEEKIIKHETLPYGRPRVLQKENTICLLSQHQFMSGYSQDIL
MPLWTSYTVDRNDSFSTEDFSNCLYQDFRIPLSPVHKCSFYKNNTKVSYGFLSPPQLNKNSSGIYSEA
LLTTNIVPMYQSFQVIWRYFHDTLLRKYAEERNGVNVVSGPVFDFDYDGRCDSLENLRQKRRVIRNQE
ILIPTHFFIVLTSCKDTSQTPLHCENLDTLAFILPHRTDNSESCVHGKHDSSWVEELLMLHRARITDV
EHITGLSFYQQRKEPVSDILKLKTHLPTFSQEDLINDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK
CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE
NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
```

[0287] 单下划线-天青杀素信号序列,双下划线-ENPP1序列的开始和结束,粗体残基-Fc序列,**表示信号序列的切割点。

[0288] SEQ ID No:3-天青杀素-ENPP1-Alb

MTRLTVLALLAGLLASSRA**APSCAKEVKSCKGRCFERTFGNCRCDAACVELGNCCLDYQETCIEPE
HIWTCNKFRCGEKRLTRSLCACSDDCKDKGDCCINYSSVCQGEKSWVEEPCESINEPQCPAGFETPPT
LLFSLDGFRAEYLHTWGGLLPVISKLKKCGTYTKNMRPVYPTKTFPNHYSIVTGLYPESHGIIDNKMY
DPKMNASFSLKSKEKFNPEWYKGEPIWVTAKYQGLKSGTFFWPGSDVEINGIFPDIYKMYNGSVPFEE
RILAVLQWLQLPKDERPHFYTLYLEEPDSSGHSYGPVSSEVIKALQRVDGMVGMLMDGLKELNLHRCL
NLILISDHGMEQGSCKKYIYLNKYLGDVKNIKVIYGPAARLRPSDVPDKYYSFNYEGIARNLSCREPN
QHFKPYLKHFLPKRLHFAKSDRIEPLTFYLDPQWQLALNPSERKYCGSGFHGSDNVFSNMQALFVGYG
PGFKHGIEADTFENIEVYNLMCDLLNLTPAPNNGTHGSLNHLLKNPVYTPKHPKEVHPLVQCPFTRNP

[0289] RDNLGCSCNPSILPIEDFQTQFNLTVAEEKIIKHETLPYGRPRVLQKENTICLLSQHQFMSGYSQDIL
MPLWTSYTVDRNDSFSTEDFSNCLYQDFRIPLSPVHKCSFYKNNTKVSYGFLSPPQLNKNSSGIYSEA
LLTTNIVPMYQSFQVIWRYFHDTLLRKYAEERNGVNVVSGPVFDFDYDGRCDSLENLRQKRRVIRNQE
ILIPTHFFIVLTSCKDTSQTPLHCENLDTLAFILPHRTDNSESCVHGKHDSSWVEELLMLHRARITDV
EHITGLSFYQQRKEPVSDILKLKTHLPTFSQEDLIN**MKWVTFLLLLFVSGSAFSRGVFRREAHKSEIA**
HRYNDLGEQHFKGLVLIAFSQYLQKCSYDEHAKLVQEVTDFAKTCVADESAANCDKSLHTLFGDKLCA
IPNLRENYGELADCCTKQEPERNECFLQHKDDNPSLPPFERPEAEAMCTSFKENPTTFMGHYLHEVAR
RHPYFYAPELLYYAEQYNEILTQCCAEADKESCLTPKLDGVKEKALVSSVRQRMKCSSMQKFGERAFK
AWAVARLSQTFPNADFAEITKLATDLTKVNKECCHGDLLECADDRAELAKYMCENQATISSKLQTCCD
KPLLKKAHCLSEVEHDTMPADLPAIAADFVEDQEVCKNYAEAKDVFLGTFLYEYSRRHPDYSVSLLLR
LAKKYEATLEKCCAEANPPACYGTVLAEFQPLVEEPKNLVKTNCDLYEKLGEYGFQNAILVRYTQKAP
QVSTPTLVEAARNLGRVGTKCCTLPEDQRLPCVEDYLSAILNRVCLLHEKTPVSEHVTKCCSGSLVER
RPCFSALTVDETYVPKEFKAETFTFHSDICTLPEKEKQIKKQTALAELVKHKPKATAEQLKTVMDDFA
QFLDTCCKAADKDTCFSTEGPNLVTRCKDALARSWSHPQFEK

[0290] 单下划线-天青杀素信号序列,双下划线-ENPP1序列的开始和结束,粗体残基-白蛋白序列,**表示信号序列的切割点。

[0291] SEQ ID No:4-天青杀素-ENPP1

MTRLTVLALLAGLLASSRA**APSCAKEVKSCKGRCFERTFGNCRCDAACVELGNCCLDYQETCIEPE
HIWTCNKFRCGEKRLTRSLCACSDDCKDKGDCCINYSSVCQGEKSWVEEPCESINEPQCPAGFETPPT
LLFSLDGFRAEYLHTWGGLLPVISKLKKCGTYTKNMRPVYPTKTFPNHYSIVTGLYPESHGIIDNKMY
DPKMNASFSLKSKEKFNPEWYKGEPIWVTAKYQGLKSGTFFWPGSDVEINGIFPDIYKMYNGSVPFEE
RILAVLQWLQLPKDERPHFYTLYLEEPDSSGHSYGPVSSEVIKALQRVDGMVGMLMDGLKELNLHRCL
NLILISDHGMEQGSCKKYIYLNKYLGDVKNIKVIYGPAARLRPSDVPDKYYSFNYEGIARNLSCREPN
QHFKPYLKHFLPKRLHFAKSDRIEPLTFYLDPQWQLALNPSERKYCGSGFHGSDNVFSNMQALFVGYG
PGFKHGIEADTFENIEVYNLMCDLLNLTPAPNNGTHGSLNHLLKNPVYTPKHPKEVHPLVQCPFTRNP
RDNLGCSCNPSILPIEDFQTQFNLTVAEEKIIKHETLPYGRPRVLQKENTICLLSQHQFMSGYSQDIL
MPLWTSYTVDRNDSFSTEDFSNCLYQDFRIPLSPVHKCSFYKNNTKVSYGFLSPPQLNKNSSGIYSEA
LLTTNIVPMYQSFQVIWRYFHDTLLRKYAEERNGVNVVSGPVFDFDYDGRCDSLENLRQKRRVIRNQE
ILIPTHFFIVLTSCKDTSQTAPSCAKEVKSCKGRCFERTFGNCRCDAACVELGNCCLDYQETCIEPEH

[0292] IWTCNKFRCGEKRLTRSLCACSDDCKDKGDCCINYSSVCQGEKSWVEEPCESINEPQCPAGFETPPTL
LFSLDGFRAEYLHTWGGLLPVISKLKKCGTYTKNMRPVYPTKTFPNHYSIVTGLYPESHGIIDNKMYD
PKMNASFSLKSKEKFNPEWYKGEPIWVTAKYQGLKSGTFFWPGSDVEINGIFPDIYKMYNGSVPFEER
ILAVLQWLQLPKDERPHFYTLYLEEPDSSGHSYGPVSSEVIKALQRVDGMVGMLMDGLKELNLHRCLN
LILISDHGMEQGSCKKYIYLNKYLGDVKNIKVIYGPAARLRPSDVPDKYYSFNYEGIARNLSCREPNQ
HFKPYLKHFLPKRLHFAKSDRIEPLTFYLDPQWQLALNPSERKYCGSGFHGSDNVFSNMQALFVGYGP
GFKHGIEADTFENIEVYNLMCDLLNLTPAPNNGTHGSLNHLLKNPVYTPKHPKEVHPLVQCPFTRNPR
DNLGCSCNPSILPIEDFQTQFNLTVAEEKIIKHETLPYGRPRVLQKENTICLLSQHQFMSGYSQDILM
PLWTSYTVDRNDSFSTEDFSNCLYQDFRIPLSPVHKCSFYKNNTKVSYGFLSPPQLNKNSSGIYSEAL
LTTNIVPMYQSFQVIWRYFHDTLLRKYAEERNGVNVVSGPVFDFDYDGRCDSLENLRQKRRVIRNQEI
LIPTHFFIVLTSCKDTSQTPLHCENLDTLAFILPHRTDNSESCVHGKHDSSWVEELLMLHRARITDVE
HITGLSFYQQRKEPVSDILKLKTHLPTFSQED

[0293] 单下划线-天青杀素信号序列,双下划线-ENPP1序列的开始和结束,**表示信号序列的切割点。

[0294] SEQ ID NO:5-ENPP2氨基酸序列-野生型

[0295]

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

[0296]

```
Gly Gln Pro Leu Trp Ile Thr Ala Thr Lys Gln Gly Val Lys Ala Gly
            260                 265                 270
Thr Phe Phe Trp Ser Val Val Ile Pro His Glu Arg Arg Ile Leu Thr
        275                 280                 285
Ile Leu Gln Trp Leu Thr Leu Pro Asp His Glu Arg Pro Ser Val Tyr
    290                 295                 300
Ala Phe Tyr Ser Glu Gln Pro Asp Phe Ser Gly His Lys Tyr Gly Pro
305                 310                 315                 320
Phe Gly Pro Glu Met Thr Asn Pro Leu Arg Glu Ile Asp Lys Ile Val
                325                 330                 335
Gly Gln Leu Met Asp Gly Leu Lys Gln Leu Lys Leu His Arg Cys Val
            340                 345                 350
Asn Val Ile Phe Val Gly Asp His Gly Met Glu Asp Val Thr Cys Asp
        355                 360                 365
Arg Thr Glu Phe Leu Ser Asn Tyr Leu Thr Asn Val Asp Asp Ile Thr
    370                 375                 380
Leu Val Pro Gly Thr Leu Gly Arg Ile Arg Ser Lys Phe Ser Asn Asn
385                 390                 395                 400
Ala Lys Tyr Asp Pro Lys Ala Ile Ile Ala Asn Leu Thr Cys Lys Lys
                405                 410                 415
Pro Asp Gln His Phe Lys Pro Tyr Leu Lys Gln His Leu Pro Lys Arg
            420                 425                 430
Leu His Tyr Ala Asn Asn Arg Arg Ile Glu Asp Ile His Leu Leu Val
        435                 440                 445
Glu Arg Arg Trp His Val Ala Arg Lys Pro Leu Asp Val Tyr Lys Lys
    450                 455                 460
Pro Ser Gly Lys Cys Phe Phe Gln Gly Asp His Gly Phe Asp Asn Lys
465                 470                 475                 480
```

[0297]

```
Val Asn Ser Met Gln Thr Val Phe Val Gly Tyr Gly Ser Thr Phe Lys
                485                 490                 495
Tyr Lys Thr Lys Val Pro Pro Phe Glu Asn Ile Glu Leu Tyr Asn Val
            500                 505                 510
Met Cys Asp Leu Leu Gly Leu Lys Pro Ala Pro Asn Asn Gly Thr His
        515                 520                 525
Gly Ser Leu Asn His Leu Leu Arg Thr Asn Thr Phe Arg Pro Thr Met
    530                 535                 540
Pro Glu Glu Val Thr Arg Pro Asn Tyr Pro Gly Ile Met Tyr Leu Gln
545                 550                 555                 560
Ser Asp Phe Asp Leu Gly Cys Thr Cys Asp Asp Lys Val Glu Pro Lys
                565                 570                 575
Asn Lys Leu Asp Glu Leu Asn Lys Arg Leu His Thr Lys Gly Ser Thr
            580                 585                 590
Glu Ala Glu Thr Arg Lys Phe Arg Gly Ser Arg Asn Glu Asn Lys Glu
        595                 600                 605
Asn Ile Asn Gly Asn Phe Glu Pro Arg Lys Glu Arg His Leu Leu Tyr
    610                 615                 620
Gly Arg Pro Ala Val Leu Tyr Arg Thr Arg Tyr Asp Ile Leu Tyr His
625                 630                 635                 640
Thr Asp Phe Glu Ser Gly Tyr Ser Glu Ile Phe Leu Met Pro Leu Trp
                645                 650                 655
Thr Ser Tyr Thr Val Ser Lys Gln Ala Glu Val Ser Ser Val Pro Asp
            660                 665                 670
His Leu Thr Ser Cys Val Arg Pro Asp Val Arg Val Ser Pro Ser Phe
        675                 680                 685
Ser Gln Asn Cys Leu Ala Tyr Lys Asn Asp Lys Gln Met Ser Tyr Gly
    690                 695                 700
Phe Leu Phe Pro Pro Tyr Leu Ser Ser Ser Pro Glu Ala Lys Tyr Asp
705                 710                 715                 720
Ala Phe Leu Val Thr Asn Met Val Pro Met Tyr Pro Ala Phe Lys Arg
                725                 730                 735
Val Trp Asn Tyr Phe Gln Arg Val Leu Val Lys Lys Tyr Ala Ser Glu
            740                 745                 750
Arg Asn Gly Val Asn Val Ile Ser Gly Pro Ile Phe Asp Tyr Asp Tyr
        755                 760                 765
Asp Gly Leu His Asp Thr Glu Asp Lys Ile Lys Gln Tyr Val Glu Gly
    770                 775                 780
Ser Ser Ile Pro Val Pro Thr His Tyr Tyr Ser Ile Ile Thr Ser Cys
785                 790                 795                 800
Leu Asp Phe Thr Gln Pro Ala Asp Lys Cys Asp Gly Pro Leu Ser Val
                805                 810                 815
Ser Ser Phe Ile Leu Pro His Arg Pro Asp Asn Glu Glu Ser Cys Asn
            820                 825                 830
Ser Ser Glu Asp Glu Ser Lys Trp Val Glu Glu Leu Met Lys Met His
        835                 840                 845
Thr Ala Arg Val Arg Asp Ile Glu His Leu Thr Ser Leu Asp Phe Phe
    850                 855                 860
Arg Lys Thr Ser Arg Ser Tyr Pro Glu Ile Leu Thr Leu Lys Thr Tyr
865                 870                 875                 880
Leu His Thr Tyr Glu Ser Glu Ile
                885
```

[0298] SEQ.ID NO:6-ENPP3的胞外结构域：

[0299]

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

[0300]

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

[0301] SEQ.ID NO:7-NPP3氨基酸序列：

[0302]

```
Met Glu Ser Thr Leu Thr Leu Ala Thr Glu Gln Pro Val Lys Lys Asn
1               5                   10                  15
Thr Leu Lys Lys Tyr Lys Ile Ala Cys Ile Val Leu Leu Ala Leu Leu
            20                  25                  30
```

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

[0303]

Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala Ile Phe
485 490 495
Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu Pro Phe
500 505 510
Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg Ile Gln
515 520 525
Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His Leu Leu Lys
530 535 540
Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys Phe Ser
545 550 555 560
Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu Asp Cys Phe
565 570 575
Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn Gln Met
580 585 590
Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val Asn Leu
595 600 605
Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val Asp His Cys Leu
610 615 620
Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala Met Arg Met
625 630 635 640
Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp Thr Ser Pro
645 650 655
Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp Val Arg Val Pro
660 665 670

[0304]

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

[0305] SEQ ID No:8-天青杀素-ENPP3-FC

[0306]

MTRLTVLALLAGLLASSRA**AKQGSCRKKCFDASFRGLENCRCDVACKDRGDCCWDFEDTC
VESTRIWMCNKFRCGETRLEASLCSCSDDCLQRKDCCADYKSVCQGETSWLEENCDTAQQSQCPEGFD

LPPVILFSMDGFRAEYLYTWDTLMPNINKLKTCGIHSKYMRAMYPTKTFPNHYTIVTGLYPESHGIID
NNMYDVNLNKNFSLSSKEQNNPAWWHGQPMNLTAMYQGLKAATYFWPGSEVAINGSFPSIYMPYNGSV
PFEERISTLLKWLDLPKAERPRFYTMYFEEPDSSGHAGGPVSARVIKALQVVDHAFGMLMEGLKQRNL
HNCVNIILLADHGMDQTYCNKMEYMTDYFPRINFFYMYEGPAPRIRAHNIPHDFFSFNSEEIVRNLSC
RKPDQHFKPYLTPDLPKRLHYAKNVRIDKVHLFVDQQWLAVRSKSNTNCGGGNHGYNNEFRSMEAIFL
AHGPSFKEKTEVEPFENIEVYNLMCDLLRIQPAPNNGTHGSLNHLLKVPFYEPSHAEEVSKFSVCGFA
NPLPTESLDCFCPHLQNSTQLEQVNQMLNLTQEEITATVKVNLPFGRPRVLQKNVDHCLLYHREYVSG
FGKAMRMPMWSSYTVPQLGDTSPLPPTVPDCLRADVRVPPSESQKCSFYLADKNITHGFLYPPASNRT
SDSQYDALITSNLVPMYEEFRKMWDYFHSVLLIKHATERNGVNVVSGPIFDYNYDGHFDAPDEITKHL
ANTDVPIPTHYFVVLTSCKNKSHTPENCPGWLDVLPFIIPHRPTNVESCPEGKPEALWVEERFTAHIA
RVRDVELLTGLDFYQDKVQPVSEILQLKTYLPTFETTI**DKTHTCPPCPAPELLGGPSVFLFPPKPKDT**
LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[0307] 单下划线-天青杀素信号序列,双下划线-ENPP3序列的开始和结束,粗体残基-Fc序列,**表示信号序列的切割点。

[0308] SEQ ID No:9-天青杀素-ENPP3-白蛋白

[0309]

MTRLTVLALLAGLLASSRA**AKQGSCRKKCFDASFRGLENCRCDVACKDRGDCCWDFEDTC
VESTRIWMCNKFRCGETRLEASLCSCSDDCLQRKDCCADYKSVCQGETSWLEENCDTAQQSQCPEGFD
LPPVILFSMDGFRAEYLYTWDTLMPNINKLKTCGIHSKYMRAMYPTKTFPNHYTIVTGLYPESHGIID
NNMYDVNLNKNFSLSSKEQNNPAWWHGQPMNLTAMYQGLKAATYFWPGSEVAINGSFPSIYMPYNGSV
PFEERISTLLKWLDLPKAERPRFYTMYFEEPDSSGHAGGPVSARVIKALQVVDHAFGMLMEGLKQRNL
HNCVNIILLADHGMDQTYCNKMEYMTDYFPRINFFYMYEGPAPRIRAHNIPHDFFSFNSEEIVRNLSC
RKPDQHFKPYLTPDLPKRLHYAKNVRIDKVHLFVDQQWLAVRSKSNTNCGGGNHGYNNEFRSMEAIFL
AHGPSFKEKTEVEPFENIEVYNLMCDLLRIQPAPNNGTHGSLNHLLKVPFYEPSHAEEVSKFSVCGFA
NPLPTESLDCFCPHLQNSTQLEQVNQMLNLTQEEITATVKVNLPFGRPRVLQKNVDHCLLYHREYVSG
FGKAMRMPMWSSYTVPQLGDTSPLPPTVPDCLRADVRVPPSESQKCSFYLADKNITHGFLYPPASNRT
SDSQYDALITSNLVPMYEEFRKMWDYFHSVLLIKHATERNGVNVVSGPIFDYNYDGHFDAPDEITKHL
ANTDVPIPTHYFVVLTSCKNKSHTPENCPGWLDVLPFIIPHRPTNVESCPEGKPEALWVEERFTAHIA
RVRDVELLTGLDFYQDKVQPVSEILQLKTYLPTFETTI**MKWVTFLLLLFVSGSAFSRGVFRREAHKSE**
IAHRYNDLGEQHFKGLVLIAFSQYLQKCSYDEHAKLVQEVTDFAKTCVADESAANCDKSLHTLFGDKL
CAIPNLRENYGELADCCTKQEPERNECFLQHKDDNPSLPPFERPEAEAMCTSFKENPTTFMGHYLHEV
ARRHPYFYAPELLYYAEQYNEILTQCCAEADKESCLTPKLDGVKEKALVSSVRQRMKCSSMQKFGERA
FKAWAVARLSQTFPNADFAEITKLATDLTKVNKECCHGDLLECADDRAELAKYMCENQATISSKLQTC
CDKPLLKKAHCLSEVEHDTMPADLPAIAADFVEDQEVCKNYAEAKDVFLGTFLYEYSRRHPDYSVSLL
LRLAKKYEATLEKCCAEANPPACYGTVLAEFQPLVEEPKNLVKTNCDLYEKLGEYGFQNAILVRYTQK
APQVSTPTLVEAARNLGRVGTKCCTLPEDQRLPCVEDYLSAILNRVCLLHEKTPVSEHVTKCCSGSLV
ERRPCFSALTVDETYVPKEFKAETFTFHSDICTLPEKEKQIKKQTALAELVKHKPKATAEQLKTVMDD
FAQFLDTCCKAADKDTCFSTEGPNLVTRCKDALARSWSHPQFEK

[0310] 单下划线-天青杀素信号序列,双下划线-ENPP3序列的开始和结束,粗体残基-白蛋白序列,**表示信号序列的切割点。

[0311] SEQ ID No:10-天青杀素-ENPP3

MTRLTVLALLAGLLASSRA**AKQGSCRKKCFDASFRGLENCRCDVACKDRGDCCWDFEDTC
VESTRIWMCNKFRCGETRLEASLCSCSDDCLQRKDCCADYKSVCQGETSWLEENCDTAQQSQCPEGFD
LPPVILFSMDGFRAEYLYTWDTLMPNINKLKTCGIHSKYMRAMYPTKTFPNHYTIVTGLYPESHGIID
NNMYDVNLNKNFSLSSKEQNNPAWWHGQPMNLTAMYQGLKAATYFWPGSEVAINGSFPSIYMPYNGSV
PFEERISTLLKWLDLPKAERPRFYTMYFEEPDSSGHAGGPVSARVIKALQVVDHAFGMLMEGLKQRNL

[0312]

HNCVNIILLADHGMDQTYCNKMEYMTDYFPRINFFYMYEGPAPRIRAHNIPHDFFSFNSEEIVRNLSC
RKPDQHFKPYLTPDLPKRLHYAKNVRIDKVHLFVDQQWLAVRSKSNTNCGGGNHGYNNEFRSMEAIFL
AHGPSFKEKTEVEPFENIEVYNLMCDLLRIQPAPNNGTHGSLNHLLKVPFYEPSHAEEVSKFSVCGFA
NPLPTESLDCFCPHLQNSTQLEQVNQMLNLTQEEITATVKVNLPFGRPRVLQKNVDHCLLYHREYVSG
FGKAMRMPMWSSYTVPQLGDTSPLPPTVPDCLRADVRVPPSESQKCSFYLADKNITHGFLYPPASNRT
SDSQYDALITSNLVPMYEEFRKMWDYFHSVLLIKHATERNGVNVVSGPIFDYNYDGHFDAPDEITKHL
ANTDVPIPTHYFVVLTSCKNKSHTPENCPGWLDVLPFIIPHRPTNVESCPEGKPEALWVEERFTAHIA
RVRDVELLTGLDFYQDKVQPVSEILQLKTYLPTFETTI

[0313] 单下划线-天青杀素信号序列,双下划线-ENPP3序列的开始和结束,**表示信号序列的切割点。

[0314] SEQ.ID NO:11-ENPP4氨基酸序列-野生型

```
      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
```

[0315]

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

```
                195                 200                 205
Lys Ile Asp Asp Leu Ile Gly Asp Leu Val Gln Arg Leu Lys Met
Leu
            210                 215                 220
Gly Leu Trp Glu Asn Leu Asn Val Ile Ile Thr Ser Asp His Gly
Met
225                 230                 235
240
Thr Gln Cys Ser Gln Asp Arg Leu Ile Asn Leu Asp Ser Cys Ile
Asp
                    245                 250                 255
His Ser Tyr Tyr Thr Leu Ile Asp Leu Ser Pro Val Ala Ala Ile
Leu
                260                 265                 270
Pro Lys Ile Asn Arg Thr Glu Val Tyr Asn Lys Leu Lys Asn Cys
Ser
                275                 280                 285
Pro His Met Asn Val Tyr Leu Lys Glu Asp Ile Pro Asn Arg Phe
Tyr
            290                 295                 300
Tyr Gln His Asn Asp Arg Ile Gln Pro Ile Ile Leu Val Ala Asp
Glu
305                 310                 315
320
Gly Trp Thr Ile Val Leu Asn Glu Ser Ser Gln Lys Leu Gly Asp
```

[0316]

```
His
                    325                 330                 335
Gly Tyr Asp Asn Ser Leu Pro Ser Met His Pro Phe Leu Ala Ala
His
                340                 345                 350
Gly Pro Ala Phe His Lys Gly Tyr Lys His Ser Thr Ile Asn Ile
Val
                355                 360                 365
Asp Ile Tyr Pro Met Met Cys His Ile Leu Gly Leu Lys Pro His
Pro
            370                 375                 380
Asn Asn Gly Thr Phe Gly His Thr Lys Cys Leu Leu Val Asp Gln
Trp
385                 390                 395
400
Cys Ile Asn Leu Pro Glu Ala Ile Ala Ile Val Ile Gly Ser Leu
Leu
                    405                 410                 415
Val Leu Thr Met Leu Thr Cys Leu Ile Ile Ile Met Gln Asn Arg
Leu
                420                 425                 430
Ser Val Pro Arg Pro Phe Ser Arg Leu Gln Leu Gln Glu Asp Asp
Asp
                435                 440                 445
Asp Pro Leu Ile Gly
            450
```

[0317] SEQ.ID NO:12-ENPP51氨基酸序列

[0318]

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

Glu Arg Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser
290 295 300
Gly His Ser His Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln
305 310 315 320
Lys Val Asp Arg Leu Val Gly Met Leu Met Asp Gly Leu Lys Asp Leu
325 330 335
Gly Leu Asp Lys Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met
340 345 350
Glu Gln Gly Ser Cys Lys Lys Tyr Val Tyr Leu Asn Lys Tyr Leu Gly
355 360 365
Asp Val Asn Asn Val Lys Val Val Tyr Gly Pro Ala Ala Arg Leu Arg
370 375 380
Pro Thr Asp Val Pro Glu Thr Tyr Tyr Ser Phe Asn Tyr Glu Ala Leu
385 390 395 400
Ala Lys Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Arg Pro Tyr
405 410 415
Leu Lys Pro Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg

[0319]

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

[0320]

```
Lys Asp Phe Glu Lys Gln Leu Asn Leu Thr Thr Glu Asp Val Asp
Asp
                    565                 570                 575
Ile Tyr His Met Thr Val Pro Tyr Gly Arg Pro Arg Ile Leu Leu
Lys
                580                 585                 590
Gln His Arg Val Cys Leu Leu Gln Gln Gln Phe Leu Thr Gly
Tyr
            595                 600                 605
Ser Leu Asp Leu Leu Met Pro Leu Trp Ala Ser Tyr Thr Phe Leu
Ser
        610                 615                 620
Asn Asp Gln Phe Ser Arg Asp Asp Phe Ser Asn Cys Leu Tyr Gln
Asp
625                 630                 635
640
Leu Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Tyr Tyr Lys
Ser
                    645                 650                 655
Asn Ser Lys Leu Ser Tyr Gly Phe Leu Thr Pro Pro Arg Leu Asn
Arg
                660                 665                 670
Val Ser Asn His Ile Tyr Ser Glu Ala Leu Leu Thr Ser Asn Ile
Val
            675                 680                 685
Pro Met Tyr Gln Ser Phe Gln Val Ile Trp His Tyr Leu His Asp
Thr
        690                 695                 700
Leu Leu Gln Arg Tyr Ala His Glu Arg Asn Gly Ile Asn Val Val
Ser
705                 710                 715
720
Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Tyr Asp Ser Leu
Glu
                    725                 730                 735
Ile Leu Lys Gln Asn Ser Arg Val Ile Arg Ser Gln Glu Ile Leu
Ile
                740                 745                 750
Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Gln Leu Ser
Glu
            755                 760                 765
Thr Pro Leu Glu Cys Ser Ala Leu Glu Ser Ser Ala Tyr Ile Leu
Pro
        770                 775                 780
His Arg Pro Asp Asn Ile Glu Ser Cys Thr His Gly Lys Arg Glu
Ser
785                 790                 795
800
Ser Trp Val Glu Glu Leu Leu Thr Leu His Arg Ala Arg Val Thr
Asp
                    805                 810                 815
Val Glu Leu Ile Thr Gly Leu Ser Phe Tyr Gln Asp Arg Gln Glu
Ser
                820                 825                 830
Val Ser Glu Leu Leu Arg Leu Lys Thr His Leu Pro Ile Phe Ser
Gln
```

```
          835                 840                 845
```

[0321] Glu Asp
850

[0322] 单下划线:信号肽序列;双下划线:NPP1的开始和结束;**=信号肽序列处的切割位置

[0323] 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
Asp Ala Ala Cys Val Ser Leu Gly Asn Cys Cys Leu Asp Phe Gln
Glu
    50                  55                  60
Thr Cys Val Glu Pro Thr His Ile Trp Thr Cys Asn Lys Phe Arg
Cys
65                  70                  75                  80
Gly Glu Lys Arg Leu Ser Arg Phe Val Cys Ser Cys Ala Asp Asp
Cys
                85                  90                  95
Lys Thr His Asn Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln
Asp
            100                 105                 110
Lys Lys Ser Trp Val Glu Glu Thr Cys Glu Ser Ile Asp Thr Pro
Glu
        115                 120                 125
Cys Pro Ala Glu Phe Glu Ser Pro Pro Thr Leu Leu Phe Ser Leu
Asp
    130                 135                 140
Gly Phe Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro
Val
145                 150                 155
160
Ile Ser Lys Leu Lys Asn Cys Gly Thr Tyr Thr Lys Asn Met Arg
Pro
                165                 170                 175
Met Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr
Gly
            180                 185                 190
Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp
Pro
        195                 200                 205
Lys Met Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn
Pro
    210                 215                 220
```

[0324]

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

[0325] Gly

355 360 365
Asp Val Asn Asn Val Lys Val Val Tyr Gly Pro Ala Ala Arg Leu Arg
370 375 380
Pro Thr Asp Val Pro Glu Thr Tyr Tyr Ser Phe Asn Tyr Glu Ala Leu
385 390 395 400
Ala Lys Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Arg Pro Tyr
405 410 415
Leu Lys Pro Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg
420 425 430
Ile Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu
435 440 445
Asn Pro Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp
450 455 460
Asn Leu Phe Ser Asn Met Gln Ala Leu Phe Ile Gly Tyr Gly Pro Ala
465 470 475 480
Phe Lys His Gly Ala Glu Val Asp Ser Phe Glu Asn Ile Glu Val Tyr
485 490 495

[0326]

```
Asn Leu Met Cys Asp Leu Leu Gly Leu Ile Pro Ala Pro Asn Asn
Gly
                500                 505                 510
Ser His Gly Ser Leu Asn His Leu Leu Lys Lys Pro Ile Tyr Asn
Pro
            515                 520                 525
Ser His Pro Lys Glu Glu Gly Phe Leu Ser Gln Cys Pro Ile Lys
Ser
        530                 535                 540
Thr Ser Asn Asp Leu Gly Cys Thr Cys Asp Pro Trp Ile Val Pro
Ile
545                 550                 555
560
Lys Asp Phe Glu Lys Gln Leu Asn Leu Thr Thr Glu Asp Val Asp
Asp
                    565                 570                 575
Ile Tyr His Met Thr Val Pro Tyr Gly Arg Pro Arg Ile Leu Leu
Lys
                580                 585                 590
Gln His Arg Val Cys Leu Leu Gln Gln Gln Gln Phe Leu Thr Gly
Tyr
            595                 600                 605
Ser Leu Asp Leu Leu Met Pro Leu Trp Ala Ser Tyr Thr Phe Leu
Ser
        610                 615                 620
Asn Asp Gln Phe Ser Arg Asp Asp Phe Ser Asn Cys Leu Tyr Gln
Asp
625                 630                 635
640
Leu Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Tyr Tyr Lys
Ser
                    645                 650                 655
Asn Ser Lys Leu Ser Tyr Gly Phe Leu Thr Pro Pro Arg Leu Asn
Arg
                660                 665                 670
Val Ser Asn His Ile Tyr Ser Glu Ala Leu Leu Thr Ser Asn Ile
Val
            675                 680                 685
Pro Met Tyr Gln Ser Phe Gln Val Ile Trp His Tyr Leu His Asp
Thr
        690                 695                 700
Leu Leu Gln Arg Tyr Ala His Glu Arg Asn Gly Ile Asn Val Val
Ser
705                 710                 715
720
Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Tyr Asp Ser Leu
Glu
                    725                 730                 735
Ile Leu Lys Gln Asn Ser Arg Val Ile Arg Ser Gln Glu Ile Leu
Ile
                740                 745                 750
Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Gln Leu Ser
Glu
            755                 760                 765
Thr Pro Leu Glu Cys Ser Ala Leu Glu Ser Ser Ala Tyr Ile Leu
Pro
```

[0327]

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

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
1085 1090 1095
Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr Lys
1100 1105 1110
Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly
1115 1120 1125
Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr
1130 1135 1140
Met Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys
1145 1150 1155
Cys Asp Lys Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val
1160 1165 1170
Glu His Asp Thr Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp
1175 1180 1185
Phe Val Glu Asp Gln Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys
1190 1195 1200
Asp Val Phe Leu Gly Thr Phe Leu Tyr Glu Tyr Ser Arg Arg His
1205 1210 1215
Pro Asp Tyr Ser Val Ser Leu Leu Leu Arg Leu Ala Lys Lys Tyr
1220 1225 1230
Glu Ala Thr Leu Glu Lys Cys Cys Ala Glu Ala Asn Pro Pro Ala
1235 1240 1245
Cys Tyr Gly Thr Val Leu Ala Glu Phe Gln Pro Leu Val Glu Glu
1250 1255 1260
Pro Lys Asn Leu Val Lys Thr Asn Cys Asp Leu Tyr Glu Lys Leu
1265 1270 1275

[0328] Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val Arg Tyr Thr Gln
1280 1285 1290
Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu Ala Ala Arg
1295 1300 1305
Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu Pro Glu Asp
1310 1315 1320
Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile Leu Asn
1325 1330 1335
Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His Val
1340 1345 1350
Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe
1355
Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys
1370 1375 1380
Ala Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu
1385 1390 1395
Lys Glu Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val
1400 1405 1410
Lys His Lys Pro Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met
1415 1420 1425
Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp
1430 1435 1440
Lys Asp Thr Cys Phe Ser Thr Glu Gly Pro Asn Leu Val Thr Arg
1445 1450 1455
Cys Lys Asp Ala Leu Ala Arg Ser Trp Ser His Pro Gln Phe Glu
1460 1465 1470
Lys

[0329] 单下划线:信号肽序列;双下划线:NPP1的开始和结束;**=信号肽序列处的切割位置;粗体残基表示白蛋白序列

[0330] SEQ.ID NO:14-ENPP5-NPP3-Fc序列

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

[0331] Phe

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

225 230 235
240
Tyr Phe Trp Pro Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro
Ser
245 250 255
Ile Tyr Met Pro Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile
Ser
260 265 270
Thr Leu Leu Lys Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg
Phe
275 280 285
Tyr Thr Met Tyr Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly
Gly
290 295 300
Pro Val Ser Ala Arg Val Ile Lys Ala Leu Gln Val Val Asp His
Ala
305 310 315
320
Phe Gly Met Leu Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn
Cys
325 330 335
Val Asn Ile Ile Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr
Cys
340 345 350
Asn Lys Met Glu Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe
Phe
355 360 365
[0332] Tyr Met Tyr Glu Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile
Pro
370 375 380
His Asp Phe Phe Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu
Ser
385 390 395
400
Cys Arg Lys Pro Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp
Leu
405 410 415
Pro Lys Arg Leu His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val
His
420 425 430
Leu Phe Val Asp Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn
Thr
435 440 445
Asn Cys Gly Gly Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser
Met
450 455 460
Glu Ala Ile Phe Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr
Glu
465 470 475
480
Val Glu Pro Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp
Leu
485 490 495
Leu Arg Ile Gln Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu
Asn
500 505 510

```
His Leu Leu Lys Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu
Val
                515                 520                 525
Ser Lys Phe Ser Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu
Ser
            530                 535                 540
Leu Asp Cys Phe Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu
Gln
545                 550                 555
560
Val Asn Gln Met Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr
Val
                    565                 570                 575
Lys Val Asn Leu Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn
Val
                580                 585                 590
Asp His Cys Leu Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly
Lys
                595                 600                 605
Ala Met Arg Met Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu
Gly
            610                 615                 620
Asp Thr Ser Pro Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala
Asp
625                 630                 635
640
Val Arg Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu
Ala
                    645                 650                 655
Asp Lys Asn Ile Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn
Arg
                660                 665                 670
Thr Ser Asp Ser Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val
Pro
                675                 680                 685
Met Tyr Glu Glu Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val
Leu
            690                 695                 700
Leu Ile Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser
Gly
705                 710                 715
720
Pro Ile Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp
Glu
                    725                 730                 735
Ile Thr Lys His Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His
Tyr
                740                 745                 750
Phe Val Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu
Asn
                755                 760                 765
Cys Pro Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg
Pro
            770                 775                 780
Thr Asn Val Glu Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp
Val
```

[0333]

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

[0334] 915 920 925

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

930 935 940

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

945 950 955 960

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

965 970 975

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

980 985 990

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

995 1000 1005

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

1010 1015 1020

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

1025 1030 1035

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

1040 1045 1050

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

1055 1060 1065

Ser Leu Ser Pro Gly Lys

1070

[0335] 单下划线:信号肽序列;双下划线:NPP33的开始和结束;**=信号肽序列处的切割位置;粗体残基表示白蛋白序列

[0336] SEQ.ID NO:15-ENPP5-NPP3-白蛋白序列

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

[0337]

225 230 235 240

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

245 250 255

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

260 265 270

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

275 280 285

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

290 295 300

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

305 310 315 320

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

325 330 335

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

340 345 350

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

355 360 365

[0338] Tyr Met Tyr Glu Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro

370 375 380

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

385 390 395 400

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

405 410 415

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

420 425 430

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

435 440 445

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

450 455 460

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

465 470 475 480

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

485 490 495

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

500 505 510

```
His Leu Leu Lys Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu
Val
                515                 520                 525
Ser Lys Phe Ser Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu
Ser
            530                 535                 540
Leu Asp Cys Phe Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu
Gln
545                 550                 555
560
Val Asn Gln Met Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr
Val
                    565                 570                 575
Lys Val Asn Leu Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn
Val
                580                 585                 590
Asp His Cys Leu Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly
Lys
                595                 600                 605
Ala Met Arg Met Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu
Gly
            610                 615                 620
Asp Thr Ser Pro Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala
Asp
625                 630                 635
640
Val Arg Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu
Ala
                    645                 650                 655
Asp Lys Asn Ile Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn
Arg
                660                 665                 670
Thr Ser Asp Ser Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val
Pro
                675                 680                 685
Met Tyr Glu Glu Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val
Leu
            690                 695                 700
Leu Ile Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser
Gly
705                 710                 715
720
Pro Ile Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp
Glu
                    725                 730                 735
Ile Thr Lys His Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His
Tyr
                740                 745                 750
Phe Val Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu
Asn
                755                 760                 765
Cys Pro Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg
Pro
            770                 775                 780
Thr Asn Val Glu Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp
Val
```

[0339]

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

[0340] Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala

930 935 940

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

945 950 955 960

Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys

965 970 975

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

980 985 990

Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met

995 1000 1005

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

1010 1015 1020

Leu His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu

1025 1030 1035

Leu Leu Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys

1040 1045 1050

Cys Ala Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp

1055 1060 1065

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

1070 1075 1080

Lys Cys Ser Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala

1085 1090 1095

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

```
     1100                1105                1110
Ala Glu  Ile Thr Lys Leu Ala  Thr Asp Leu Thr Lys  Val Asn Lys
     1115                1120                1125
Glu Cys  Cys His Gly Asp Leu  Leu Glu Cys Ala Asp  Asp Arg Ala
     1130                1135                1140
Glu Leu  Ala Lys Tyr Met Cys  Glu Asn Gln Ala Thr  Ile Ser Ser
     1145                1150                1155
Lys Leu  Gln Thr Cys Cys Asp  Lys Pro Leu Leu Lys  Lys Ala His
     1160                1165                1170
Cys Leu  Ser Glu Val Glu His  Asp Thr Met Pro Ala  Asp Leu Pro
     1175                1180                1185
Ala Ile  Ala Ala Asp Phe Val  Glu Asp Gln Glu Val  Cys Lys Asn
     1190                1195                1200
Tyr Ala  Glu Ala Lys Asp Val  Phe Leu Gly Thr Phe  Leu Tyr Glu
     1205                1210                1215
Tyr Ser  Arg Arg His Pro Asp  Tyr Ser Val Ser Leu  Leu Leu Arg
     1220                1225                1230
Leu Ala  Lys Lys Tyr Glu Ala  Thr Leu Glu Lys Cys  Cys Ala Glu
     1235                1240                1245
Ala Asn  Pro Pro Ala Cys Tyr  Gly Thr Val Leu Ala  Glu Phe Gln
     1250                1255                1260
Pro Leu  Val Glu Glu Pro Lys  Asn Leu Val Lys Thr  Asn Cys Asp
     1265                1270                1275
Leu Tyr  Glu Lys Leu Gly Glu  Tyr Gly Phe Gln Asn  Ala Ile Leu
     1280                1285                1290
Val Arg  Tyr Thr Gln Lys Ala  Pro Gln Val Ser Thr  Pro Thr Leu
     1295                1300                1305
Val Glu  Ala Ala Arg Asn Leu  Gly Arg Val Gly Thr  Lys Cys Cys
     1310                1315                1320
Thr Leu  Pro Glu Asp Gln Arg  Leu Pro Cys Val Glu  Asp Tyr Leu
     1325                1330                1335
Ser Ala  Ile Leu Asn Arg Val  Cys Leu Leu His Glu  Lys Thr Pro
     1340                1345                1350
Val Ser  Glu His Val Thr Lys  Cys Cys Ser Gly Ser  Leu Val Glu
     1355                1360                1365
Arg Arg  Pro Cys Phe Ser Ala  Leu Thr Val Asp Glu  Thr Tyr Val
     1370                1375                1380
Pro Lys  Glu Phe Lys Ala Glu  Thr Phe Thr Phe His  Ser Asp Ile
     1385                1390                1395
Cys Thr  Leu Pro Glu Lys Glu  Lys Gln Ile Lys Lys  Gln Thr Ala
     1400                1405                1410
Leu Ala  Glu Leu Val Lys His  Lys Pro Lys Ala Thr  Ala Glu Gln
     1415                1420                1425
Leu Lys  Thr Val Met Asp Asp  Phe Ala Gln Phe Leu  Asp Thr Cys
     1430                1435                1440
Cys Lys  Ala Ala Asp Lys Asp  Thr Cys Phe Ser Thr  Glu Gly Pro
     1445                1450                1455
Asn Leu  Val Thr Arg Cys Lys  Asp Ala Leu Ala
     1460                1465
```

[0341]

[0342] 单下划线:信号肽序列;双下划线:NPP3的开始和结束;**=信号肽序列处的切割位置;粗体残基表示白蛋白序列

[0343] 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
[0344]    1               5                   10                  15
          Leu Ser Thr Thr Phe Ser Xaa
                      20
```

[0345] SEQ.ID NO:17-ENPP51-Fc

```
          Met Thr Ser Lys Phe Leu Leu Val Ser Phe Ile Leu Ala Ala Leu
      Ser
          1               5                   10                  15
          Leu Ser Thr Thr Phe Ser**Gly Leu Lys Pro Ser Cys Ala Lys Glu
      Val
                      20                  25                  30
          Lys Ser Cys Lys Gly Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys
      Arg
                  35                  40                  45
          Cys Asp Ala Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr
      Gln
              50                  55                  60
          Glu Thr Cys Ile Glu Pro Glu His Ile Trp Thr Cys Asn Lys Phe
      Arg
          65                  70                  75                  80
          Cys Gly Glu Lys Arg Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp
      Asp
                          85                  90                  95
          Cys Lys Asp Lys Gly Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys
      Gln
                      100                 105                 110
          Gly Glu Lys Ser Trp Val Glu Glu Pro Cys Glu Ser Ile Asn Glu
[0346] Pro
                  115                 120                 125
          Gln Cys Pro Ala Gly Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser
      Leu
              130                 135                 140
          Asp Gly Phe Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu
      Pro
          145                 150                 155
      160
          Val Ile Ser Lys Leu Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met
      Arg
                          165                 170                 175
          Pro Val Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val
      Thr
                      180                 185                 190
          Gly Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr
      Asp
                  195                 200                 205
          Pro Lys Met Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe
      Asn
              210                 215                 220
          Pro Glu Trp Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr
      Gln
```

225 230 235 240

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

245 250 255

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

260 265 270

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

275 280 285

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

290 295 300

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

305 310 315 320

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

325 330 335

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

340 345 350

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

355 360 365

[0347] Gly Asp Val Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu

370 375 380

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

385 390 395 400

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

405 410 415

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

420 425 430

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

435 440 445

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

450 455 460

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

465 470 475 480

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

485 490 495

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

500 505 510

```
Gly Thr His Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr
Thr
                515                 520                 525
Pro Lys His Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe
Thr
            530                 535                 540
Arg Asn Pro Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile
Leu
545                 550                 555
560
Pro Ile Glu Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu
Glu
                    565                 570                 575
Lys Ile Ile Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val
Leu
                580                 585                 590
Gln Lys Glu Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met
Ser
                595                 600                 605
Gly Tyr Ser Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr
Val
            610                 615                 620
Asp Arg Asn Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu
Tyr
625                 630                 635
640
Gln Asp Phe Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe
Tyr
                    645                 650                 655
Lys Asn Asn Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln
Leu
                660                 665                 670
Asn Lys Asn Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr
Asn
                675                 680                 685
Ile Val Pro Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe
His
            690                 695                 700
Asp Thr Leu Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn
Val
705                 710                 715
720
Val Ser Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp
Ser
                    725                 730                 735
Leu Glu Asn Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu
Ile
                740                 745                 750
Leu Ile Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp
Thr
                755                 760                 765
Ser Gln Thr Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe
Ile
            770                 775                 780
Leu Pro His Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys
His
```

[0348]

```
          785                 790                 795
800
Asp Ser Ser Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg
Ile
                    805                 810                 815
Thr Asp Val Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg
Lys
               820                 825                 830
Glu Pro Val Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr
Phe
          835                 840                 845
Ser Gln Glu Asp Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
Pro
     850                 855                 860
Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
Lys
865                 870                 875
880
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
Val
                    885                 890                 895
Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
Asp
               900                 905                 910
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
Tyr
          915                 920                 925
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
Asp
     930                 935                 940
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
Leu
945                 950                 955
960
Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
Arg
                    965                 970                 975
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
Lys
               980                 985                 990
Asn Gln Val Ser Leu Thr Cys Leu  Val Lys Gly Phe Tyr  Pro Ser
Asp
          995                 1000                1005
Ile Ala  Val Glu Trp Glu Ser  Asn Gly Gln Pro Glu  Asn Asn Tyr
     1010                1015                1020
Lys Thr  Thr Pro Pro Val Leu  Asp Ser Asp Gly Ser  Phe Phe Leu
     1025                1030                1035
Tyr Ser  Lys Leu Thr Val Asp  Lys Ser Arg Trp Gln  Gln Gly Asn
     1040                1045                1050
Val Phe  Ser Cys Ser Val Met  His Glu Ala Leu His  Asn His Tyr
     1055                1060                1065
Thr Gln  Lys Ser Leu Ser Leu  Ser Pro Gly Lys
     1070                1075
```

[0349]

[0350] 单下划线:信号肽序列;双下划线:NPP3的开始和结束;**=信号肽序列处的切割位置;粗体残基表示Fc序列

[0351] SEQ.ID NO:18-ENPP71-Fc氨基酸序列

[0352]

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

```
Gly Leu Lys Ser Gly Thr Phe Phe Trp Pro Gly Ser Asp Val Glu
Ile
                    245                 250                 255
Asn Gly Ile Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val
Pro
                260                 265                 270
Phe Glu Glu Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro
Lys
            275                 280                 285
Asp Glu Arg Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp
Ser
        290                 295                 300
Ser Gly His Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala
Leu
305                 310                 315
320
Gln Arg Val Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys
Glu
                    325                 330                 335
Leu Asn Leu His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His
Gly
                340                 345                 350
Met Glu Gln Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr
Leu
            355                 360                 365
Gly Asp Val Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg
Leu
        370                 375                 380
Arg Pro Ser Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu
Gly
385                 390                 395
400
Ile Ala Arg Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys
Pro
                    405                 410                 415
Tyr Leu Lys His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser
Asp
                420                 425                 430
Arg Ile Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu
Ala
            435                 440                 445
Leu Asn Pro Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly
Ser
        450                 455                 460
Asp Asn Val Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly
Pro
465                 470                 475
480
Gly Phe Lys His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu
Val
                    485                 490                 495
Tyr Asn Leu Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn
Asn
                500                 505                 510
Gly Thr His Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr
Thr
```

[0353]

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

[0354]

```
Asp Ser Ser Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg
Ile
                  805                 810                 815
Thr Asp Val Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg
Lys
              820                 825                 830
Glu Pro Val Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr
Phe
          835                 840                 845
Ser Gln Glu Asp Leu Ile Asn Asp Lys Thr His Thr Cys Pro Pro
Cys
      850                 855                 860
Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
Pro
865                 870                 875
880
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
Cys
                  885                 890                 895
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
Trp
              900                 905                 910
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
Glu
          915                 920                 925
[0355]    Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
Leu
      930                 935                 940
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
Asn
945                 950                 955
960
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
Gly
                  965                 970                 975
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
Glu
              980                 985                 990
Met Thr Lys Asn Gln Val Ser Leu  Thr Cys Leu Val Lys  Gly Phe
Tyr
          995                 1000                1005
Pro Ser  Asp Ile Ala Val Glu  Trp Glu Ser Asn Gly  Gln Pro Glu
     1010                1015                1020
Asn Asn  Tyr Lys Thr Thr Pro  Pro Val Leu Asp Ser  Asp Gly Ser
     1025                1030                1035
Phe Phe  Leu Tyr Ser Lys Leu  Thr Val Asp Lys Ser  Arg Trp Gln
     1040                1045                1050
Gln Gly  Asn Val Phe Ser Cys  Ser Val Met His Glu  Ala Leu His
     1055                1060                1065
Asn His  Tyr Thr Gln Lys Ser  Leu Ser Leu Ser Pro  Gly Lys
     1070                1075                1080
```

[0356] 单下划线:信号肽序列;双下划线:NPP1的开始和结束;**=信号肽序列处的切割位置;粗体残基表示Fc序列

[0357] SEQ.ID NO:19-ENPP71(缺乏NPP1 N末端GLK)氨基酸序列:

[0358]

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

```
Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu
Glu
                260                 265                 270
Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu
Arg
            275                 280                 285
Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly
His
        290                 295                 300
Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg
Val
305                 310                 315
320
Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn
Leu
                    325                 330                 335
His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu
Gln
                340                 345                 350
Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp
Val
            355                 360                 365
Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro
Ser
        370                 375                 380
Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala
Arg
385                 390                 395
400
Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu
Lys
                    405                 410                 415
His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile
Glu
                420                 425                 430
Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn
Pro
            435                 440                 445
Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn
Val
        450                 455                 460
Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe
Lys
465                 470                 475
480
His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn
Leu
                    485                 490                 495
Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr
His
                500                 505                 510
Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys
His
            515                 520                 525
Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn
Pro
```

[0359]

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
[0360] 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
```

[0361]

[0362] 单下划线:信号肽序列;双下划线:NPP3的开始和结束;**=信号肽序列处的切割位置

[0363] SEQ.ID NO:20-ENPP71(缺乏NPP1 N末端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
Lys Gly Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp
Ala
        35                  40                  45
Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr
Cys
    50                  55                  60
Ile Glu Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly
Glu
65                  70                  75                  80
Lys Arg Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys
Asp
                85                  90                  95
Lys Gly Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu
Lys
            100                 105                 110
Ser Trp Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys
Pro
        115                 120                 125
Ala Gly Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly
Phe
    130                 135                 140
Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile
Ser
145                 150                 155
160
Lys Leu Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val
Tyr
                165                 170                 175
Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu
Tyr
            180                 185                 190
Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys
Met
```

[0364]

```
                195                 200                 205
Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu
Trp
    210                 215                 220
Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu
Lys
225                 230                 235
240
Ser Gly Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly
Ile
                245                 250                 255
Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu
Glu
            260                 265                 270
Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu
Arg
        275                 280                 285
Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly
His
    290                 295                 300
Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg
Val
305                 310                 315
320
Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn
Leu
                325                 330                 335
His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu
Gln
            340                 345                 350
Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp
Val
        355                 360                 365
Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro
Ser
    370                 375                 380
Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala
Arg
385                 390                 395
400
Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu
Lys
                405                 410                 415
His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile
Glu
            420                 425                 430
Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn
Pro
        435                 440                 445
Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn
Val
    450                 455                 460
Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe
Lys
465                 470                 475
480
```

[0365]

[0366]

```
His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn
Leu
                    485                 490                 495
Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr
His
                500                 505                 510
Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys
His
            515                 520                 525
Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn
Pro
        530                 535                 540
Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile
Glu
545                 550                 555
560
Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile
Ile
                    565                 570                 575
Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys
Glu
                580                 585                 590
Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr
Ser
            595                 600                 605
Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg
Asn
        610                 615                 620
Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp
Phe
625                 630                 635
640
Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn
Asn
                    645                 650                 655
Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys
Asn
                660                 665                 670
Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val
Pro
            675                 680                 685
Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr
Leu
        690                 695                 700
Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser
Gly
705                 710                 715
720
Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu
Asn
                    725                 730                 735
Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile
Pro
                740                 745                 750
Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln
Thr
```

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

[0367]

[0368]

[0369] 单下划线:信号肽序列;双下划线:NPP1的开始和结束;**=信号肽序列处的切割位置;粗体残基表示Fc序列

[0370] SEQ.ID NO:21-ENPP71(缺乏NPP1 N末端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
          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
[0371] Ser Trp Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys
Pro
              115                 120                 125
      Ala Gly Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly
Phe
          130                 135                 140
      Arg Ala Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile
Ser
      145                 150                 155
160
      Lys Leu Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val
Tyr
                      165                 170                 175
      Pro Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu
Tyr
                  180                 185                 190
      Pro Glu Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys
Met
              195                 200                 205
      Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu
Trp
          210                 215                 220
```

```
Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu
Lys
225                 230                 235
240
Ser Gly Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly
Ile
                    245                 250                 255
Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu
Glu
                260                 265                 270
Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu
Arg
            275                 280                 285
Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly
His
        290                 295                 300
Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg
Val
305                 310                 315
320
Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn
Leu
                    325                 330                 335
His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu
Gln
                340                 345                 350
Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp
[0372] Val
            355                 360                 365
Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro
Ser
        370                 375                 380
Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala
Arg
385                 390                 395
400
Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu
Lys
                    405                 410                 415
His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile
Glu
                420                 425                 430
Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn
Pro
            435                 440                 445
Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn
Val
        450                 455                 460
Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe
Lys
465                 470                 475
480
His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn
Leu
                    485                 490                 495
```

[0373]

```
Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr
His
                500                 505                 510
Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys
His
            515                 520                 525
Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn
Pro
        530                 535                 540
Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile
Glu
545                 550                 555
560
Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile
Ile
                    565                 570                 575
Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys
Glu
                580                 585                 590
Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr
Ser
            595                 600                 605
Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg
Asn
        610                 615                 620
Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp
Phe
625                 630                 635
640
Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn
Asn
                    645                 650                 655
Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys
Asn
                660                 665                 670
Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val
Pro
            675                 680                 685
Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr
Leu
        690                 695                 700
Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser
Gly
705                 710                 715
720
Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu
Asn
                    725                 730                 735
Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile
Pro
                740                 745                 750
Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln
Thr
            755                 760                 765
Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro
His
```

[0374]

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

Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
1085 1090 1095
Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr Lys
1100 1105 1110
Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly
1115 1120 1125
Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr
1130 1135 1140
Met Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys
1145 1150 1155
Cys Asp Lys Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val
1160 1165 1170
Glu His Asp Thr Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp
1175 1180 1185
Phe Val Glu Asp Gln Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys
1190 1195 1200
Asp Val Phe Leu Gly Thr Phe Leu Tyr Glu Tyr Ser Arg Arg His
1205 1210 1215
Pro Asp Tyr Ser Val Ser Leu Leu Leu Arg Leu Ala Lys Lys Tyr
1220 1225 1230
Glu Ala Thr Leu Glu Lys Cys Cys Ala Glu Ala Asn Pro Pro Ala
1235 1240 1245
Cys Tyr Gly Thr Val Leu Ala Glu Phe Gln Pro Leu Val Glu Glu
1250 1255 1260
Pro Lys Asn Leu Val Lys Thr Asn Cys Asp Leu Tyr Glu Lys Leu
1265 1270 1275

[0375] Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val Arg Tyr Thr Gln
1280 1285 1290
Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu Ala Ala Arg
1295 1300 1305
Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu Pro Glu Asp
1310 1315 1320
Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile Leu Asn
1325 1330 1335
Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His Val
1340 1345 1350
Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe
1355 1360 1365
Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys
1370 1375 1380
Ala Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu
1385 1390 1395
Lys Glu Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val
1400 1405 1410
Lys His Lys Pro Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met
1415 1420 1425
Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp
1430 1435 1440
Lys Asp Thr Cys Phe Ser Thr Glu Gly Pro Asn Leu Val Thr Arg
1445 1450 1455
Cys Lys Asp Ala Leu Ala Arg Ser Trp Ser His Pro Gln Phe Glu
1460 1465 1470
Lys

[0376] 单下划线:信号肽序列;双下划线:NPP1的开始和结束;**=信号肽序列处的切割位置;粗体残基表示白蛋白序列

[0377] SEQ.ID NO:22-ENPP7-NPP3-Fc序列：

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

[0378]

```
Trp Pro Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser Ile
Tyr
                    245                 250                 255
Met Pro Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser Thr
Leu
                260                 265                 270
Leu Lys Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr
Thr
            275                 280                 285
Met Tyr Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly Pro
Val
        290                 295                 300
Ser Ala Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala Phe
Gly
305                 310                 315
320
Met Leu Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys Val
Asn
                    325                 330                 335
Ile Ile Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys Asn
Lys
                340                 345                 350
Met Glu Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr
Met
            355                 360                 365
Tyr Glu Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro His
Asp
        370                 375                 380
Phe Phe Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser Cys
Arg
385                 390                 395
400
Lys Pro Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro
Lys
                    405                 410                 415
Arg Leu His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His Leu
Phe
                420                 425                 430
Val Asp Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr Asn
Cys
            435                 440                 445
Gly Gly Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu
Ala
        450                 455                 460
Ile Phe Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu Val
Glu
465                 470                 475
480
Pro Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu
Arg
                    485                 490                 495
Ile Gln Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His
Leu
                500                 505                 510
Leu Lys Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val Ser
Lys
```

[0379]

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

[0380]

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

[0381]

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

[0382] 单下划线:信号肽序列;双下划线:NPP3的开始和结束;**=信号肽序列处的切割位置;粗体残基表示Fc序列

[0383] SEQ.ID NO:23-ENPP71-白蛋白

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

[0384]

```
Glu Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys Asp
Glu
                275                 280                 285
Arg Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser
Gly
            290                 295                 300
His Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln
Arg
305                 310                 315
320
Val Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu Leu
Asn
                    325                 330                 335
Leu His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met
Glu
                340                 345                 350
Gln Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly
Asp
                355                 360                 365
Val Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg
Pro
            370                 375                 380
Ser Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile
Ala
385                 390                 395
400
Arg Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro Tyr
Leu
```

[0385]

```
                    405                 410                 415
Lys His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg
Ile
                420                 425                 430
Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu
Asn
                435                 440                 445
Pro Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp
Asn
            450                 455                 460
Val Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly
Phe
465                 470                 475
480
Lys His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr
Asn
                    485                 490                 495
Leu Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly
Thr
                500                 505                 510
His Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr Pro
Lys
                515                 520                 525
His Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr Arg
Asn
            530                 535                 540
Pro Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro
Ile
```

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

[0386]

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

[0387]

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

[0388]

[0389] 单下划线:信号肽序列;双下划线:NPP3的开始和结束;**=信号肽序列处的切割位置;粗体残基表示Fc序列

[0390] 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
```

[0391]

```
Asp
        35                  40                  45
Arg Gly Asp Cys Cys Trp Asp Phe Glu Asp Thr Cys Val Glu Ser
Thr
    50                  55                  60
Arg Ile Trp Met Cys Asn Lys Phe Arg Cys Gly Glu Arg Leu Glu
Ala
65                  70                  75                  80
```

```
Ser Leu Cys Ser Cys Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys
Cys
                    85                  90                  95
Ala Asp Tyr Lys Ser Val Cys Gln Gly Glu Thr Ser Trp Leu Glu
Glu
                100                 105                 110
Asn Cys Asp Thr Ala Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp
Leu
            115                 120                 125
Pro Pro Val Ile Leu Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr
Leu
        130                 135                 140
Tyr Thr Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys Thr
Cys
145                 150                 155
160
Gly Ile His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr
Phe
                    165                 170                 175
Pro Asn His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser His
Gly
                180                 185                 190
Ile Ile Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn Phe
Ser
            195                 200                 205
Leu Ser Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly Gln
Pro
        210                 215                 220
```

[0392]

```
Met Trp Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr
Phe
225                 230                 235
240
Trp Pro Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser Ile
Tyr
                    245                 250                 255
Met Pro Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser Thr
Leu
                260                 265                 270
Leu Lys Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr
Thr
            275                 280                 285
Met Tyr Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly Pro
Val
        290                 295                 300
Ser Ala Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala Phe
Gly
305                 310                 315
320
Met Leu Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys Val
Asn
                    325                 330                 335
Ile Ile Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys Asn
Lys
                340                 345                 350
Met Glu Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr
Met
```

```
                355                 360                 365
Tyr Glu Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro His
Asp
            370                 375                 380
Phe Phe Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser Cys
Arg
385                 390                 395
400
Lys Pro Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro
Lys
                    405                 410                 415
Arg Leu His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His Leu
Phe
                420                 425                 430
Val Asp Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr Asn
Cys
                435                 440                 445
Gly Gly Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu
Ala
            450                 455                 460
Ile Phe Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu Val
Glu
465                 470                 475
480
Pro Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu
Arg
                    485                 490                 495
Ile Gln Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His
Leu
                500                 505                 510
Leu Lys Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val Ser
Lys
                515                 520                 525
Phe Ser Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu
Asp
            530                 535                 540
Cys Phe Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln Val
Asn
545                 550                 555
560
Gln Met Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val Lys
Val
                    565                 570                 575
Asn Leu Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val Asp
His
                580                 585                 590
Cys Leu Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala
Met
                595                 600                 605
Arg Met Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp
Thr
            610                 615                 620
Ser Pro Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp Val
Arg
625                 630                 635
640
```

[0393]

[0394]

```
Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp
Lys
                    645                 650                 655
Asn Ile Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr
Ser
                660                 665                 670
Asp Ser Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro Met
Tyr
            675                 680                 685
Glu Glu Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu Leu
Ile
        690                 695                 700
Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro
Ile
705                 710                 715
720
Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu Ile
Thr
                    725                 730                 735
Lys His Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr Phe
Val
                740                 745                 750
Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys
Pro
            755                 760                 765
Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro Thr
Asn
        770                 775                 780
Val Glu Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val Glu
Glu
785                 790                 795
800
Arg Phe Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu
Thr
                    805                 810                 815
Gly Leu Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile
Leu
                820                 825                 830
Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile Gly Gly
Gly
            835                 840                 845
Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Met Lys Trp Val
Thr
        850                 855                 860
Phe Leu Leu Leu Leu Phe Val Ser Gly Ser Ala Phe Ser Arg Gly
Val
865                 870                 875
880
Phe Arg Arg Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn
Asp
                    885                 890                 895
Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser
Gln
                900                 905                 910
Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln
Glu
```

[0395]

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

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

[0396]

[0397] 单下划线:信号肽序列;双下划线:NPP3的开始和结束;**=信号肽序列处的切割位置;粗体残基表示白蛋白序列

[0398] SEQ.ID NO:25-ENPP7-ENPP3-白蛋白

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

[0399]

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

[0400]

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
[0401]
Cys Phe Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln Val
Asn
545 550 555
560
Gln Met Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val Lys
Val
565 570 575
Asn Leu Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val Asp
His
580 585 590
Cys Leu Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala
Met
595 600 605
Arg Met Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp
Thr
610 615 620
Ser Pro Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp Val
Arg
625 630 635
640
Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp
Lys
645 650 655
Asn Ile Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr
Ser
660 665 670
Asp Ser Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro Met
Tyr

675 680 685
Glu Glu Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu Leu
Ile
690 695 700
Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro
Ile
705 710 715
720
Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu Ile
Thr
725 730 735
Lys His Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr Phe
Val
740 745 750
Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys
Pro
755 760 765
Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro Thr
Asn
770 775 780
Val Glu Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val Glu
Glu
785 790 795
800
Arg Phe Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu
Thr
805 810 815
[0402] Gly Leu Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile
Leu
820 825 830
Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile Asp Lys
Thr
835 840 845
His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
Ser
850 855 860
Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
Arg
865 870 875
880
Thr Pro Glu Val Thr Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
Gly
885 890 895
Gly Gly Ser **Met Lys Trp Val Thr Phe Leu Leu Leu Leu Phe Val**
Ser
900 905 910
Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg Glu Ala His Lys
Ser
915 920 925
Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys
Gly
930 935 940
Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr
Asp
945 950 955
960

```
Glu His Ala Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr
Cys
                    965                 970                 975
Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr
Leu
                980                 985                 990
Phe Gly Asp Lys Leu Cys Ala Ile  Pro Asn Leu Arg Glu  Asn Tyr
Gly
            995                1000                1005
Glu Leu  Ala Asp Cys Cys Thr  Lys Gln Glu Pro Glu  Arg Asn Glu
    1010                1015                1020
Cys Phe  Leu Gln His Lys Asp  Asp Asn Pro Ser Leu  Pro Pro Phe
    1025                1030                1035
Glu Arg  Pro Glu Ala Glu Ala  Met Cys Thr Ser Phe  Lys Glu Asn
    1040                1045                1050
Pro Thr  Thr Phe Met Gly His  Tyr Leu His Glu Val  Ala Arg Arg
    1055                1060                1065
His Pro  Tyr Phe Tyr Ala Pro  Glu Leu Leu Tyr Tyr  Ala Glu Gln
    1070                1075                1080
Tyr Asn  Glu Ile Leu Thr Gln  Cys Cys Ala Glu Ala  Asp Lys Glu
    1085                1090                1095
Ser Cys  Leu Thr Pro Lys Leu  Asp Gly Val Lys Glu  Lys Ala Leu
    1100                1105                1110
Val Ser  Ser Val Arg Gln Arg  Met Lys Cys Ser Ser  Met Gln Lys
    1115                1120                1125
Phe Gly  Glu Arg Ala Phe Lys  Ala Trp Ala Val Ala  Arg Leu Ser
    1130                1135                1140
Gln Thr  Phe Pro Asn Ala Asp  Phe Ala Glu Ile Thr  Lys Leu Ala
    1145                1150                1155
Thr Asp  Leu Thr Lys Val Asn  Lys Glu Cys Cys His  Gly Asp Leu
    1160                1165                1170
Leu Glu  Cys Ala Asp Asp Arg  Ala Glu Leu Ala Lys  Tyr Met Cys
    1175                1180                1185
Glu Asn  Gln Ala Thr Ile Ser  Ser Lys Leu Gln Thr  Cys Cys Asp
    1190                1195                1200
Lys Pro  Leu Leu Lys Lys Ala  His Cys Leu Ser Glu  Val Glu His
    1205                1210                1215
Asp Thr  Met Pro Ala Asp Leu  Pro Ala Ile Ala Ala  Asp Phe Val
    1220                1225                1230
Glu Asp  Gln Glu Val Cys Lys  Asn Tyr Ala Glu Ala  Lys Asp Val
    1235                1240                1245
Phe Leu  Gly Thr Phe Leu Tyr  Glu Tyr Ser Arg Arg  His Pro Asp
    1250                1255                1260
Tyr Ser  Val Ser Leu Leu Leu  Arg Leu Ala Lys Lys  Tyr Glu Ala
    1265                1270                1275
Thr Leu  Glu Lys Cys Cys Ala  Glu Ala Asn Pro Pro  Ala Cys Tyr
    1280                1285                1290
Gly Thr  Val Leu Ala Glu Phe  Gln Pro Leu Val Glu  Glu Pro Lys
    1295                1300                1305
Asn Leu  Val Lys Thr Asn Cys  Asp Leu Tyr Glu Lys  Leu Gly Glu
    1310                1315                1320
Tyr Gly  Phe Gln Asn Ala Ile  Leu Val Arg Tyr Thr  Gln Lys Ala
    1325                1330                1335
Pro Gln  Val Ser Thr Pro Thr  Leu Val Glu Ala Ala  Arg Asn Leu
    1340                1345                1350
Gly Arg  Val Gly Thr Lys Cys  Cys Thr Leu Pro Glu  Asp Gln Arg
```

[0403]

```
     1355                1360                1365
Leu Pro  Cys Val Glu Asp Tyr  Leu Ser Ala Ile Leu  Asn Arg Val
     1370                1375                1380
Cys Leu  Leu His Glu Lys Thr  Pro Val Ser Glu His  Val Thr Lys
     1385                1390                1395
Cys Cys  Ser Gly Ser Leu Val  Glu Arg Arg Pro Cys  Phe Ser Ala
     1400                1405                1410
Leu Thr  Val Asp Glu Thr Tyr  Val Pro Lys Glu Phe  Lys Ala Glu
     1415                1420                1425
Thr Phe  Thr Phe His Ser Asp  Ile Cys Thr Leu Pro  Glu Lys Glu
     1430                1435                1440
Lys Gln  Ile Lys Lys Gln Thr  Ala Leu Ala Glu Leu  Val Lys His
     1445                1450                1455
Lys Pro  Lys Ala Thr Ala Glu  Gln Leu Lys Thr Val  Met Asp Asp
     1460                1465                1470
Phe Ala  Gln Phe Leu Asp Thr  Cys Cys Lys Ala Ala  Asp Lys Asp
     1475                1480                1485
Thr Cys  Phe Ser Thr Glu Gly  Pro Asn Leu Val Thr  Arg Cys Lys
     1490                1495                1500
Asp Ala  Leu Ala
     1505
```

[0404]

[0405] 单下划线:信号肽序列;双下划线:NPP3的开始和结束;**=信号肽序列处的切割位置;粗体残基表示白蛋白序列

[0406] SEQ.ID NO:26-ENPP71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
Gly Glu Lys Ser Trp Val Glu Glu Pro Cys Glu Ser Ile Asn Glu
Pro
        115                 120                 125
```

[0407]

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
[0408] Pro
260 265 270
Phe Glu Glu Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro
Lys
275 280 285
Asp Glu Arg Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp
Ser
290 295 300
Ser Gly His Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala
Leu
305 310 315
320
Gln Arg Val Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys
Glu
325 330 335
Leu Asn Leu His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His
Gly
340 345 350
Met Glu Gln Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr
Leu
355 360 365
Gly Asp Val Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg
Leu
370 375 380
Arg Pro Ser Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu
Gly
385 390 395
400

[0409]

```
Ile Ala Arg Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys
Pro
                    405                 410                 415
Tyr Leu Lys His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser
Asp
                420                 425                 430
Arg Ile Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu
Ala
            435                 440                 445
Leu Asn Pro Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly
Ser
        450                 455                 460
Asp Asn Val Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly
Pro
465                 470                 475
480
Gly Phe Lys His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu
Val
                    485                 490                 495
Tyr Asn Leu Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn
Asn
                500                 505                 510
Gly Thr His Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr
Thr
            515                 520                 525
Pro Lys His Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe
Thr
        530                 535                 540
Arg Asn Pro Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile
Leu
545                 550                 555
560
Pro Ile Glu Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu
Glu
                    565                 570                 575
Lys Ile Ile Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val
Leu
                580                 585                 590
Gln Lys Glu Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met
Ser
            595                 600                 605
Gly Tyr Ser Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr
Val
        610                 615                 620
Asp Arg Asn Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu
Tyr
625                 630                 635
640
Gln Asp Phe Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe
Tyr
                    645                 650                 655
Lys Asn Asn Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln
Leu
                660                 665                 670
Asn Lys Asn Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr
Asn
```

675 680 685
Ile Val Pro Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe
His
690 695 700
Asp Thr Leu Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn
Val
705 710 715
720
Val Ser Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp
Ser
725 730 735
Leu Glu Asn Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu
Ile
740 745 750
Leu Ile Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp
Thr
755 760 765
[0410] Ser Gln Thr Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe
Ile
770 775 780
Leu Pro His Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys
His
785 790 795
800
Asp Ser Ser Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg
Ile
805 810 815
Thr Asp Val Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg
Lys
820 825 830
Glu Pro Val Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr
Phe
835 840 845
Ser Gln Glu Asp
850

[0411] 单下划线:信号肽序列;双下划线:NPP1的开始和结束;**=信号肽序列处的切割位置

[0412] 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
[0413] Gly
20 25 30
Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala
Ser
35 40 45

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

[0414]

325 330 335
Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Leu
Ala
340 345 350
Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His Phe
Tyr
355 360 365
Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr Gly
Pro
370 375 380
Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly Met
Val
385 390 395
400
Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg Cys
Leu
405 410 415
Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser Cys
Lys
420 425 430
Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn Ile
Lys
435 440 445
Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val Pro
Asp
450 455 460
Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu Ser
[0415] Cys
465 470 475
480
Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe Leu
Pro
485 490 495
Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu Thr
Phe
500 505 510
Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu Arg
Lys
515 520 525
Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser Asn
Met
530 535 540
Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys His Gly Ile
Glu
545 550 555
560
Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp
Leu
565 570 575
Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu
Asn
580 585 590
His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His Pro Lys Glu
Val
595 600 605

```
His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp Asn
Leu
610 615 620
Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe Gln
Thr
625 630 635
640
Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His Glu
Thr
645 650 655
Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr Ile
Cys
660 665 670
Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp Ile
Leu
675 680 685
Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser Phe
Ser
690 695 700
Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile Pro
Leu
705 710 715
720
Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val
Ser
725 730 735
Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser Gly
```

[0416]

```
Ile
740 745 750
Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln
Ser
755 760 765
Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys
Tyr
770 775 780
Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val Phe
Asp
785 790 795
800
Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln
Lys
805 810 815
Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe
Phe
820 825 830
Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His
Cys
835 840 845
Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp
Asn
850 855 860
Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu
Glu
865 870 875
880
```

```
      Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile
Thr
                    885                 890                 895
      Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile
Leu
                900                 905                 910
      Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp
                915                 920                 925
```

[0417]

[0418] 单下划线:信号肽序列;双下划线:NPP1的开始和结束;**=信号肽序列处的切割位置

[0419] 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
      Gly Arg Ala Pro Arg Glu Gly Pro Ala Gly Asn Gly Arg Asp Arg
Gly
                20                  25                  30
      Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala
Ser
           35                  40                  45
      Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala
Ala
      50                  55                  60
      Arg Ala Arg Thr Ala Lys Asp Pro Asn Thr Tyr Lys Ile Ile Ser
Leu
      65                  70                  75                  80
      Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly**Phe Thr Ala
Gly
                    85                  90                  95
      Leu Lys Pro Ser Cys Ala Lys Glu Val Lys Ser Cys Lys Gly Arg
Cys
                100                 105                 110
      Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala Ala Cys Val
Glu
           115                 120                 125
      Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys Ile Glu Pro
Glu
      130                 135                 140
      His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu Lys Arg Leu
Thr
      145                 150                 155
160
      Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp Lys Gly Asp
Cys
                    165                 170                 175
      Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp Val
Glu
                180                 185                 190
```

[0420]

```
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
```

[0421]

```
325 330 335
Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Leu
Ala
340 345 350
Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His Phe
Tyr
355 360 365
Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr Gly
Pro
370 375 380
Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly Met
Val
385 390 395
400
Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg Cys
Leu
405 410 415
Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser Cys
Lys
420 425 430
Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn Ile
Lys
435 440 445
Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val Pro
Asp
450 455 460
Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu Ser
Cys
```

```
      465                 470                 475
480
      Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe Leu
Pro
                      485                 490                 495
      Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu Thr
Phe
                  500                 505                 510
      Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu Arg
Lys
              515                 520                 525
      Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser Asn
Met
          530                 535                 540
      Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys His Gly Ile
Glu
      545                 550                 555
560
      Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp
Leu
                      565                 570                 575
      Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu
Asn
                  580                 585                 590
      His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His Pro Lys Glu
Val
              595                 600                 605
      His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp Asn
Leu
          610                 615                 620
      Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe Gln
Thr
      625                 630                 635
640
      Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His Glu
Thr
                      645                 650                 655
      Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr Ile
Cys
                  660                 665                 670
      Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp Ile
Leu
              675                 680                 685
      Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser Phe
Ser
          690                 695                 700
      Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile Pro
Leu
      705                 710                 715
720
      Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val
Ser
                      725                 730                 735
      Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser Gly
Ile
                  740                 745                 750
```

[0422]

```
Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln
Ser
          755                 760                 765
Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys
Tyr
      770                 775                 780
Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val Phe
Asp
785                 790                 795
800
Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln
Lys
                    805                 810                 815
Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe
Phe
               820                 825                 830
Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His
Cys
          835                 840                 845
Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp
Asn
      850                 855                 860
Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu
Glu
865                 870                 875
880
Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile
Thr
[0423]                  885                 890                 895
Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile
Leu
               900                 905                 910
Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp Leu Ile
Asn
          915                 920                 925
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
Gly
      930                 935                 940
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
Met
945                 950                 955
960
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
His
                    965                 970                 975
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
Val
               980                 985                 990
His Asn Ala Lys Thr Lys Pro Arg  Glu Glu Gln Tyr Asn  Ser Thr
Tyr
          995                 1000                1005
Arg Val  Val Ser Val Leu Thr  Val Leu His Gln Asp  Trp Leu Asn
     1010                1015                1020
Gly Lys  Glu Tyr Lys Cys Lys  Val Ser Asn Lys Ala  Leu Pro Ala
     1025                1030                1035
Pro Ile  Glu Lys Thr Ile Ser  Lys Ala Lys Gly Gln  Pro Arg Glu
```

```
     1040                1045                1050
Pro Gln  Val Tyr Thr Leu Pro  Pro Ser Arg Glu Glu  Met Thr Lys
     1055                1060                1065
Asn Gln  Val Ser Leu Thr Cys  Leu Val Lys Gly Phe  Tyr Pro Ser
     1070                1075                1080
Asp Ile  Ala Val Glu Trp Glu  Ser Asn Gly Gln Pro  Glu Asn Asn
     1085                1090                1095
Tyr Lys  Thr Thr Pro Pro Val  Leu Asp Ser Asp Gly  Ser Phe Phe
     1100                1105                1110
Leu Tyr  Ser Lys Leu Thr Val  Asp Lys Ser Arg Trp  Gln Gln Gly
     1115                1120                1125
Asn Val  Phe Ser Cys Ser Val  Met His Glu Ala Leu  His Asn His
     1130                1135                1140
Tyr Thr  Gln Lys Ser Leu Ser  Leu Ser Pro Gly Lys
     1145                1150                1155
```

[0424]

[0425] 单下划线:信号肽序列;双下划线:NPP1的开始和结束;**=信号肽序列处的切割位置;粗体残基表示Fc序列

[0426] 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
     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
```

[0427]

```
                                165                 170                 175
Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp Val
Glu
                            180                 185                 190
Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro Ala Gly Phe
Glu
                        195                 200                 205
Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe Arg Ala Glu
Tyr
                    210                 215                 220
Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser Lys Leu Lys
Lys
225                 230                 235
240
Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr Lys
Thr
                                245                 250                 255
Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu Ser
His
                            260                 265                 270
Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala Ser
Phe
                        275                 280                 285
Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys Gly
Glu
                    290                 295                 300
Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly Thr
Phe
305                 310                 315
320
Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro Asp
Ile
                                325                 330                 335
Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Leu
Ala
                            340                 345                 350
Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His Phe
Tyr
                        355                 360                 365
Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr Gly
Pro
                    370                 375                 380
Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly Met
Val
385                 390                 395
400
Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg Cys
Leu
                                405                 410                 415
Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser Cys
Lys
                            420                 425                 430
Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn Ile
Lys
                        435                 440                 445
```

[0428]

```
Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val Pro
Asp
 450                 455                 460
Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu Ser
Cys
465                 470                 475
480
Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe Leu
Pro
                485                 490                 495
Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu Thr
Phe
            500                 505                 510
Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu Arg
Lys
        515                 520                 525
Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser Asn
Met
    530                 535                 540
Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys His Gly Ile
Glu
545                 550                 555
560
Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp
Leu
                565                 570                 575
Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu
Asn
            580                 585                 590
His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His Pro Lys Glu
Val
        595                 600                 605
His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp Asn
Leu
    610                 615                 620
Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe Gln
Thr
625                 630                 635
640
Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His Glu
Thr
                645                 650                 655
Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr Ile
Cys
            660                 665                 670
Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp Ile
Leu
        675                 680                 685
Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser Phe
Ser
    690                 695                 700
Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile Pro
Leu
705                 710                 715
720
```

[0429]

```
Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val
Ser
                  725                 730                 735
Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser Gly
Ile
              740                 745                 750
Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln
Ser
          755                 760                 765
Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys
Tyr
      770                 775                 780
Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val Phe
Asp
785                 790                 795
800
Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln
Lys
                  805                 810                 815
Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe
Phe
              820                 825                 830
Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His
Cys
          835                 840                 845
Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp
Asn
      850                 855                 860
Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu
Glu
865                 870                 875
880
Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile
Thr
                  885                 890                 895
Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile
Leu
              900                 905                 910
Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp Arg Ser
Gly
          915                 920                 925
Ser Gly Gly Ser Met Lys Trp Val Thr Phe Leu Leu Leu Leu Phe
Val
      930                 935                 940
Ser Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg Glu Ala His
Lys
945                 950                 955
960
Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe
Lys
                  965                 970                 975
Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser
Tyr
              980                 985                 990
Asp Glu His Ala Lys Leu Val Gln  Glu Val Thr Asp Phe  Ala Lys
Thr
```

[0430]

[0431]

```
          995                 1000                1005
Cys Val  Ala Asp Glu Ser Ala  Ala Asn Cys Asp Lys  Ser Leu His
    1010                1015                1020
Thr Leu  Phe Gly Asp Lys Leu  Cys Ala Ile Pro Asn  Leu Arg Glu
    1025                1030                1035
Asn Tyr  Gly Glu Leu Ala Asp  Cys Cys Thr Lys Gln  Glu Pro Glu
    1040                1045                1050
Arg Asn  Glu Cys Phe Leu Gln  His Lys Asp Asp Asn  Pro Ser Leu
    1055                1060                1065
Pro Pro  Phe Glu Arg Pro Glu  Ala Glu Ala Met Cys  Thr Ser Phe
    1070                1075                1080
Lys Glu  Asn Pro Thr Thr Phe  Met Gly His Tyr Leu  His Glu Val
    1085                1090                1095
Ala Arg  Arg His Pro Tyr Phe  Tyr Ala Pro Glu Leu  Leu Tyr Tyr
    1100                1105                1110
Ala Glu  Gln Tyr Asn Glu Ile  Leu Thr Gln Cys Cys  Ala Glu Ala
    1115                1120                1125
Asp Lys  Glu Ser Cys Leu Thr  Pro Lys Leu Asp Gly  Val Lys Glu
    1130                1135                1140
Lys Ala  Leu Val Ser Ser Val  Arg Gln Arg Met Lys  Cys Ser Ser
    1145                1150                1155
Met Gln  Lys Phe Gly Glu Arg  Ala Phe Lys Ala Trp  Ala Val Ala
    1160                1165                1170
Arg Leu  Ser Gln Thr Phe Pro  Asn Ala Asp Phe Ala  Glu Ile Thr
    1175                1180                1185
Lys Leu  Ala Thr Asp Leu Thr  Lys Val Asn Lys Glu  Cys Cys His
    1190                1195                1200
Gly Asp  Leu Leu Glu Cys Ala  Asp Asp Arg Ala Glu  Leu Ala Lys
    1205                1210                1215
Tyr Met  Cys Glu Asn Gln Ala  Thr Ile Ser Ser Lys  Leu Gln Thr
    1220                1225                1230
Cys Cys  Asp Lys Pro Leu Leu  Lys Lys Ala His Cys  Leu Ser Glu
    1235                1240                1245
Val Glu  His Asp Thr Met Pro  Ala Asp Leu Pro Ala  Ile Ala Ala
    1250                1255                1260
Asp Phe  Val Glu Asp Gln Glu  Val Cys Lys Asn Tyr  Ala Glu Ala
    1265                1270                1275
Lys Asp  Val Phe Leu Gly Thr  Phe Leu Tyr Glu Tyr  Ser Arg Arg
    1280                1285                1290
His Pro  Asp Tyr Ser Val Ser  Leu Leu Leu Arg Leu  Ala Lys Lys
    1295                1300                1305
Tyr Glu  Ala Thr Leu Glu Lys  Cys Cys Ala Glu Ala  Asn Pro Pro
    1310                1315                1320
Ala Cys  Tyr Gly Thr Val Leu  Ala Glu Phe Gln Pro  Leu Val Glu
    1325                1330                1335
Glu Pro  Lys Asn Leu Val Lys  Thr Asn Cys Asp Leu  Tyr Glu Lys
    1340                1345                1350
Leu Gly  Glu Tyr Gly Phe Gln  Asn Ala Ile Leu Val  Arg Tyr Thr
    1355                1360                1365
Gln Lys  Ala Pro Gln Val Ser  Thr Pro Thr Leu Val  Glu Ala Ala
    1370                1375                1380
Arg Asn  Leu Gly Arg Val Gly  Thr Lys Cys Cys Thr  Leu Pro Glu
    1385                1390                1395
Asp Gln  Arg Leu Pro Cys Val  Glu Asp Tyr Leu Ser  Ala Ile Leu
    1400                1405                1410
Asn Arg  Val Cys Leu Leu His  Glu Lys Thr Pro Val  Ser Glu His
```

```
     1415                1420                1425
Val Thr  Lys Cys Cys Ser Gly  Ser Leu Val Glu Arg  Arg Pro Cys
     1430                1435                1440
Phe Ser  Ala Leu Thr Val Asp  Glu Thr Tyr Val Pro  Lys Glu Phe
     1445                1450                1455
Lys Ala  Glu Thr Phe Thr Phe  His Ser Asp Ile Cys  Thr Leu Pro
     1460                1465                1470
Glu Lys  Glu Lys Gln Ile Lys  Lys Gln Thr Ala Leu  Ala Glu Leu
     1475                1480                1485
Val Lys  His Lys Pro Lys Ala  Thr Ala Glu Gln Leu  Lys Thr Val
     1490                1495                1500
Met Asp  Asp Phe Ala Gln Phe  Leu Asp Thr Cys Cys  Lys Ala Ala
     1505                1510                1515
Asp Lys  Asp Thr Cys Phe Ser  Thr Glu Gly Pro Asn  Leu Val Thr
     1520                1525                1530
Arg Cys  Lys Asp Ala Leu Ala  Arg Ser Trp Ser His  Pro Gln Phe
     1535                1540                1545
Glu Lys
     1550
```

[0432]

[0433] 单下划线:信号肽序列;双下划线:NPP1的开始和结束;**=信号肽序列处的切割位置;粗体残基表示白蛋白序列

[0434] SEQ.ID NO:30-ENPP121-NPP3-Fc序列

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

[0435]

```
Asn Lys Phe Arg Cys Gly Glu Arg Leu Glu Ala Ser Leu Cys Ser
Cys
145                 150                 155
160
Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys Cys Ala Asp Tyr Lys
Ser
                    165                 170                 175
Val Cys Gln Gly Glu Thr Ser Trp Leu Glu Glu Asn Cys Asp Thr
Ala
                180                 185                 190
Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp Leu Pro Pro Val Ile
Leu
            195                 200                 205
Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr Leu Tyr Thr Trp Asp
Thr
        210                 215                 220
Leu Met Pro Asn Ile Asn Lys Leu Lys Thr Cys Gly Ile His Ser
Lys
225                 230                 235
240
Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr
Thr
                    245                 250                 255
Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn
Asn
                260                 265                 270
Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser Leu Ser Ser Lys
[0436] Glu
            275                 280                 285
Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro Met Trp Leu Thr
Ala
        290                 295                 300
Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe Trp Pro Gly Ser
Glu
305                 310                 315
320
Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr Met Pro Tyr Asn
Gly
                    325                 330                 335
Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu Leu Lys Trp Leu
Asp
                340                 345                 350
Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr Met Tyr Phe Glu
Glu
            355                 360                 365
Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val Ser Ala Arg Val
Ile
        370                 375                 380
Lys Ala Leu Gln Val Val Asp His Ala Phe Gly Met Leu Met Glu
Gly
385                 390                 395
400
Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn Ile Ile Leu Leu
Ala
                    405                 410                 415
```

```
Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys Met Glu Tyr Met
Thr
                420                 425                 430
Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr Met Tyr Glu Gly Pro
Ala
            435                 440                 445
Pro Arg Ile Arg Ala His Asn Ile Pro His Asp Phe Phe Ser Phe
Asn
        450                 455                 460
Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg Lys Pro Asp Gln
His
465                 470                 475
480
Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys Arg Leu His Tyr
Ala
                    485                 490                 495
Lys Asn Val Arg Ile Asp Lys Val His Leu Phe Val Asp Gln Gln
Trp
                500                 505                 510
Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys Gly Gly Gly Asn
His
            515                 520                 525
Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala Ile Phe Leu Ala
His
        530                 535                 540
Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu Pro Phe Glu Asn
Ile
545                 550                 555
560
Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg Ile Gln Pro Ala
Pro
                    565                 570                 575
Asn Asn Gly Thr His Gly Ser Leu Asn His Leu Leu Lys Val Pro
Phe
                580                 585                 590
Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys Phe Ser Val Cys
Gly
            595                 600                 605
Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu Asp Cys Phe Cys Pro
His
        610                 615                 620
Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn Gln Met Leu Asn
Leu
625                 630                 635
640
Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val Asn Leu Pro Phe
Gly
                    645                 650                 655
Arg Pro Arg Val Leu Gln Lys Asn Val Asp His Cys Leu Leu Tyr
His
                660                 665                 670
Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala Met Arg Met Pro Met
Trp
            675                 680                 685
Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp Thr Ser Pro Leu Pro
Pro
```

[0437]

[0438]

```
                690                 695                 700
Thr Val Pro Asp Cys Leu Arg Ala Asp Val Arg Val Pro Pro Ser
Glu
705                 710                 715
720
Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys Asn Ile Thr His
Gly
                725                 730                 735
Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser Asp Ser Gln Tyr
Asp
            740                 745                 750
Ala Leu Ile Thr Ser Asn Leu Val Pro Met Tyr Glu Glu Phe Arg
Lys
        755                 760                 765
Met Trp Asp Tyr Phe His Ser Val Leu Leu Ile Lys His Ala Thr
Glu
    770                 775                 780
Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile Phe Asp Tyr Asn
Tyr
785                 790                 795
800
Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr Lys His Leu Ala
Asn
                805                 810                 815
Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val Val Leu Thr Ser
Cys
            820                 825                 830
Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro Gly Trp Leu Asp
Val
        835                 840                 845
Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn Val Glu Ser Cys
Pro
    850                 855                 860
Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu Arg Phe Thr Ala
His
865                 870                 875
880
Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr Gly Leu Asp Phe
Tyr
                885                 890                 895
Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu Gln Leu Lys Thr
Tyr
            900                 905                 910
Leu Pro Thr Phe Glu Thr Thr Ile Asp Lys Thr His Thr Cys Pro
Pro
        915                 920                 925
Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
Pro
    930                 935                 940
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
Thr
945                 950                 955
960
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
Asn
                965                 970                 975
```

[0439]

```
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
Arg
                980                 985                 990
Glu Glu Gln Tyr Asn Ser Thr Tyr  Arg Val Val Ser Val  Leu Thr
Val
           995                 1000                1005
Leu His  Gln Asp Trp Leu Asn  Gly Lys Glu Tyr Lys  Cys Lys Val
      1010                1015                1020
Ser Asn  Lys Ala Leu Pro Ala  Pro Ile Glu Lys Thr  Ile Ser Lys
      1025                1030                1035
Ala Lys  Gly Gln Pro Arg Glu  Pro Gln Val Tyr Thr  Leu Pro Pro
      1040                1045                1050
Ser Arg  Glu Glu Met Thr Lys  Asn Gln Val Ser Leu  Thr Cys Leu
      1055                1060                1065
Val Lys  Gly Phe Tyr Pro Ser  Asp Ile Ala Val Glu  Trp Glu Ser
      1070                1075                1080
Asn Gly  Gln Pro Glu Asn Asn  Tyr Lys Thr Thr Pro  Pro Val Leu
      1085                1090                1095
Asp Ser  Asp Gly Ser Phe Phe  Leu Tyr Ser Lys Leu  Thr Val Asp
      1100                1105                1110
Lys Ser  Arg Trp Gln Gln Gly  Asn Val Phe Ser Cys  Ser Val Met
      1115                1120                1125
His Glu  Ala Leu His Asn His  Tyr Thr Gln Lys Ser  Leu Ser Leu
      1130                1135                1140
Ser Pro  Gly Lys
      1145
```

[0440] 单下划线:信号肽序列;双下划线:NPP1的开始和结束;**=信号肽序列处的切割位置;粗体残基表示Fc序列

[0441] SEQ.ID NO:31-ENPP121-NPP3-白蛋白序列

[0442]

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

```
                    100                 105                 110
Glu Asn Cys Arg Cys Asp Val Ala Cys Lys Asp Arg Gly Asp Cys
Cys
                115                 120                 125
Trp Asp Phe Glu Asp Thr Cys Val Glu Ser Thr Arg Ile Trp Met
Cys
            130                 135                 140
Asn Lys Phe Arg Cys Gly Glu Arg Leu Glu Ala Ser Leu Cys Ser
Cys
145                 150                 155
160
Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys Cys Ala Asp Tyr Lys
Ser
                    165                 170                 175
Val Cys Gln Gly Glu Thr Ser Trp Leu Glu Glu Asn Cys Asp Thr
Ala
                180                 185                 190
Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp Leu Pro Pro Val Ile
Leu
                195                 200                 205
Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr Leu Tyr Thr Trp Asp
Thr
            210                 215                 220
Leu Met Pro Asn Ile Asn Lys Leu Lys Thr Cys Gly Ile His Ser
Lys
225                 230                 235
240
[0443]  Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr
Thr
                    245                 250                 255
Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn
Asn
                260                 265                 270
Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser Leu Ser Ser Lys
Glu
                275                 280                 285
Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro Met Trp Leu Thr
Ala
            290                 295                 300
Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe Trp Pro Gly Ser
Glu
305                 310                 315
320
Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr Met Pro Tyr Asn
Gly
                    325                 330                 335
Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu Leu Lys Trp Leu
Asp
                340                 345                 350
Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr Met Tyr Phe Glu
Glu
                355                 360                 365
Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val Ser Ala Arg Val
Ile
            370                 375                 380
```

```
Lys Ala Leu Gln Val Val Asp His Ala Phe Gly Met Leu Met Glu
Gly
385                 390                 395
400
Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn Ile Ile Leu Leu
Ala
                    405                 410                 415
Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys Met Glu Tyr Met
Thr
                420                 425                 430
Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr Met Tyr Glu Gly Pro
Ala
            435                 440                 445
Pro Arg Ile Arg Ala His Asn Ile Pro His Asp Phe Phe Ser Phe
Asn
        450                 455                 460
Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg Lys Pro Asp Gln
His
465                 470                 475
480
Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys Arg Leu His Tyr
Ala
                    485                 490                 495
Lys Asn Val Arg Ile Asp Lys Val His Leu Phe Val Asp Gln Gln
Trp
                500                 505                 510
Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys Gly Gly Gly Asn
His
            515                 520                 525
Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala Ile Phe Leu Ala
His
        530                 535                 540
Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu Pro Phe Glu Asn
Ile
545                 550                 555
560
Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg Ile Gln Pro Ala
Pro
                    565                 570                 575
Asn Asn Gly Thr His Gly Ser Leu Asn His Leu Leu Lys Val Pro
Phe
                580                 585                 590
Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys Phe Ser Val Cys
Gly
            595                 600                 605
Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu Asp Cys Phe Cys Pro
His
        610                 615                 620
Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn Gln Met Leu Asn
Leu
625                 630                 635
640
Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val Asn Leu Pro Phe
Gly
                    645                 650                 655
```

[0444]

```
Arg Pro Arg Val Leu Gln Lys Asn Val Asp His Cys Leu Leu Tyr
His
                660                 665                 670
Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala Met Arg Met Pro Met
Trp
            675                 680                 685
Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp Thr Ser Pro Leu Pro
Pro
        690                 695                 700
Thr Val Pro Asp Cys Leu Arg Ala Asp Val Arg Val Pro Pro Ser
Glu
705                 710                 715
720
Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys Asn Ile Thr His
Gly
                725                 730                 735
Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser Asp Ser Gln Tyr
Asp
                740                 745                 750
Ala Leu Ile Thr Ser Asn Leu Val Pro Met Tyr Glu Glu Phe Arg
Lys
            755                 760                 765
Met Trp Asp Tyr Phe His Ser Val Leu Leu Ile Lys His Ala Thr
Glu
        770                 775                 780
Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile Phe Asp Tyr Asn
Tyr
785                 790                 795
800
Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr Lys His Leu Ala
Asn
                805                 810                 815
Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val Val Leu Thr Ser
Cys
                820                 825                 830
Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro Gly Trp Leu Asp
Val
            835                 840                 845
Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn Val Glu Ser Cys
Pro
        850                 855                 860
Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu Arg Phe Thr Ala
His
865                 870                 875
880
Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr Gly Leu Asp Phe
Tyr
                885                 890                 895
Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu Gln Leu Lys Thr
Tyr
                900                 905                 910
Leu Pro Thr Phe Glu Thr Thr Ile Gly Gly Gly Ser Gly Gly Gly
Gly
            915                 920                 925
Ser Gly Gly Gly Gly Ser Met Lys Trp Val Thr Phe Leu Leu Leu
Leu
```

[0445]

930 935 940

Phe Val Ser Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg Glu Ala

945 950 955 960

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

965 970 975

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

980 985 990

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

995 1000 1005

Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys Ser
1010 1015 1020

Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu
1025 1030 1035

Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu
1040 1045 1050

Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
1055 1060 1065

Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met Cys Thr
1070 1075 1080

Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly His Tyr Leu His
1085 1090 1095

Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
1100 1105 1110

[0446]

Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys Ala
1115 1120 1125

Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val
1130 1135 1140

Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys
1145 1150 1155

Ser Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala
1160 1165 1170

Val Ala Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu
1175 1180 1185

Ile Thr Lys Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys
1190 1195 1200

Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu
1205 1210 1215

Ala Lys Tyr Met Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu
1220 1225 1230

Gln Thr Cys Cys Asp Lys Pro Leu Leu Lys Lys Ala His Cys Leu
1235 1240 1245

Ser Glu Val Glu His Asp Thr Met Pro Ala Asp Leu Pro Ala Ile
1250 1255 1260

Ala Ala Asp Phe Val Glu Asp Gln Glu Val Cys Lys Asn Tyr Ala
1265 1270 1275

Glu Ala Lys Asp Val Phe Leu Gly Thr Phe Leu Tyr Glu Tyr Ser
1280 1285 1290

Arg Arg His Pro Asp Tyr Ser Val Ser Leu Leu Leu Arg Leu Ala
1295 1300 1305

Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys Cys Ala Glu Ala Asn
1310 1315 1320

[0447]

```
Pro Pro  Ala Cys Tyr Gly Thr  Val Leu Ala Glu Phe  Gln Pro Leu
1325                 1330                 1335
Val Glu  Glu Pro Lys Asn Leu  Val Lys Thr Asn Cys  Asp Leu Tyr
1340                 1345                 1350
Glu Lys  Leu Gly Glu Tyr Gly  Phe Gln Asn Ala Ile  Leu Val Arg
1355                 1360                 1365
Tyr Thr  Gln Lys Ala Pro Gln  Val Ser Thr Pro Thr  Leu Val Glu
1370                 1375                 1380
Ala Ala  Arg Asn Leu Gly Arg  Val Gly Thr Lys Cys  Cys Thr Leu
1385                 1390                 1395
Pro Glu  Asp Gln Arg Leu Pro  Cys Val Glu Asp Tyr  Leu Ser Ala
1400                 1405                 1410
Ile Leu  Asn Arg Val Cys Leu  Leu His Glu Lys Thr  Pro Val Ser
1415                 1420                 1425
Glu His  Val Thr Lys Cys Cys  Ser Gly Ser Leu Val  Glu Arg Arg
1430                 1435                 1440
Pro Cys  Phe Ser Ala Leu Thr  Val Asp Glu Thr Tyr  Val Pro Lys
1445                 1450                 1455
Glu Phe  Lys Ala Glu Thr Phe  Thr Phe His Ser Asp  Ile Cys Thr
1460                 1465                 1470
Leu Pro  Glu Lys Glu Lys Gln  Ile Lys Lys Gln Thr  Ala Leu Ala
1475                 1480                 1485
Glu Leu  Val Lys His Lys Pro  Lys Ala Thr Ala Glu  Gln Leu Lys
1490                 1495                 1500
Thr Val  Met Asp Asp Phe Ala  Gln Phe Leu Asp Thr  Cys Cys Lys
1505                 1510                 1515
Ala Ala  Asp Lys Asp Thr Cys  Phe Ser Thr Glu Gly  Pro Asn Leu
1520                 1525                 1530
Val Thr  Arg Cys Lys Asp Ala  Leu Ala
1535                 1540
```

[0448] 单下划线:信号肽序列;双下划线:NPP3的开始和结束;**=信号肽序列处的切割位置;粗体残基表示白蛋白序列

[0449] SEQ.ID NO:32-ENPP121GLK蛋白输出信号序列

[0450]

```
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
```

[0451]

[0452] SEQ.ID NO:33-白蛋白序列

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

[0453]

[0454]

```
Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
Ala
                    245                 250                 255
Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr
Lys
                260                 265                 270
Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly
Asp
            275                 280                 285
Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met
Cys
        290                 295                 300
Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys Cys Asp
Lys
305                 310                 315
320
Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val Glu His Asp
Thr
                    325                 330                 335
Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp Phe Val Glu Asp
Gln
                340                 345                 350
Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
Thr
            355                 360                 365
Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Asp Tyr Ser Val Ser
Leu
        370                 375                 380
Leu Leu Arg Leu Ala Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys
Cys
385                 390                 395
400
Ala Glu Ala Asn Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu
Phe
                    405                 410                 415
Gln Pro Leu Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys
Asp
                420                 425                 430
Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu
Val
            435                 440                 445
Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val
Glu
        450                 455                 460
Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu
Pro
465                 470                 475
480
Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile
Leu
                    485                 490                 495
Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His
Val
                500                 505                 510
Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe
Ser
```

```
                515                 520                 525
      Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys Ala
Glu
            530                 535                 540
      Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu Lys Glu
Lys
      545                 550                 555
560
      Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val Lys His Lys
Pro
                    565                 570                 575
      Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met Asp Asp Phe Ala
Gln
                580                 585                 590
      Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp Lys Asp Thr Cys Phe
Ser
                595                 600                 605
      Thr Glu Gly Pro Asn Leu Val Thr Arg Cys Lys Asp Ala Leu Ala
            610                 615                 620
```

[0455]

[0456] 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
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
Val
    50                  55                  60
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
Tyr
65                  70                  75                  80
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
Gly
                85                  90                  95
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
Ile
            100                 105                 110
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
Val
        115                 120                 125
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
Ser
    130                 135                 140
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
Glu
145                 150                 155
160
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
Pro


                    165                 170                 175
 Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
 Val
                180                 185                 190
 Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
 Met
            195                 200                 205
 His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
 Ser
        210                 215                 220
 Pro Gly Lys
 225
```

[0457]

[0458] SEQ.ID NO:35-白蛋白序列

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

```
Val Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys
Cys
 210                 215                 220
Ser Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala
Val
225                 230                 235
240
Ala Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile
Thr
                245                 250                 255
Lys Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His
Gly
            260                 265                 270
Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr
Met
        275                 280                 285
Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys Cys
Asp
 290                 295                 300
Lys Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val Glu His
Asp
305                 310                 315
320
Thr Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp Phe Val Glu
Asp
                325                 330                 335
Gln Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu
Gly
            340                 345                 350
Thr Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Asp Tyr Ser Val
Ser
        355                 360                 365
Leu Leu Leu Arg Leu Ala Lys Lys Tyr Glu Ala Thr Leu Glu Lys
Cys
 370                 375                 380
Cys Ala Glu Ala Asn Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala
Glu
385                 390                 395
400
Phe Gln Pro Leu Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn
Cys
                405                 410                 415
Asp Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile
Leu
            420                 425                 430
Val Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu
Val
        435                 440                 445
Glu Ala 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
```

[0459]

```
Leu Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu
His
                    485                 490                 495
Val Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys
Phe
                500                 505                 510
Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys
Ala
            515                 520                 525
Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu Lys
Glu
        530                 535                 540
Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val Lys His
Lys
545                 550                 555
560
Pro Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met Asp Asp Phe
Ala
                    565                 570                 575
Gln Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp Lys Asp Thr Cys
Phe
                580                 585                 590
Ser Thr Glu Gly Pro Asn Leu Val Thr Arg Cys Lys Asp Ala Leu
Ala
            595                 600                 605
Arg Ser Trp Ser His Pro Gln Phe Glu Lys
        610                 615
```

[0460]

[0461] SEQ.ID NO:36-ENPP2信号肽

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

[0462]

[0463] 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
1               5                   10                  15
Ala Pro Gly Ala
            20
```

[0464]

[0465] 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
1               5                   10                  15
Ala Pro Gly Ala Gly Ala
            20
```

[0466]

[0467] 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
1 5 10 15
Gly Arg Ala Pro Arg Glu Gly Pro Ala Gly Asn Gly Arg Asp Arg Gly
20 25 30
Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala Ser
35 40 45
Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala
50 55 60
Arg Ala Arg Thr Ala Lys Asp Pro Asn Thr Tyr Lys Ile Ile Ser Leu
65 70 75 80
Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly Phe Thr Ala
85 90 95

[0468]

[0469] SEQ.ID NO:40-exENPP3

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

[0470]

[0471] 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
Leu Ser Thr Thr Phe Ser
20

[0472]

[0473] SEQ ID NO:42-信号序列-天青杀素

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

[0474]

Ser Arg Ala

[0475] SEQ.ID NO:43-接头

[0476] Asp Ser Ser

[0477] SEQ.ID NO:44-接头

[0478] Glu Ser Ser

[0479] SEQ.ID NO:45-接头

[0480] Arg Gln Gln

[0481] SEQ.ID NO:46-接头

[0482] Lys Arg

[0483] SEQ.ID NO:47-接头

[0484] $(Arg)_m$; m=0-15

[0485] SEQ.ID NO:48-接头

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

[0486]

[0487] SEQ.ID NO:49-接头

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

[0488]

1 5 10

[0489] SEQ.ID NO:50-接头

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

[0490]

1 5 10

[0491] SEQ.ID NO:51-接头

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

[0492]

1 5 10

[0493] SEQ.ID NO:52-接头

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

[0494]

1 5 10

[0495] SEQ.ID NO:53-接头

[0496] $(Glu)_m$; m=1-15

[0497] SEQ.ID NO:54-接头

[0498] Leu Ile Asn

[0499] SEQ.ID NO:55-接头

Gly Gly Ser Gly Gly Ser

[0500]

1 5

[0501] SEQ.ID NO:56-接头

Arg Ser Gly Ser Gly Gly Ser

[0502]

1 5

[0503] SEQ.ID NO:57-接头

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

[0504]

1

[0505] SEQ.ID NO:58-接头

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

[0506]

1 5 10 15

[0507] SEQ.ID NO:59-接头

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

[0508]

1 5 10 15

[0509] SEQ.ID NO:60-接头

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

[0510]

1 5 10

[0511] SEQ.ID NO:61-接头

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

[0512]

1 5 10

[0513] SEQ.ID NO:62-接头

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

[0514]

1 5 10

[0515] SEQ.ID NO:63-接头

Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys

[0516]

1 5 10

[0517] SEQ.ID NO:64-接头

Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys

[0518]

1 5 10

[0519] SEQ.ID NO:65-接头

Leu Gly Leu Gly Leu Gly Leu Arg Lys

[0520]

1 5

[0521] SEQ.ID NO:66-接头

Gly Leu Gly Leu Gly Leu Arg Lys

[0522]

1 5

[0523] SEQ.ID NO:67-接头

Leu Gly Leu Gly Leu Arg Lys

[0524]

1 5

[0525] SEQ.ID NO:68-接头

Gly Leu Gly Leu Arg Lys

[0526]

1 5

[0527] SEQ.ID NO:69-接头

Leu Gly Leu Arg Lys

[0528]

1 5

[0529] SEQ.ID NO:70-接头

Gly Leu Arg Lys

[0530]

1

[0531] SEQ.ID NO:71-接头

Leu Arg Lys

[0532]

1

[0533] SEQ.ID NO:72-接头

Arg Lys

[0534]

1

[0535] SEQ.ID NO:73-接头

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

[0536]

1

[0537] SEQ.ID NO:74-接头

[0538] D_m; m=1-15

[0539] SEQ.ID NO:75-接头

[0540] $(GGGGS)_n$; n=1-10

[0541] SEQ.ID NO:76-ENPP3核苷酸序列

[0542]

```
atggaatcta cgttgacttt agcaacggaa caacctgtta agaagaacac tcttaagaaa      60
tataaaatag cttgcattgt tcttcttgct ttgctggtga tcatgtcact tggattaggc     120
ctggggcttg gactcaggaa actggaaaag caaggcagct gcaggaagaa gtgctttgat     180
gcatcattta gaggactgga gaactgccgg tgtgatgtgg catgtaaaga ccgaggtgat     240
tgctgctggg attttgaaga cacctgtgtg gaatcaactc gaatatggat gtgcaataaa     300
tttcgttgtg gagagaccag attagaggcc agcctttgct cttgttcaga tgactgtttg     360
cagaggaaag attgctgtgc tgactataag agtgtttgcc aaggagaaac ctcatggctg     420
gaagaaaact gtgacacagc ccagcagtct cagtgcccag aagggtttga cctgccacca     480
gttatcttgt tttctatgga tggatttaga gctgaatatt tatacacatg ggatacttta     540
atgccaaata tcaataaact gaaaacatgt ggaattcatt caaaatacat gagagctatg     600
tatcctacca aaaccttccc aaatcattac accattgtca cgggcttgta tccagagtca     660
catggcatca ttgacaataa tatgtatgat gtaaatctca acaagaattt ttcactttct     720
tcaaaggaac aaaataatcc agcctggtgg catgggcaac caatgtggct gacagcaatg     780
tatcaaggtt taaaagccgc tacctacttt tggcccggat cagaagtggc tataaatggc     840
tcctttcctt ccatatacat gccttacaac ggaagtgtcc catttgaaga gaggatttct     900
acactgttaa aatggctgga cctgcccaaa gctgaaagac ccaggtttta taccatgtat     960
tttgaagaac ctgattcctc tggacatgca ggtggaccag tcagtgccag agtaattaaa    1020
gccttacagg tagtagatca tgcttttggg atgttgatgg aaggcctgaa gcagcggaat    1080
ttgcacaact gtgtcaatat catccttctg gctgaccatg gaatggacca gacttattgt    1140
aacaagatgg aatacatgac tgattatttt cccagaataa acttcttcta catgtacgaa    1200
gggcctgccc cccgcatccg agctcataat atacctcatg actttttag ttttaattct    1260
gaggaaattg ttagaaacct cagttgccga aaacctgatc agcatttcaa gccctatttg    1320
actcctgatt tgccaaagcg actgcactat gccaagaacg tcagaatcga caaagttcat    1380
ctctttgtgg atcaacagtg gctggctgtt aggagtaaat caaatacaaa ttgtggagga    1440
ggcaaccatg gttataacaa tgagtttagg agcatggagg ctatctttct ggcacatgga    1500
cccagtttta aagagaagac tgaagttgaa ccatttgaaa atattgaagt ctataaccta    1560
atgtgtgatc ttctacgcat tcaaccagca ccaaacaatg gaacccatgg tagtttaaac    1620
catcttctga aggtgccttt ttatgagcca tcccatgcag aggaggtgtc aaagttttct    1680
gtttgtggct ttgctaatcc attgcccaca gagtctcttg actgtttctg ccctcaccta    1740
caaaatagta ctcagctgga acaagtgaat cagatgctaa atctcaccca agaagaaata    1800
```

acagcaacag tgaaagtaaa tttgccattt gggaggccta gggtactgca gaagaacgtg 1860

gaccactgtc tcctttacca cagggaatat gtcagtggat ttggaaaagc tatgaggatg 1920

cccatgtgga gttcatacac agtcccccag ttgggagaca catcgcctct gcctcccact 1980

gtcccagact gtctgcgggc tgatgtcagg gttcctcctt ctgagagcca aaaatgttcc 2040

ttctatttag cagacaagaa tatcacccac ggcttcctct atcctcctgc cagcaataga 2100

acatcagata gccaatatga tgctttaatt actagcaatt tggtacctat gtatgaagaa 2160

ttcagaaaaa tgtgggacta cttccacagt gttcttctta taaaacatgc cacagaaaga 2220

[0543]

aatggagtaa atgtggttag tggaccaata tttgattata attatgatgg ccattttgat 2280

gctccagatg aaattaccaa acatttagcc aacactgatg ttcccatccc aacacactac 2340

tttgtggtgc tgaccagttg taaaaacaag agccacacac cggaaaactg ccctgggtgg 2400

ctggatgtcc tacccttttat catccctcac cgacctacca acgtggagag ctgtcctgaa 2460

ggtaaaccag aagctctttg ggttgaagaa agatttacag ctcacattgc ccgggtccgt 2520

gatgtagaac ttctcactgg gcttgacttc tatcaggata aagtgcagcc tgtctctgaa 2580

attttgcaac taaagacata tttaccaaca tttgaaacca ctatt 2625

[0544] SEQ.ID NO:77-ENPP1核苷酸序列：

atggaacggg acggctgtgc cggcggagga tcaagaggcg gagaaggcgg cagagccccc 60

agagaaggac ctgccggcaa cggcagagac agaggcagat ctcatgccgc cgaagccccc 120

ggcgatcctc aggctgctgc ttctctgctg gcccccatgg atgtgggcga ggaacctctg 180

gaaaaggccg ccagagccag aaccgccaag gaccccaaca cctacaaggt gctgagcctg 240

gtgctgtccg tgtgcgtgct gaccaccatc ctgggctgca tcttcggcct gaagcccagc 300

tgcgccaaag aagtgaagtc ctgcaagggc cggtgcttcg agcggacctt cggcaactgc 360

agatgcgacg ccgcctgtgt ggaactgggc aactgctgcc tggactacca ggaaacctgc 420

atcgagcccg agcacatctg gacctgcaac aagttcagat gcggcgagaa gcggctgacc 480

agatccctgt gtgcctgcag cgacgactgc aaggacaagg gcgactgctg catcaactac 540

[0545] agcagcgtgt gccagggcga gaagtcctgg gtggaagaac cctgcgagag catcaacgag 600

ccccagtgcc ctgccggctt cgagacacct cctaccctgc tgttcagcct ggacggcttt 660

cgggccgagt acctgcacac atggggaggc ctgctgcccg tgatcagcaa gctgaagaag 720

tgcggcacct acaccaagaa catgcggccc gtgtacccca ccaagacctt ccccaaccac 780

tactccatcg tgaccggcct gtaccccgag agccacggca tcatcgacaa caagatgtac 840

gaccccaaga tgaacgccag cttcagcctg aagtccaaag agaagttcaa ccccgagtgg 900

tataagggcg agcccatctg ggtcaccgcc aagtaccagg gcctgaaaag cggcacattc 960

ttttggcccg gcagcgacgt ggaaatcaac ggcatcttcc ccgacatcta taagatgtac 1020

aacggcagcg tgcccttcga ggaacggatc ctggctgtgc tgcagtggct gcagctgccc 1080

aaggatgagc ggccccactt ctacaccctg tacctggaag aacctgacag cagcggccac 1140

agctacggcc ctgtgtccag cgaagtgatc aaggccctgc agcgggtgga cggcatggtg 1200

ggaatgctga tggacggcct gaaagagctg aacctgcaca gatgcctgaa cctgatcctg 1260

atcagcgacc acggcatgga acagggatcc tgcaagaagt acatctacct gaacaagtac 1320

ctgggcgacg tgaagaacat caaagtgatc tacggcccag ccgccagact gaggcctagc 1380

gacgtgcccg acaagtacta cagcttcaac tacgagggaa tcgcccggaa cctgagctgc 1440

agagagccca accagcactt caagccctac ctgaagcact tcctgcccaa gcggctgcac 1500

ttcgccaaga gcgacagaat cgagcccctg accttctacc tggaccccca gtggcagctg 1560

gccctgaatc ccagcgagag aaagtactgc ggcagcggct tccacggctc cgacaacgtg 1620

ttcagcaaca tgcaggccct gttcgtgggc tacggacccg gctttaagca cggcatcgag 1680

gccgacacct tcgagaacat cgaggtgtac aatctgatgt gcgacctgct gaatctgacc 1740

cctgccccca acaatggcac ccacggcagc ctgaaccatc tgctgaagaa ccccgtgtac 1800

acccctaagc accccaaaga ggtgcacccc ctggtgcagt gcccccttcac cagaaacccc 1860

agagacaacc tgggctgtag ctgcaacccc agcatcctgc ccatcgagga cttccagacc 1920

cagttcaacc tgaccgtggc cgaggaaaag atcatcaagc acgagacact gccctacggc 1980

[0546] agaccccggg tgctgcagaa agagaacacc atctgcctgc tgagccagca ccagttcatg 2040

agcggctact cccaggacat cctgatgccc ctgtggacca gctacaccgt ggaccggaac 2100

gacagcttct ccaccgagga tttcagcaac tgcctgtacc aggatttccg gatccccctg 2160

agccccgtgc acaagtgcag cttctacaag aacaacacca aggtgtccta cggcttcctg 2220

agccctcccc agctgaacaa gaacagctcc ggcatctaca gcgaggccct gctgactacc 2280

aacatcgtgc ccatgtacca gagcttccaa gtgatctggc ggtacttcca cgacaccctg 2340

ctgcggaagt acgccgaaga acggaacggc gtgaacgtgg tgtccggccc agtgttcgac 2400

ttcgactacg acggcagatg tgacagcctg gaaaatctgc ggcagaaaag aagagtgatc 2460

cggaaccagg aaattctgat ccctacccac ttctttatcg tgctgacaag ctgcaaggat 2520

accagccaga ccccccctgca ctgcgagaac ctggataccc tggccttcat cctgcctcac 2580

cggaccgaca acagcgagag ctgtgtgcac ggcaagcacg acagctcttg ggtggaagaa 2640

ctgctgatgc tgcaccgggc cagaatcacc gatgtggaac acatcaccgg cctgagcttt 2700

taccagcagc ggaaagaacc cgtgtccgat atcctgaagc tgaaaaccca tctgcccacc 2760

ttcagccagg aagat 2775

[0547] SEQ ID NO:78-天青杀素-ENPP1-FC核苷酸序列

[0548] ggtaccgccacc**atg**acaagactgacagtgctggctctgctggccggactgttggcctcttctagagc
t**gct**ccttcctgcgccaaagaagtgaagtcctgcaagggcagatgcttcgagcggaccttcggcaact
gtagatgtgacgccgcttgcgtggaactgggcaactgctgcctggactaccaagagacatgcatcgag
cccgagcacatctggacctgcaacaagttcagatgcggcgagaagcggctgaccagatctctgtgcgc
ctgctctgacgactgcaaggacaagggcgactgctgcatcaactactcctctgtgtgccagggcgaga
agtcctgggttgaagaaccctgcgagtccatcaacgagcctcagtgtcctgccggcttcgagacacct

[0549]

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cattccccaaccactactccatcgtgaccggcctgtatcctgagagccacggcatcatcgacaacaag
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gtgtgacctgctgaatctgacccctgctcctaacaacggcacccacggatctctgaaccatctgctga
agaatcccgtgtacacccctaagcaccccaaagaggttcaccctctggtccagtgtcctttcaccaga
aatcctcgggacaacctgggctgctcttgcaacccttctatcctgcctatcgaggactttcagaccca
gttcaacctgaccgtggccgaggaaaagatcatcaagcacgagacactgccctacggcagacctagag
tgctgcagaaagagaacaccatctgcctgctgtcccagcaccagttcatgtccggctactcccaggac
atcctgatgcctctgtggacctcctacaccgtggaccggaacgatagcttctccaccgaggacttcag
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caagagatcctgattcctacacacttctttatcgtgctgaccagctgcaaggatacctctcagacccc
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gatgtggaacacatcaccggcctgagcttctaccagcagcggaaagaacctgtgtccgatatcctgaa
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catgtcctgctccagaactgctcggaggcccctctgtgttcctgtttccacctaagccaaaggacaca
ctgatgatctctcggacccctgaagtgacctgcgtggtggtggatgtgtctcacgaagatcccgaagt
caagttcaattggtacgtggacggcgtggaagtgcacaacgccaagaccaagcctagagaggaacagt
acaactccacctacagagtggtgtccgtgctgactgtgctgcaccaggattggctgaacggcaaagag
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ccagcctcgggaacctcaggtttacaccctgcctccatctcgggaagagatgaccaagaaccaggtgt
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cctgagaacaactacaagacaacccctcctgtgctggacagcgacggctcattcttcctgtactctaa
gctgacagtggacaagtcccggtggcagcaaggcaatgtgttttcctgctctgtgatgcacgaggccc
tccacaatcactacacccagaagtccctgtctctgtcccctggcaaa**tgatag**ctcgag

[0550] 图例-粗体＝起始/终止密码子;下划线＝信号肽的核苷酸序列。

[0551] SEQ ID NO:79-天青杀素-ENPP3-FC核苷酸序列

[0552]

atgaccagactgaccgtgctggccctgctggccggcctgctggccagcagcagagccgccaa
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tggcctgcaaggacagaggcgactgctgctgggacttcgaggacacctgcgtggagagcaccagaatc
tggatgtgcaacaagttcagatgcggcgagaccagactggaggccagcctgtgcagctgcagcgacga
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[0553]
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agcctggactgcttctgccccacctgcagaacagcacccagctggagcaggtgaaccagatgctgaa
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agaagaacgtggaccactgcctgctgtaccacagagagtacgtgagcggcttcggcaaggccatgaga
atgcccatgtggagcagctacaccgtgccccagctgggcgacaccagccccctgcccccccaccgtgcc
cgactgcctgagagccgacgtgagagtgccccccagcgagagccagaagtgcagcttctacctggccg
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ctgctgaccggcctggacttctaccaggacaaggtgcagcccgtgagcgagatcctgcagctgaagac
ctacctgcccaccttcgagaccaccatcgacaagacccacacctgccccccctgccccgccccgagc
tgctgggcggccccagcgtgttcctgttcccccccaagcccaaggacaccctgatgatcagcagaacc
cccgaggtgacctgcgtggtggtggacgtgagccacgaggaccccgaggtgaagttcaactggtacgt
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tggtgagcgtgctgaccgtgctgcaccaggactggctgaacggcaaggagtacaagtgcaaggtgagc
aacaaggccctgcccgccccccatcgagaagaccatcagcaaggccaagggccagcccagagagccccca
ggtgtacaccctgcccccccagcagagaggagatgaccaagaaccaggtgagcctgacctgcctggtga
agggcttctaccccagcgacatcgccgtggagtgggagagcaacggccagcccgagaacaactacaag
accacccccccccgtgctggacagcgacggcagcttcttcctgtacagcaagctgaccgtggacaagag
cagatggcagcagggcaacgtgttcagctgcagcgtgatgcacgaggccctgcacaaccactacaccc
agaagagcctgagcctgagccccggcaag

[0554] ENPP1融合多肽和ENPP3融合多肽的克隆和表达

[0555] ENPP1或ENPP1多肽如US 2015/0359858 A1中所述制备,所述文献通过引用以其整体并入本文。ENPP1是定位于具有不同膜内结构域的细胞表面的跨膜蛋白。为了使ENPP1表达为可溶性胞外蛋白,可以将ENPP1的跨膜结构域替换为ENPP2的跨膜结构域或信号肽序列,如天青杀素,这导致可溶性重组ENPP1在杆状病毒培养物的胞外液中累积。也可以使用任何其它已知蛋白质的信号序列以靶向ENPP1的胞外结构域以进行分泌,如但不限于免疫球蛋白κ和λ轻链蛋白的信号序列。进一步地,本公开不应被解释为限于本文所述的多肽,而是还包含包括ENPP1胞外结构域的任何酶促活性截短的多肽。

[0556] ENPP1是通过省略跨膜结构域而变为可溶的。人ENPP1(SEQ ID NO:1)被修饰成通过用人ENPP2(NCBI登录NP 00112433 5,例如,残基12-30)或天青杀素信号序列(SEQ ID 42)的对应的亚结构域替换其跨膜区(例如,残基77-98)以表达可溶性重组蛋白。

[0557] 将经修饰的ENPP1序列克隆到在C末端9-F lIS标签之后具有TEV蛋白酶切割位点的经修饰的pFastbac FIT载体中并且在昆虫细胞中进行克隆和表达,并且使两种蛋白质如先前所述(Albright等人,2012,《血液(Blood)》120:4432-4440;Saunders等人,2011,《生物化学杂志(J.Biol.Chem.)》18:994-1004;Saunders等人,2008,《分子癌症疗法(Mol.Cancer Ther.)》7:3352-3362)在杆状病毒系统中表达,从而使可溶性重组蛋白在胞外液中累积。

[0558] ENPP3很差地导出到细胞表面。可溶性ENPP3多肽是通过用其它ENPP或天青杀素的天然信号序列或合适的信号序列替代ENPP3的信号序列构建的。ENPP3融合构建体的几个实例公开于WO 2017/087936中。可溶性ENPP3构建体是通过使用其它ENPP酶的信号输出信号序列,如但不限于ENPP7和/或ENPP5来制备。可溶性ENPP3构建体是使用包括ENPP1和ENPP2的信号序列(下文中的“ENPP1-2-1”或“ENPP121”)的组合的信号序列制备的。也可以使用任何其它已知蛋白质的信号序列以靶向ENPP3的胞外结构域以进行分泌,如但不限于免疫球蛋白κ和λ轻链蛋白的信号序列。进一步地,本公开不应被解释为限于本文所述的构建体,而是还包含包括ENPP3胞外结构域的任何酶促活性截短的构建体。

[0559] 在某些实施例中,ENPP3多肽是可溶性的。在一些实施例中,本公开的多肽包含缺乏ENPP3跨膜结构域的ENPP3多肽。在另一实施例中,本公开的多肽包含ENPP3多肽,其中ENPP3跨膜结构域已被去除并且被另一种多肽的跨膜结构域,如作为非限制性实例,ENPP2、ENPPS或ENPP7或天青杀素信号序列代替。

[0560] 在一些实施例中,本公开的多肽包括IgG Fc结构域。在某些实施例中,本公开的多肽包括白蛋白结构域。在其它实施例中,白蛋白结构域位于ENPP3多肽的C末端区。在又其它实施例中,IgG Fc结构域位于ENPP3多肽的C末端区。在又其它实施例中,IgG Fc结构域或白蛋白结构域的存在增加了半衰期、溶解度,降低了免疫原性并且提高了ENPP3多肽的活性。

[0561] 在某些实施例中,本公开的多肽包括引起ENPP3多肽的前体分泌的信号肽,所述前体经历蛋白水解处理以得到ENPP3多肽。在其它实施例中,信号肽选自由ENPP2、ENPP5和ENPP7的信号肽组成的组。在又其它实施例中,信号肽选自由以下组成的组:SEQ ID NO:36-42。

[0562] 在某些实施例中,IgG Fc结构域或白蛋白结构域通过接头区与ENPP3多肽的C末端区连接。在其它实施例中,接头选自SEQ ID NO:43至75,其中n是范围为1至20的整数。

[0563] ENPP1融合多肽和ENPP3融合多肽的产生和纯化

[0564] 为了产生用于体外使用的可溶性重组ENPP1多肽,将编码ENPP1的胞外结构域的多核苷酸(人NPP1(NCBI登录NP_006199))与IgG的Fc结构域(被称为“ENPP1-Fc”)融合,并且使其在稳定CHO细胞系中表达。在一些实施例中,编码NCBI登录NP_006199的残基96至925的ENPP1多核苷酸与Fc结构域融合以产生ENPP1多肽。

[0565] 可替代地,还可以使用合适的载体从HEK293细胞、杆状病毒昆虫细胞系统或CHO细胞或毕赤酵母表达系统中表达ENPP1多肽。ENPP1多肽可以在粘附细胞或悬浮细胞中产生。优选地,ENPP1多肽在CHO细胞中表达。为了建立稳定的细胞系,将编码ENPP1构建体的核酸序列克隆到适当的载体中,以供大规模蛋白质产生。

[0566] ENPP3是通过在CHO或HEK293哺乳动物细胞中建立稳定转染产生的。将编码ENPP3的ENPP3多核苷酸(人NPP3(UniProtKB/Swiss-Prot:O14638.2)与IgG的Fc结构域(被称为“ENPP3-Fc”)融合,并且使其在稳定CHO细胞系中表达。在一些实施例中,将编码UniProtKB/

Swiss-Prot:O14638.2的残基49-875的ENPP3多核苷酸与Fc结构域融合以产生ENPP3多肽。ENPP3多肽可以在粘附细胞或悬浮细胞中产生。为了建立稳定细胞系,将本公开的编码NPP3融合多肽的核酸序列建立成适当载体以供大规模蛋白质产生。存在各种可从商业来源获得的这些载体,并且可以使用那些载体中的任何载体。ENPP3多肽是遵循WO 2017/087936中确立的方案产生的,所述方案的内容特此通过引用以其整体并入。ENPP1多肽是遵循Albright等人,2015,《自然通信》6:10006中确立的方案产生的,所述方案的内容特此通过引用以其整体并入。

[0567] 含有ENPP1或ENPP3的期望多肽构建体的合适质粒可以使用确立的技术,如电穿孔或脂转染胺(lipofectamine)稳定地转染到表达质粒中,并且细胞可以在抗生素选择下生长以针对经稳定转染的细胞增强。然后确立单个经稳定转染的细胞的克隆并筛选期望融合蛋白的高表达克隆。可以在96孔板中使用如前所述合成酶促底物pNP-TMP以高通量方式完成对用于ENPP1多肽表达或ENPP3多肽表达的单细胞克隆的筛选(Saunders等人,2008,《分子癌症疗法》7(10):3352-62;Albright,等人,2015,《自然通信》6:10006)。

[0568] 在通过筛选鉴定用于ENPP3多肽或ENPP1多肽的高表达克隆后,可以在先前针对ENPP1描述的摇瓶或生物反应器中实现蛋白质产生(Albright等人,2015,《自然通信》6:10006)。ENPP3多肽或ENPP1多肽的纯化可以使用本领域已知的标准纯化技术的组合来完成。这些技术是本领域众所周知的,并且选自如柱色谱法、超离心、过滤和沉淀的技术。柱色谱法纯化是使用如蛋白质A和蛋白质G树脂等亲和色谱法、如镍或铜等金属亲和树脂、疏水交换色谱法以及使用C8-C14树脂的反相高压色谱法(HPLC)完成的。还可以采用离子交换,如使用可商购获得的树脂,如Q-琼脂糖凝胶(阴离子交换)和SP-琼脂糖凝胶(阳离子交换)、蓝色琼脂糖凝胶树脂和蓝色葡聚糖凝胶树脂以及羟基磷灰石树脂的阴离子和阳离子交换色谱法。也可以采用使用可商购获得的S-75和S200超敏葡琼凝胶树脂的尺寸排阻色谱法,如本领域已知的。用于使蛋白质溶解并且提供用于上述色谱法步骤的选择介质的缓冲液是蛋白质化学领域和科学的从业者已知的标准生物缓冲液。

[0569] 制备中使用的缓冲液的一些实例包含本领域众所周知的柠檬酸盐、磷酸盐、乙酸盐、三(羟甲基)氨基甲烷、盐水缓冲液、甘氨酸-HCL缓冲液、卡可酸盐缓冲液和巴比妥钠缓冲液。使用单一技术或一系列组合的技术,并且适当的缓冲液系统在考马斯染色的聚丙烯酰胺凝胶上在单个纯化步骤之后并排纯化ENPP3和粗制起始材料。然后,可以使用如上所述的另外的技术和/或色谱法步骤对ENPP3蛋白进行另外纯化,为了达到基本上更高的纯度,例如调节至适当pH的约99%纯度,可以将所描述的来自粗制材料的ENPP1多肽或ENPP3多肽纯化至大于99%纯度。

[0570] 纯化后,将ENPP1-Fc或ENPP3-Fc透析到补充有Zn2+和Mg2+的PBS(PBSplus)中,所述PBS被浓缩至介于5mg/ml至7mg/ml之间并且在-80℃下以200-500μl的等分试样冷冻。就在使用之前将等分试样解冻,并且通过在PBSplus中稀释将溶液的比活性调节至31.25au/ml(或约0.7mg/ml,这取决于制备物)。

[0571] 剂量和施用模式

[0572] 在另一实施例中,分别以含有约1.0mg/kg至约5.0mg/kg NPP1或约1.0mg/kg至约5.0mg/kg NPP3的一个或多个剂量施用hsNPP1或hsNPP3。在另一实施例中,以含有约1.0mg/kg至约10.0mg/kg NPP1或约1.0mg/kg至约10.0mg/kg NPP3的一个或多个剂量施用hsNPP1

或hsNPP3。

[0573] hsNPP1或hsNPP3的剂量之间的时间段为至少2天，并且可以更长，例如至少3天、至少1周、2周或1个月。在一个实施例中，施用为每周、每两周或每月。

[0574] 重组hsNPP1或hsNPP3可以以任何合适的方式，如静脉内、皮下或腹膜内施用。

[0575] 重组hsNPP1或hsNPP3可以与一种或多种另外的治疗剂组合施用。示例性治疗剂包含但不限于双膦酸酯、他汀(statin)、贝特(fibrate)、烟酸、阿司匹林(Aspirin)、氯吡格雷(Clopidogrel)和华法林(warfarin)。

[0576] 在一些实施例中，重组hsNPP1或hsNPP3和另外的治疗剂是单独施用的以及同时或依次施用的。在一些实施例中，重组hsNPP1或hsNPP3是在施用另外的治疗剂之前施用的。在一些实施例中，重组hsNPP1或hsNPP3是在施用另外的治疗剂之后施用的。在其它实施例中，重组hsNPP1或hsNPP3和另外的治疗剂是一起施用的。

[0577] 核酸施用和疗法

[0578] 用于ENPP1和ENPP3的体内表达的病毒载体

[0579] 编码可用于本公开内的多肽的核酸可以在基因疗法方案中使用以治疗本文所设想的疾病或病症。可以将编码多肽的经改进的构建体插入到适当的基因疗法载体中，并且施用于患者以治疗或预防所关注的疾病或病症。

[0580] 在现有技术中已经使用了如病毒载体等载体来将基因引入到多种不同靶细胞中。通常，将载体暴露于靶细胞，使得可以在充足比例的细胞中发生转化，以从期望多肽(例如受体)的表达中提供有用的治疗或预防作用。可以将经转染的核酸永久掺入到靶细胞中的每个靶细胞的基因组中，以提供持久的作用，或者可替代地治疗必须周期性地重复。在某些实施例中，(病毒)载体与编码本公开的多肽的遗传物质一起在体内转染肝细胞。

[0581] 多种载体，即病毒载体和质粒载体两者都是本领域已知的(参见例如美国专利第5,252,479号和第WO 93/07282号)。具体地，许多病毒已被用作基因转移载体，包含如SV40等乳多空病毒、牛痘病毒、包含HSV和EBV的疱疹病毒以及逆转录病毒。现有技术中的许多基因疗法方案已经采用了禁用的鼠逆转录病毒。若干项最近发布的专利涉及用于进行基因疗法的方法和组合物(参见例如美国专利第6,168,916号;第6,135,976号;第5,965,541号和第6,129,705号)。前述专利中的每个专利均通过引用以其整体并入本文。因此，可以将如包括NPP1序列或NPP3序列的多核苷酸等遗传物质引入到哺乳动物体内以治疗VSMC增殖。

[0582] 某些经修饰的病毒通常用作用于承载编码序列的载体，因为在施用于哺乳动物之后，病毒感染细胞并表达经编码的蛋白质。可根据本公开使用的经修饰的病毒源自包含例如以下的病毒:细小病毒、小RNA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(如多瘤和SV40)或疱疹病毒(如爱泼斯坦-巴尔病毒(Epstein-Barr Virus)、水痘带状疱疹病毒、巨细胞病毒、带状疱疹以及单纯疱疹病毒1型和2型)、RNA病毒或如莫洛尼鼠白血病病毒(Moloney murine leukemia virus)或慢病毒(即，源自人免疫缺陷病毒、猫免疫缺陷病毒、马感染性贫血病毒等)等逆转录病毒。可根据本公开使用的DNA病毒为:腺相关病毒、腺病毒、甲病毒和慢病毒。

[0583] 病毒载体通常通过注射，最通常静脉内(通过IV)直接施用于体内，或直接施用于特定组织中，病毒载体在所述身体或特定组织中被单独细胞摄取。替代地，病毒载体可以通过使病毒载体与患者细胞的样品离体接触，由此允许病毒载体感染细胞来施用，并且含有

载体的细胞然后被返回到患者。在递送病毒载体时，编码序列进行表达并且产生功能蛋白质。通常，病毒载体对细胞的感染和转导通过一系列连续事件发生，如下：病毒衣壳与受体在靶细胞的表面上相互作用、通过内吞内化、通过内吞隔室/蛋白酶体隔室进行的细胞内贩运、核内体逃逸、核输入、病毒体脱壳和引起重组编码序列益处的转录和表达的病毒DNA双链转化。(Colella等人，《分子疗法方法临床发展(Mol Ther Methods Clin Dev.)》2017年12月1日；8:87-104.)。

[0584] 根据本公开的腺相关病毒载体

[0585] AAV是指属于细小病毒科的依赖病毒属的病毒。AAV基因组为大约4.7千碱基长并且是由线性单链脱氧核糖核酸(ssDNA)构成的，所述线性脱氧核糖核酸可以是正感测的或负感测的。基因组包括位于DNA链的两端的反向末端重复序列(ITR)和两个开放阅读框(ORF)：rep和cap。rep框是由编码AAV生命周期所需的非结构性复制(Rep)蛋白的四个重叠基因制成的。cap框含有结构性VP衣壳蛋白的重叠核苷酸序列：VP1、VP2和VP3，所述衣壳蛋白其一起相互作用以形成二十面体对称的衣壳。

[0586] 末端145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，从而用作用于细胞DNA聚合酶复合物的引物。在哺乳动物细胞中完成野生型AAV感染之后，rep基因(即Rep78和Rep52)分别从P5启动子和P19启动子进行表达，并且两种Rep蛋白在病毒基因组的复制中具有功能。rep ORF中的剪接事件引起实际上四种Rep蛋白(即Rep78、Rep68、Rep52和Rep40)的表达。然而，已显示出，哺乳动物细胞中的编码Rep78和Rep52蛋白的未经剪接的mRNA足以产生AAV载体。在昆虫细胞中，Rep78和Rep52蛋白也足以产生AAV载体。

[0587] AAV是辅助依赖性病毒，即，其需要与辅助病毒(例如，腺病毒、疱疹病毒或牛痘病毒)共感染以形成功能上完整的AAV病毒体。在不存在与辅助病毒的共感染的情况下，AAV确立了潜伏状态，在所述潜伏状态下病毒基因组插入到宿主细胞染色体中或以游离形式存在，但未产生感染性病毒体。随后被辅助病毒感染“拯救”了整合的基因组，允许其复制并封装到病毒衣壳中，由此重组感染性病毒体。虽然AAV可以感染来自不同物种的细胞，但辅助病毒必须与宿主细胞属于同一物种。因此，例如，人AAV在已经共感染了犬腺病毒的犬细胞中复制。

[0588] 为了产生含有异源核酸序列的感染性重组AAV(rAAV)，可以用含有异源核酸序列但缺乏AAV辅助功能基因rep和cap的AAV载体对合适的宿主细胞系进行转染。然后可以在单独载体上提供AAV辅助功能基因。而且，可以在载体上仅提供AAV产生所需的辅助病毒基因(即，附属功能基因)，而不是提供具有复制能力的辅助病毒(如腺病毒、疱疹病毒或牛痘)。

[0589] 总之，可以在一个或多个载体上提供AAV辅助功能基因(即rep和cap)和附属功能基因。然后可以在宿主细胞中表达辅助基因产物和附属功能基因产物，在所述宿主细胞中所述辅助基因产物和所述附属功能基因产物将反式作用于含有异源核酸序列的rAAV载体。然后将含有异源核酸序列的rAAV载体复制并封装，就像其是野生型(wt)AAV基因组一样，从而形成重组病毒体。当患者的细胞感染了产生的rAAV病毒体时，异源核酸序列进入患者的细胞并在患者的细胞中表达。

[0590] 由于患者的细胞缺乏rep和cap基因以及附属功能基因，因此rAAV不能进一步复制和封装其基因组。此外，在没有5个rep和cap基因的来源的情况下，在患者的细胞中不能形

成wtAAV。

[0591] AAV载体通常缺乏rep和cap帧。此类AAV载体在存在于已用编码并表达rep和cap基因产物(即AAV Rep和Cap蛋白)的载体转染的宿主细胞中时可以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的蛋白质的载体转染。

[0592] 通过首先产生包括编码所关注蛋白质的DNA的AAV载体,并且然后将所述载体施用于哺乳动物来完成将所关注蛋白质递送到哺乳动物的细胞。因此,本公开应被解释为包含包括编码所关注多肽的DNA的AAV载体。一旦装备了本公开,包括编码此/这些多肽的DNA的AAV载体的产生对于技术人员将是显而易见的。

[0593] 在一个实施例中,本公开涉及一种腺相关病毒(AAV)表达载体,所述AAV表达载体包括编码哺乳动物ENPP1或哺乳动物ENPP3的序列,并且在施用于哺乳动物时,所述载体使ENPP1前体或ENPP3前体在细胞中表达,所述前体包含在其羧基末端处与ENPP1或ENPP3的氨基末端融合的天青杀素信号肽。ENPP1或ENPP3前体可以包含稳定结构域,如IgG Fc区或人白蛋白。在前体从细胞中分泌时,信号肽被切割,并且胞外提供酶促活性的可溶性哺乳动物ENPP1或ENPP3。

[0594] AAV表达载体可以包含表达盒,所述表达盒包括与核苷酸序列操作性地连接的转录调节区,所述核苷酸序列包括与编码多肽的重组核酸序列操作性地连接的转录调节区,所述多肽包括天青杀素信号肽序列和胞外核苷酸焦磷酸酶/磷酸二酯酶(ENPP1)多肽序列。

[0595] 在一些实施例中,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多腺苷酸化信号。

[0596] 在一些实施例中,根据本公开的AAV载体的AAV重组基因组缺乏rep开放阅读框和/或cap开放阅读框。

[0597] 根据本公开的AAV载体包括来自任何血清型的衣壳。一般来说,AAV血清型在氨基酸水平和核酸水平下具有显著同源的基因组序列,提供相同的遗传功能集合,并且通过几乎相同的机制复制和组装。具体地,本公开的AAV可以属于AAV的血清型1(AAV1)、AAV2、AAV3(包含3A型和3B型)、AAV4、AAV5、AAV6、AAV7、AAV8、AAV9、AAV10、AAVrh10、AAV11、禽AAV、牛AAV、犬AAV、马AAV或羊AAV。

[0598] 不同AAV血清型的基因组序列的实例可以在文献或如GenBank等公共数据库中找到。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)。

[0599] 在一些实施例中,根据本公开的腺相关病毒载体包括衍生自血清型的衣壳,所述血清型选自由以下组成的组:AAV2、AAV5、AAV7、AAV8、AAV9、AAV10和AAVrh10血清型。在另一实施例中,AAV的血清型为AAV8。如果病毒载体包括编码衣壳蛋白的序列,则这些序列可以被修饰以包括外源性序列以将AAV引导到一种或多种特定细胞类型中,或增加所靶向载体递送至细胞的效率,或促进AAV的纯化或检测,或减少宿主应答。

[0600] 在某些实施例中,本公开的rAAV载体包括几种必需DNA元件。在某些实施例中,这些DNA元件包含至少两个拷贝的AAV ITR序列、启动子/增强子元件、转录终止信号、侧接编

码所关注蛋白质或其生物活性片段的DNA的任何必需的5'或3'非翻译区。本公开的rAAV载体还可以包含所关注蛋白质的内含子的一部分。另外，任选地，本公开的rAAV载体包括编码所关注经突变的多肽的DNA。

[0601] 在某些实施例中，载体包括能够在许多不同细胞类型中将异源基因的表达驱动到高水平的启动子/调控序列，所述启动子/调控序列包括混杂启动子。此类启动子包含但不限于巨细胞病毒(CMV)立即早期启动子/增强子序列、劳斯氏肉瘤病毒启动子/增强子序列等。在某些实施例中，本公开的rAAV载体中的启动子/调节序列是CMV立即早期启动子/增强子。然而，用于驱动异源基因的表达的启动子序列还可以是诱导型启动子，例如但不限于类固醇诱导型启动子，或者可以是组织特异性启动子，如但不限于骨骼-肌动蛋白启动子，所述骨骼-肌动蛋白启动子为肌肉组织特异性启动子/增强子和肌肉肌酸激酶启动子/增强子等。

[0602] 在某些实施例中，本公开的rAAV载体包括转录终止信号。虽然任何转录终止信号可以包含在本公开的载体中，但在某些实施例中，转录终止信号为SV40转录终止信号。

[0603] 在某些实施例中，本公开的rAAV载体包括编码所关注多肽的分离的DNA 5或所关注多肽的生物活性片段。本公开应被理解为包含所关注多肽的已知或未知的任何哺乳动物序列。因此，本公开应被解释为包含来自除人之外的哺乳动物的基因，所述哺乳动物多肽以与人多肽基本上相似的方式起作用。优选地，包括编码所关注多肽的基因的核苷酸序列与编码所关注多肽的基因约50％同源，更优选地约70％同源，甚至更优选地约80％同源，并且最优选地约90％同源。

[0604] 此外，本公开应被解释为包含野生型蛋白质序列的天然存在的变体或重组衍生的突变体，所述变体或突变体使由此编码的多肽与全长多肽在治疗上一样有效，或甚至在本公开的基因疗法方法中比全长多肽在治疗上更有效。

[0605] 本公开还应被解释为包含保留多肽的生物活性的DNA编码变体。此类变体包含已经或可以使用重组DNA技术修饰的蛋白质或多肽，使得所述蛋白质或多肽具有增强其用于本文所描述的方法的适合性的另外的性质，例如但不限于赋予血浆中的蛋白质增强的稳定性和赋予蛋白质增强的比活性的变体。类似物可以通过保守氨基酸序列差异或不影响序列的修饰或通过两者而与天然存在的蛋白质或肽相异。例如，可以进行保守氨基酸改变，所述保守氨基酸改变尽管改变了蛋白质或肽的一级序列，但通常不会改变其功能。

[0606] 本公开不限于实验实例中例示的特定rAAV载体；相反，本公开应被解释为包含任何合适的AAV载体，包含但不限于基于AAV-1、AAV-3、AAV-4和AAV-6等的载体。本公开中还包含一种以有效提供治疗效果的量治疗患有疾病或病症的哺乳动物的方法。

[0607] 所述方法包括向所述哺乳动物施用编码所关注多肽的rAAV载体。优选地，哺乳动物是人。通常，在单次注射中施用的病毒载体基因组/哺乳动物的数目在约1×108至约5×1016的范围内。优选地，在单次注射中施用的病毒载体基因组/哺乳动物的数目为约1×10^{10}至约1×10^{15}，更优选地，在单次注射中施用的病毒载体基因组/哺乳动物的数目为约5×10^{10}至约5×10^{15}；并且最优选地，在单次注射中施用于哺乳动物的病毒载体基因组的数目为约5×10^{10}至约5×10^{14}。

[0608] 当本公开的方法包括多位点同时注射或包括在几个小时的时间段(例如，约少于一小时到约两小时到三小时)内注射到不同部位的几个多位点注射时，所施用的病毒载体

基因组的总数量可以与单位点注射方法中所引用的数量相同、或为其分数或为其乘数15。

[0609] 为了以单位点注射施用本公开的rAAV载体，在某些实施例中，将包括病毒的组合物直接注射到受试者的器官(如但不限于受试者的肝脏)中。

[0610] 为了施用于哺乳动物，rAAV载体可以在约7.8的pH下悬浮在药学上可接受的载体，例如HEPES缓冲盐水中。其它有用的药学上可接受的载体包含但不限于甘油、水、盐水、乙醇和其它药学上可接受的盐溶液，如磷酸盐和有机酸的盐。这些以及其它药学上可接受的载体的实例在《雷明顿药物科学(Remington's Pharmaceutical Sciences)》(1991,新泽西州的麦克出版公司(Mack Publication Co.,New Jersey))中描述。本公开的rAAV载体也可以以试剂盒的形式提供，所述试剂盒包括例如，载体于干盐调配物中的冻干制剂、用于使载体/盐组合物悬浮的无菌水以及用于使载体悬浮并且向哺乳动物施用组合物的说明书。

[0611] 所公开申请US 2017/0290926-Smith等人详细描述了通过其产生、递送和施用AAV载体的过程，所述申请的内容通过引用以其整体并入本文。

[0612] ENPP1多肽和ENPP3多肽的基于RNA的体内表达

[0613] 本公开提供了用于产生和递送本文所述的重组双链RNA分子(编码ENPP1多肽或ENPP3多肽的dsRNA)的组合物和方法。双链RNA颗粒(dsRP)可以含有封闭在衣壳或外被蛋白中的dsRNA分子。dsRNA分子可以是病毒基因组或基因组的一部分，其可以源自野生型病毒基因组。RNA分子可以编码RNA依赖性RNA聚合酶(RDRP)和形成衣壳或外被蛋白的至少一部分的多蛋白。RNA分子还可以含有编码由宿主细胞的细胞组分翻译的ENPP1多肽或ENPP3多肽的RNA子序列。在将dsRP转染到宿主细胞中时，可以由宿主细胞的细胞机制对子序列进行翻译以产生ENPP1多肽或ENPP3多肽。

[0614] 另一方面，本公开提供了一种在宿主细胞中产生蛋白质产物的方法。所述方法包含用具有重组双链RNA分子(dsRNA)和衣壳或外被蛋白的dsRP转染宿主细胞。RNA分子可以编码RNA依赖性RNA聚合酶和形成衣壳或外被蛋白的至少一部分的多蛋白，并且dsRP能够在宿主细胞中复制。RNA分子具有编码由宿主细胞的细胞组分翻译的ENPP1多肽或ENPP3多肽的至少一个RNA子序列。

[0615] 另一方面，本公开提供了可由宿主细胞翻译的RNA分子。RNA分子可以是编码本文所述的ENPP1多肽或ENPP3多肽的任何RNA分子。在一个实施例中，RNA分子编码RNA依赖性RNA聚合酶和形成dsRP的衣壳或外被蛋白的至少一部分的多蛋白，并且任选地，可以具有编码另外的蛋白质产物的至少一个RNA子序列。

[0616] dsRP的产生

[0617] 本公开的dsRP也可以通过向宿主细胞呈递编码本公开的dsRP或编码dsRP的基因的质粒或其它DNA分子来产生。然后将含有编码所需蛋白质的核苷酸序列的质粒或DNA分子，如ENPP1多肽或ENPP3多肽，转染到宿主细胞中，并且宿主细胞开始产生本公开的dsRP。dsRP还可以在宿主细胞中通过向宿主细胞呈递编码dsRP的基因的RNA分子产生。RNA分子可以是(+)-链RNA。

[0618] 在已将本公开的dsRP呈递给宿主细胞(或编码本公开的dsRP的基因的质粒，或编码dsRP的基因的RNA分子)后，将在宿主细胞内使用宿主细胞的细胞组分产生dsRP。因此，本公开的dsRP在宿主细胞内是自维持的，并且在宿主细胞内传播。宿主细胞可以是任何合适的宿主细胞，例如真核细胞、哺乳动物细胞、真菌细胞、细菌细胞、昆虫细胞或酵母细胞。宿

主细胞可以在本公开的重组dsRNA分子或编码本公开的dsRP的DNA分子呈递给宿主细胞并被宿主细胞摄取之后传播重组dsRP。

[0619] 产生dsRNA病毒或dsRP的方法

[0620] 本公开还提供了产生本公开的dsRP的方法。可以将双链或单链RNA或DNA分子呈递给宿主细胞。dsRNA分子在宿主细胞中的扩增利用许多类型的宿主细胞(例如酵母)中已经存在的天然产生和组装过程。因此,可以通过向宿主细胞呈递本公开的单链或双链RNA或DNA分子来应用本公开,所述单链或双链RNA或DNA分子被宿主细胞摄取并且用于使用宿主细胞的细胞组分产生由RNA子序列编码的重组dsRP和蛋白质或肽。本公开还可以通过向宿主细胞提供含有编码RNA依赖性RNA聚合酶的一个或多个序列的直链或环状DNA分子(例如质粒或载体)、形成dsRP的衣壳或外被蛋白的至少一部分的多蛋白以及编码所关注蛋白质,如本文所公开的ENPP1多肽或ENPP3多肽的子序列来应用。

[0621] 本公开的dsRNA或ssRNA分子的呈递可以以任何合适的方式进行,例如通过将本公开的RNA分子直接呈递给宿主细胞作为“裸”或未经修饰的单链或双链RNA。RNA分子可以通过任何合适的方法,例如通过电穿孔、宿主细胞暴露于磷酸钙或通过产生与细胞膜融合并使病毒序列沉积在内部的脂质体转染(或转化)到酵母宿主细胞、细菌宿主细胞或哺乳动物宿主细胞中。其还可以通过将dsRNA从杀伤病毒或异源dsRNA直接引入宿主细胞中的特定机制来进行。此步骤可以使用报告子系统,如红色荧光蛋白(RFP)或通过靶向宿主细胞基因组内的特异性组成性基因转录物来进行优化。这可以通过使用具有明显表型的靶或通过定量逆转录酶PCR(RT-PCR)进行监测来完成。

[0622] 在一些实施例中,将编码本公开的RNA分子的DNA分子(例如,质粒或其它载体)引入到宿主细胞中。DNA分子可以含有编码本公开的dsRP的RNA分子的序列。DNA分子可以编码dsRP的整个基因组或其一部分。DNA分子可以进一步编码产生另外的(异源)蛋白质产物的RNA的至少一个子序列。DNA序列还可以编码gag蛋白或gag-pol蛋白,以及支持分子的表达和目的的任何必要或期望启动子或其它序列。DNA分子可以是线性DNA、环状DNA、质粒、酵母人工染色体,或者可以采取便于特定应用的另一种形式。

[0623] 在一个实施例中,DNA分子可以进一步包括用于产生多联体和发夹结构的T7端,因此允许病毒或dsRP序列在宿主细胞中传播。DNA分子可以转染或转化到宿主细胞中,并且然后可以使用宿主细胞机制转录,并且因此可以向宿主细胞提供具有至少一个RNA子序列的dsRNA分子。然后宿主细胞可以产生经编码的所需ENPP1多肽或ENPP3多肽。可以使用宿主细胞的代谢过程和机制以与野生型病毒相同的方式包装dsRNA。ENPP1多肽或ENPP3多肽也是使用宿主细胞的代谢过程和细胞组分产生的。

[0624] Brown等人的专利US 10266834详细描述了通过其产生、递送和施用编码多肽的dsRNA颗粒的过程,所述专利的内容通过引用以其整体并入本文。

[0625] 药物组合物和调配物

[0626] 本公开提供了在本文所述的方法内包括本公开的多肽的药物组合物。此药物组合物呈适于施用于受试者的形式,或者所述药物组合物可以进一步包括一种或多种药学上可接受的载体、一种或多种另外的成分或这些的某种组合。药物组合物的各种组分可以生理学上可接受的盐的形式存在,如与生理学上可接受的阳离子或阴离子组合,如本领域众所周知的。

[0627] 在一实施例中，可用于实践本公开的方法的药物组合物可以施用为递送介于1ng/kg/天与100mg/kg/天之间的剂量。在其它实施例中，可用于实践本公开的药物组合物可以施用于递送介于1ng/kg/天与500mg/kg/天之间的剂量。

[0628] 本公开的药物组合物中的活性成分、药学上可接受的载体以及任何另外的成分的相对量将根据所治疗的受试者的同一性、大小和状况并且进一步地根据组合物所施用的途径而变化。举例来说，所述组合物可以包括约0.1％至约100％(w/w)的活性成分。

[0629] 可用于本公开的方法的药物组合物可以适当地针对吸入、口服、直肠、阴道、肠胃外、局部、经皮、肺、鼻内、颊、眼、鞘内、静脉内或另一种施用途径来开发。其它所设想的调配物包含投射的纳米颗粒、脂质体制剂、含有活性成分的再密封的红细胞以及基于免疫学的调配物。施用途径对于本领域的技术人员是显而易见的，并且取决于任何多种因素，包含所治疗的疾病的类型以及严重性、所治疗的兽医患者或人类患者的类型和年龄等。

[0630] 本文描述的药物组合物的调配物可以通过药理学领域已知的或今后开发的任何方法来制备。通常，此类制备方法包含以下步骤：使活性成分与载体或一种或多种其它辅助成分缔合，并且然后如果需要或期望，则将产物成形或包装成期望的单剂量或多剂量单位。

[0631] 如本文所用，“单位剂量”是包括预定量的活性成分的药物组合物的离散量。活性成分的量通常等于将施用于受试者的活性成分的剂量或此剂量的方便分数，例如此剂量的一半或三分之一。单位剂型可以是单个日剂量或多个日剂量之一(例如约1到4次或更多次每天)。当使用多个日剂量时，单位剂型对于每个剂量来说可以是相同的或不同的。

[0632] 施用方案可能影响构成有效量的内容。例如，可以每天或依序施用若干个分开的剂量以及交错的剂量，或者剂量可以连续输注或可以是团注。进一步地，治疗调配物的剂量可以成比例增加或减少，如治疗或预防情况的迫切情况所指示的。在某些实施例中，本公开的化合物施用于受试者将受试者的血浆PPi升高至接近正常的水平，其中哺乳动物的PPi的正常水平为1-3μM。“接近正常”是指0μM至1.2μM或正常以下或以上0-40％、30nM至0.9μM或正常以下或以上1-30％15、0μM至0.6μM或正常以上或以下0-20％、或0μM至0.3μM或正常以上或以下0-10％。

[0633] 本公开的组合物施用于患者，如哺乳动物，如人，可以使用已知程序，以有效治疗患者的疾病或病症的剂量和时间段进行。实现治疗作用所需的治疗化合物的有效量可以根据各种因素而变化，如所采用的特定化合物的活性；施用时间；化合物的排泄率；治疗的持续时间；其它药物；化合物或与化合物组合使用的材料；所治疗的患者的疾病或病症的状态、年龄、性别、体重、状况、一般健康和先前病史；以及医学领域众所周知的类似因素。剂量方案可以调整以提供最优治疗应答。剂量是基于治疗化合物的生物活性确定的，所述生物活性进而取决于治疗化合物曲线的半衰期和血浆时间下面积。根据本公开的多肽以每2天或每4天或每周或每月的适当时间间隔施用，以实现血浆PPi的接近正常(1-3μM)水平或高于PPi的正常水平(比正常水平高30％-50％)的连续水平。还可以基于半衰期或治疗多肽从体内清除的速率来确定本公开的多肽的治疗剂量。根据本公开的多肽以每2天或每4天、每周或每月的适当的时间间隔施用，以便实现ENPP1多肽或ENPP3多肽的恒定水平的酶促活性。

[0634] 例如，可以每天施用若干个分开的剂量，或者剂量可以成比例减少，如治疗情况的迫切情况所指示的。本公开的治疗化合物的有效剂量范围的非限制性实例为约0.01mg/kg

体重/天至50mg/kg体重/天。在某些实施例中，本公开的治疗化合物的有效剂量范围为约50ng/kg体重至500ng/kg体重，优选地100ng/kg体重至300ng/kg体重。本领域的普通技术人员将能够研究相关因素，并且在不进行过度实验的情况下进行关于治疗化合物的有效量的确定。

[0635] 化合物可以每天几次频繁地施用于患者，或者其可以不太频繁地施用，如每天一次、每周一次、每两周一次、每月一次或甚至不太频繁地施用，如每几个月一次或甚至每年一次或更少。应当理解，每天给药的化合物的量在非限制性实例中可以每天、每隔一天、每2天、每3天、每4天或每5天施用。例如，在每隔一天施用的情况下，可以在星期一开始给药5mg每天剂量，并且在星期三施用第一随后的5mg每天剂量，在星期五施用第二随后的5mg每天剂量等。剂量的频率对于技术人员是显而易见的，并且取决于任何数目的因素，如但不限于所治疗的疾病的类型和严重性以及患者的类型和年龄。本公开的药物组合物中的活性成分的实际剂量水平可以变化，以获得有效实现对特定患者、组合物以及施用模式的期望治疗应答而对患者无毒性的量的活性成分。

[0636] 具有本领域的普通技能的医生，例如医师，可以容易地确定并且开出所需的有效量的药物组合物。例如，医师或兽医可以以比为了实现期望治疗作用所需的水平低的水平来开始药物组合物中采用的本公开的化合物的剂量，并且逐渐增加剂量直到实现期望作用。

[0637] 在某些实施例中，本公开的组合物以范围为每天一至五次或更多次的剂量施用于患者。在其它实施例中，本公开的组合物以包含但不限于以下的剂量范围施用于患者：每天一次、每两天一次、每三天一次至每周一次，以及每两周一次。本公开的各种组合性组合物的施用频率因受试者而异，这取决于许多因素，包含但不限于年龄、待治疗的疾病或病症、性别、整体健康和其它因素。因此，本公开不应被解释为限于任何特定剂量方案，并且要施用于任何患者的精确剂量和组合物将由主治医师考虑到关于患者的所有其它因素来确定。

[0638] 在某些实施例中，本公开涉及一种经封装的药物组合物，其包括：容器，所述容器保持单独的或与第二药剂组合的治疗有效量的本公开的化合物；以及用于使用所述化合物来治疗、预防或减少患者的疾病或病症的一种或多种症状的说明书。

[0639] 施用途径

[0640] 本公开的组合物中的任何组合物的施用途径包含吸入、口服、鼻、直肠、肠胃外、舌下、经皮、经粘膜(例如，舌下、舌、(经)颊、(经)尿道、阴道(例如、经阴道和阴道周)、鼻(内)以及(经)直肠、膀胱内、肺内、十二指肠内、胃内、鞘内、皮下、肌肉内、皮内、动脉内、静脉内、支气管内、吸入和局部施用。

[0641] 合适的组合物和剂型包含例如片剂、胶囊、微囊、丸剂、胶囊锭、锭剂、分散剂、悬浮剂、溶液、糖浆、颗粒剂、珠剂、经皮贴剂、凝胶剂、粉剂、丸粒、乳浆剂、糖锭、霜剂、糊剂、膏药、洗剂、圆片、栓剂、用于鼻或口服施用的液体喷雾剂、用于吸入的干粉末或雾化调配物、用于膀胱内施用的组合物和调配物等。将可用于本公开中的调配物和组合物不限于本文所述的特定调配物和组合物。

[0642] “肠胃外施用”药物组合物包含特征在于物理破坏受试者的组织和通过破坏组织施用药物组合物的任何施用途径。肠胃外施用因此包含但不限于借助于注射组合物来施用药物组合物、借助于通过外科手术切口应用组合物、借助于通过穿透组织的非外科手术伤

口应用组合物等。具体地，设想了肠胃外施用包含但不限于皮下、静脉内、腹膜内、肌肉内、胸骨内注射和肾透析输注技术。

[0643] 实例

[0644] 通过以下实例进一步例示本公开。实例仅出于说明性目的，并且不旨在也不应该被解释为以任何方式限制本公开。

[0645] 实例1:ENPP1和ENPP1-Fc融合蛋白在小鼠主动脉移植物中的功效

[0646] 同种异体移植物血管病仍然是阻碍移植物长期存活的主要并发症之一，因此是实体器官移植患者死亡的主要风险因素。本实例的目的是评估ENPP1-Fc融合蛋白或ENPP1蛋白在主动脉同种异体移植物的小鼠模型中的功效。根据实体器官移植后抑制狭窄的能力评估ENPP1或ENPP1-Fc融合蛋白的治疗效果。

[0647] 将5周至6周龄的雌性DBA/2(H-2^d)和C57BL/6J(H-2^b)小鼠分别用作供体和受体小鼠。(Bickerstaff等人，小鼠肾同种异体移植物:自发接受与调节的T细胞介导免疫相关(Murine renal allografts:spontaneous acceptance is associated with regulated T cell-mediated immunity)，2001，《免疫学杂志(J.Immunol.)》167，4821-4827)。如前所述，将DBA/2小鼠的下行胸主动脉移植到肾下位置的C57CL/6小鼠中。(Seppelt等人，腺病毒基因疗法后马凡氏小鼠(mgR/mgR)内皮屏障丧失导致严重炎症(Loss of Endothelial Barrier in Marfan Mice(mgR/mgR)Results in Severe Inflammation after Adenoviral Gene Therapy)，2016，《公共科学图书馆·综合》11，e0148012)。

[0648] 用CO_2对供体小鼠实施安乐死。打开胸腔，穿刺左心室，并且用5mL NaCl(4℃，0.9％)灌注动脉循环系统。采集降主动脉并移植到受体小鼠体内，以建立主动脉同种异体移植物模型。可替代地，如图2所示，可以采集供体小鼠的整个心脏并将其移植到受体小鼠体内，以建立实体器官移植小鼠模型。

[0649] 受体C57BL/6J小鼠通过吸入5％的异氟烷麻醉。腹膜内注射Novalgin(500mg/mL；200mg/kg体重)和Carprive(50mg/mL卡洛芬(carprofen)，5mg/kg体重)。打开受体小鼠的腹腔，并且解剖肾下主动脉。应用钛夹，并且切断主动脉。移植物通过两个端对端吻合连接到受体主动脉(Prolene 11-0，尼龙黑，瑞士纽豪森的S&T公司(S&T，Neuhausen，Switzerland))。取出夹子后，重新灌注移植物。(Remes等人，《分子疗法:方法与临床开发(Molecular Therapy:Methods&Clinical Development)》第15卷2019年12月)。

[0650] 用tris缓冲盐水处理含有移植的主动脉(n＝5)的受体小鼠的对照子集，并且用ENPP1或ENPP1-Fc处理具有移植的主动脉(n＝5)的受体小鼠的实验子集，以确定ENPP1或ENPP1-Fc对同种异体移植物中血管平滑肌细胞增殖的影响。ENPP1或ENPP1-Fc处理(每天皮下注射10mg/kg体重的ENPP1或ENPP1-Fc)在实验小鼠组的主动脉移植后开始，并且持续28天，直到采集移植的主动脉。类似地，对照小鼠组在主动脉移植后通过皮下注射每天用pH 7.4的Tris缓冲盐水处理，持续28天，直到采集移植的主动脉。然后用PBS中的4％多聚甲醛固定动脉进行形态学分析。

[0651] 收集连续切片(每个切片5μm)。从不同间隔中随机选择整个移植的移植物的5-μm厚的冷冻主动脉切片(Microtom，HM 500O)，并且使用弹性van Gieson染色(德国卡尔斯鲁厄的Roth公司(Roth，Karlsruhe，Germany))进行染色。使用了ImageJ软件测量外部弹性膜、内部弹性膜和内腔边缘的圆周。之后，使用ImageJ(斐济版本1.51p，美国国立卫生研究院

(NIH,USA))测量新生内膜和内侧区域,两名研究人员对处理方案不知情。两个分析的参数的比率用作内腔阻塞的度量。计算了中层面积、内膜面积和内膜/中层比率(I/M比率)。

[0652] 使用学生t检验(Student's t test)(针对平均值的未配对双样品检验)进行统计分析。多个组的比较使用单向ANOVA,之后用GraphPad Prism软件版本7进行邦费罗尼后测试(Bonferroni's post hoc test)。概率值$p<0.05$被认为是显著的。形态测定分析显示,对照未经处理的小鼠出现血管病变和强烈重塑,伴有高度的血管内腔阻塞。

[0653] 在移植后用ENPP1或ENPP1-Fc处理的实验小鼠中,将内膜增生程度与未接受ENPP1或ENPP1-Fc的对照小鼠进行比较。未经处理的对照小鼠移植主动脉的连续切片的定量分析预期显示出显著增加的新生内膜增殖,并且这也与移植后28天或之后ENPP1或ENPP1-Fc处理的小鼠进行了比较。预期对照小鼠显示动脉内膜增厚,并且这与处理的小鼠进行了比较。相应地,比较了对照和处理的小鼠的I/M比率。

[0654] 实例2:ENPP1-Fc的预防作用

[0655] 修改实例1中所描述的相同实验,以通过在主动脉移植前一周向实验组施用ENPP1或ENPP1-Fc来确定ENPP1或ENPP1-Fc在预防或减少同种异体移植物血管病方面的预防作用,如图1所示。同样,在主动脉移植前一周向对照组施用Tris缓冲盐水。然后,在移植后用10mg/kg剂量的ENPP1或ENPP1-Fc处理实验组,并且在移植后用Tris缓冲盐水处理对照组,重复上述过程。形态分析预期表明,与对照小鼠相比,接受皮下ENPP1或ENPP1-Fc的实验小鼠的内膜面积预期会显著减少,而外部内膜与内部内膜之间的中层面积保持恒定。I/M比率显示,与媒剂处理的对照小鼠相比,ENPP1或ENPP1-Fc处理的实验小鼠在统计学上显著降低,表明主动脉移植前预防性处理ENPP1或ENPP1-Fc可通过降低VSMC增殖水平发挥保护作用。

[0656] 实例3:主动脉同种异体移植物的大鼠模型

[0657] 可以使用大鼠模型代替小鼠模型进行与实例1中描述的相同的实验。用于移植的大鼠模型在以下中进行了描述:Bogossian等人,(2016)《心血管疗法(Cardiovasc Ther)》34(4):183。在移植外科手术后28天比较ENPP1或ENPP1-Fc处理的大鼠和具有主动脉同种异体移植物移植的对照大鼠(接受Tris缓冲盐水)。

[0658] 实例4:ENPP1或ENPP1-Fc融合蛋白对猪心脏移植模型中心脏同种异体移植物血管病(CAV)的功效

[0659] 供体-受体对的选择基于混合淋巴细胞反应(MLR)的主要组织相容性复合体不相容性。刺激指数(SI)通过下式计算:(同种异体MLR的平均cpm)/(自体MLR的平均cpm)。供体心脏通过肾下同种异体移植异位移植到受体猪腹部。选择的移植供体和受体使用唑来泰(Zoletil)(替利他明(tiletamine)加唑拉西泮(zolazepam),5mg/kg)和琥珀胆碱(1.1mg/kg)和阿托品(atropine)(0.6mg/kg)进行麻醉,并且在插管后通过呼吸机施用使用异氟烷(3%/1.5升/分钟)维持麻醉。将受体置于左侧卧位,并且建立血管通路,用于施用免疫抑制药物。

[0660] 建立右胁腹切口,并且通过腹膜后途径,分离肾下主动脉和下腔静脉(参见图3)。接下来,将供体肝素化(静脉内注射(i.v.)300IU/kg),并在使用冷(4℃)心脏停搏液实现心脏停止后采集供体心脏。在每个供体心脏中建立房间隔缺损,并且对二尖瓣去功能化,以最小化左心室萎缩和腔内血栓形成。将受体肝素化(300IU/kg i.v.),并且用连续的5-0聚丙

烯缝合线将供体的肺动脉与下腔静脉的1cm至2cm静脉切口进行端对端吻合。随后,以类似的方式将供体心脏的升主动脉与受体的腹主动脉吻合,然后施用鱼精蛋白(1.5mg/kg;)以止血。(Hsu等人,《移植》2018年12月;102(12):2002-2011)。

[0661] 每天通过触诊监测心脏同种异体移植物的起搏频率,并且每周进行两次心电图。当同种异体移植物的起搏频率降低时,进行超声心动图评估收缩功能。随访持续到同种异体移植物停止或研究结束日期(150天)。

[0662] 用tris缓冲盐水处理含有移植的心脏(n=12)的受体猪的对照子集,并且用ENPP1或ENPP1-Fc处理具有移植的心脏(n=12)的受体猪的实验子集,以确定ENPP1对实体器官移植中血管平滑肌细胞增殖的影响。ENPP1或ENPP1-Fc处理(每四天皮下注射10mg/kg体重的ENPP1-Fc或ENPP1)在实验猪组的心脏移植后开始,并且持续150天,直到采集移植的心脏。类似地,对照猪组在心脏移植后通过腹膜内注射每4天用pH 7.4的Tris缓冲盐水处理,持续150天,直到采集移植的心脏。

[0663] 福尔马林固定的心脏样本包埋在石蜡中,切片、脱蜡、再水合,然后进行苏木精和伊红(HE)或地衣红染色。使用蔡司显微镜(Zeiss microscope)检查血管移植物的内膜增生,并且根据地衣红染色的切片的计算机图像确定。使用图像分析程序(图像J,版本1.46r,NIH图像)计算由内部弹性膜(IELA)包围的面积和内腔面积(LA)。内膜增生的严重程度使用下式计算:[(IELA-LA)/IELA]×100%。计算后,在5个切片的每个冠状动脉截面的3个随机选择的区域中,以盲检方式评估每个移植物内膜增生的严重程度,并且将评估的严重程度取平均值进行统计分析。

[0664] 使用学生t检验(针对平均值的未配对双样品检验)进行统计分析。多个组的比较使用单向ANOVA,之后用GraphPad Prism软件版本7进行邦费罗尼后测试。概率值$p<0.05$被认为是显著的。形态测定分析显示,对照未经处理的猪出现血管病变和强烈重塑,伴有高度的血管内腔阻塞。

[0665] 在移植后用ENPP1或ENPP1-Fc处理的实验猪中,通过对连续切片进行定量和定性分析,确定对照以及ENPP1或ENPP1处理的猪的内膜增生程度。预期对照猪在移植后150天会表现出明显增加的新生内膜增殖。预期对照猪显示动脉内膜增厚,并且将处理的猪与对照进行比较。相应地,比较了对照和处理的猪的I/M比率。还确定了对照以及ENPP1或ENPP1处理组的中值存活时间。还确定了对照以及ENPP1或ENPP1处理组的移植物存活时间。

[0666] 实例5:ENPP3或ENPP3-Fc融合蛋白在小鼠主动脉移植物中的功效

[0667] 将5周至6周龄的雌性DBA/2(H-2^d)和C57BL/6J(H-2^b)小鼠分别用作供体和受体小鼠。(Bickerstaff等人,小鼠肾同种异体移植物:自发接受与调节的T细胞介导免疫相关,2001,《免疫学杂志》167,4821-4827)。如前所述,将DBA/2小鼠的下行胸主动脉移植到肾下位置的C57CL/6小鼠中。(Seppelt等人,腺病毒基因疗法后马凡氏小鼠(mgR/mgR)内皮屏障丧失导致严重炎症,2016,《公共科学图书馆·综合》11,e0148012)。

[0668] 用CO_2对供体小鼠实施安乐死。打开胸腔,穿刺左心室,并且用5mL NaCl(4℃,0.9%)灌注动脉循环系统。采集降主动脉并移植到受体小鼠体内,以建立主动脉同种异体移植物模型。可替代地,如图2所示,可以采集供体小鼠的整个心脏并将其移植到受体小鼠体内,以建立实体器官移植小鼠模型。

[0669] 受体C57BL/6J小鼠通过吸入5%的异氟烷麻醉。腹膜内注射Novalgin(500mg/mL;

200mg/kg体重)和Carprive(50mg/mL卡洛芬,5mg/kg体重)。打开受体小鼠的腹腔,并且解剖肾下主动脉。应用钛夹,并且切断主动脉。移植物通过两个端对端吻合连接到受体主动脉(Prolene 11-0,尼龙黑,瑞士纽豪森的S&T公司(S&T,Neuhausen,Switzerland))。取出夹子后,重新灌注移植物。(Remes等人,《分子疗法:方法与临床开发》第15卷2019年12月)。

[0670] 用tris缓冲盐水处理含有移植的主动脉(n=5)的受体小鼠的对照子集,并且用ENPP3或ENPP3-Fc处理具有移植的主动脉(n=5)的受体小鼠的实验子集,以确定ENPP3-Fc对同种异体移植物中血管平滑肌细胞增殖的影响。ENPP3-Fc处理(每天皮下注射10mg/kg体重的ENPP3-Fc)在实验小鼠组的主动脉移植后开始,并且持续28天,直到采集移植的主动脉。类似地,对照小鼠组在主动脉移植后通过皮下注射每天用pH 7.4的Tris缓冲盐水处理,持续28天,直到采集移植的主动脉。然后用PBS中的4%多聚甲醛固定动脉进行形态学分析。

[0671] 收集连续切片(每个切片5μm)。从不同间隔中随机选择整个移植的移植物的5-μm厚的冷冻主动脉切片(Microtom,HM 5000),并且使用弹性van Gieson染色(德国卡尔斯鲁厄的Roth公司)进行染色。使用了ImageJ软件测量外部弹性膜、内部弹性膜和内腔边缘的圆周。之后,使用ImageJ(斐济版本1.51p,美国国立卫生研究院)测量新生内膜和内侧区域,两名研究人员对处理方案不知情。两个分析的参数的比率用作内腔阻塞的度量。计算了中层面积、内膜面积和内膜/中层比率(I/M比率)。

[0672] 使用学生t检验(针对平均值的未配对双样品检验)进行统计分析。多个组的比较使用单向ANOVA,之后用GraphPad Prism软件版本7进行邦费罗尼后测试。概率值$p<0.05$被认为是显著的。形态测定分析显示,对照未经处理的小鼠出现血管病变和强烈重塑,伴有高度的血管内腔阻塞。

[0673] 在移植后用ENPP3或ENPP3-Fc处理的实验小鼠中,将内膜增生程度与未接受ENPP3或ENPP3-Fc的对照小鼠进行比较。未经处理的对照小鼠移植主动脉的连续切片的定量分析预期显示出显著增加的新生内膜增殖,并且这也与移植后28天或之后ENPP3或ENPP3-Fc处理的小鼠进行了比较。预期对照小鼠显示动脉内膜增厚,并且这与处理的小鼠进行了比较。相应地,比较了对照和处理的小鼠的I/M比率。

[0674] 实例6:ENPP3或ENPP3-Fc的预防作用

[0675] 修改实例5中所描述的相同实验,以通过在主动脉移植前一周向实验组施用ENPP3或ENPP3-Fc来确定ENPP3或ENPP3-Fc在预防或减少同种异体移植物血管病方面的预防作用,如图1所示。同样,在主动脉移植前一周向对照组施用Tris缓冲盐水。然后,在移植后用10mg/kg剂量的ENPP3或ENPP3-Fc处理实验组,并且在移植后用Tris缓冲盐水处理对照组,重复上述过程。形态分析预期表明,与对照小鼠相比,接受皮下ENPP3或ENPP3-Fc的实验小鼠的内膜面积预期会显著减少,而外部内膜与内部内膜之间的中层面积保持恒定。I/M比率显示,与媒剂处理的对照小鼠相比,ENPP3或ENPP3-Fc处理的实验小鼠在统计学上显著降低,表明在主动脉移植前预防性处理ENPP3和ENPP3-Fc显示出通过降低VSMC增殖水平的保护作用。

[0676] 实例7:主动脉同种异体移植物的大鼠模型

[0677] 可以使用大鼠模型代替小鼠模型进行与实例5中描述的相同的实验。用于移植的大鼠模型在以下中进行了描述:Bogossian等人,(2016)《心血管疗法》34(4):183。在移植外科手术后28天比较ENPP3或ENPP3-Fc处理的大鼠和接受主动脉同种异体移植物的对照大鼠

(接受Tris缓冲盐水)。

[0678] 实例8:ENPP3-Fc融合蛋白对猪心脏移植模型中心脏同种异体移植物血管病(CAV)的功效

[0679] CAV仍然是移植1年后同种异体移植物失效的主要原因。心脏同种异体移植物血管病表现为加速的弥漫性冠状动脉硬化,其发病机制与传统的天然冠状动脉疾病(CAD)不同。ENPP3或ENPP3-Fc融合蛋白的功效在器官移植的大型动物模型中进行了评估,特别是家(约克郡(Yorkshire))猪的心脏移植中。评估了ENPP3或ENPP3-Fc融合蛋白在约克郡猪心脏移植后抑制狭窄的能力。

[0680] 供体-受体对的选择基于混合淋巴细胞反应(MLR)的主要组织相容性复合体不相容性。刺激指数(SI)通过下式计算:(同种异体MLR的平均cpm)/(自体MLR的平均cpm)。供体心脏通过肾下同种异体移植异位移植到受体猪腹部。选择的移植供体和受体使用唑来泰(替利他明加唑拉西泮,5mg/kg)和琥珀胆碱(1.1mg/kg)和阿托品(0.6mg/kg)进行麻醉,并且在插管后通过呼吸机施用使用异氟烷(3%/1.5升/分钟)维持麻醉。将受体置于左侧卧位,并且建立血管通路,用于施用免疫抑制药物。

[0681] 建立右胁腹切口,并且通过腹膜后途径,分离肾下主动脉和下腔静脉(参见图3)。接下来,将供体肝素化(静脉内注射(i.v.)300IU/kg),并在使用冷(4℃)心脏停搏液实现心脏停止后采集供体心脏。在每个供体心脏中建立房间隔缺损,并且对二尖瓣去功能化,以最小化左心室萎缩和腔内血栓形成。将受体肝素化(300IU/kg i.v.),并且用连续的5-0聚丙烯缝合线将供体的肺动脉与下腔静脉的1cm至2cm静脉切口进行端对端吻合。随后,以类似的方式将供体心脏的升主动脉与受体的腹主动脉吻合,然后施用鱼精蛋白(1.5mg/kg;)以止血。(Hsu等人,《移植》2018年12月;102(12):2002-2011)。

[0682] 每天通过触诊监测心脏同种异体移植物的起搏频率,并且每周进行两次心电图。当同种异体移植物的起搏频率降低时,进行超声心动图评估收缩功能。随访持续到同种异体移植物停止或研究结束日期(150天)。

[0683] 用tris缓冲盐水处理含有移植的心脏(n=12)的受体猪的对照子集,并且用ENPP3或ENPP3-Fc处理具有移植的心脏(n=12)的受体猪的实验子集,以确定ENPP3多肽对实体器官移植中血管平滑肌细胞增殖的影响。ENPP3或ENPP3-Fc处理(每四天皮下注射10mg/kg体重的ENPP3或ENPP3-Fc)在实验猪组的心脏移植后开始,并且持续150天,直到采集移植的心脏。类似地,对照猪组在心脏移植后通过腹膜内注射每4天用pH 7.4的Tris缓冲盐水处理,持续150天,直到采集移植的心脏。

[0684] 福尔马林固定的心脏样本包埋在石蜡中,切片、脱蜡、再水合,然后进行苏木精和伊红(HE)或地衣红染色。使用蔡司显微镜检查血管移植物的内膜增生,并且根据地衣红染色的切片的计算机图像确定。使用图像分析程序(图像J,版本1.46r,NIH图像)计算由内部弹性膜(IELA)包围的面积和内腔面积(LA)。内膜增生的严重程度使用下式计算:[(IELA-LA)/IELA]×100%。计算后,在5个切片的每个冠状动脉截面的3个随机选择的区域中,以盲检方式评估每个移植物内膜增生的严重程度,并且将评估的严重程度取平均值进行统计分析。

[0685] 使用学生t检验(针对平均值的未配对双样品检验)进行统计分析。多个组的比较使用单向ANOVA,之后用GraphPad Prism软件版本7进行邦费罗尼后测试。概率值$p<0.05$被

认为是显著的。形态测定分析显示,对照未经处理的猪出现血管病变和强烈重塑,伴有高度的血管内腔阻塞。

[0686] 在移植后用ENPP3或ENPP3-Fc处理的实验猪中,通过对连续切片进行定量和定性分析,确定对照以及ENPP3处理的猪的内膜增生程度。预期对照猪在移植后150天会表现出明显增加的新生内膜增殖。预期对照猪显示动脉内膜增厚,并且将处理的猪与对照进行比较。相应地,比较了对照和处理的猪的I/M比率。还确定了对照以及ENPP3处理组的中值存活时间。还确定了对照以及ENPP3处理组的移植物存活时间。

[0687] 实例9:ENPP1-Fc融合蛋白在支架内再狭窄模型中的功效

[0688] 在外周血管损伤的大型动物模型中评估了ENPP1-Fc融合蛋白的功效,特别是在家(约克郡)猪外周血管系统的支架内再狭窄病变中。评估了ENPP1-Fc融合蛋白的治疗效果,以评估其抑制先前受伤且支架化外周动脉的约克郡猪血管成形术后狭窄的能力。

[0689] 在每只动物中创建四个外周动脉部位以诱导新生内膜应答;在四条动脉(双侧深动脉和股浅动脉)中各选择一个部位。

[0690] 在第0天,在第一剂量的ENPP1-Fc或仅媒剂对照前10天,以及在重复损伤前14天,所有靶部位都受到损伤,以建立支架内再狭窄模型。使用定量血管性血管造影术(QVA)绘制四个外周动脉部位,以选择治疗部位和正确尺寸的球囊和支架。损伤是通过用标准的血管成形术球囊导管在靶标130%的过度拉伸下对动脉进行过度拉伸造成的;进行三次充气。损伤后立即展开裸金属支架。外周支架是可自膨胀的,目标是约120%的过度拉伸。

[0691] ENPP1-Fc治疗从第10天开始全身性进行,并且每4天皮下给药一次,直到终止。在第14天,通过血管造影术和光学相干断层扫描(OCT)评估所有血管。然后,让先前受伤的和支架化的动脉部位经历再损伤事件,所述再损伤事件由以下组成:动脉过度拉伸,标准血管成形术球囊导管在与最初支架植入前损伤相同的压力/直径(基线参考直径的130%)下进行单次充气。再损伤干预后,还记录了选定外周部位的最终术后血管造影术和OCT。

[0692] 在第14天再损伤事件后四周,动脉经历了血管造影术和血管内成像(OCT)的重复成像。将处理过的外周节段移出并储存在10%中性缓冲福尔马林中。

[0693] 如图4所示,血管造影术显示在给予媒剂对照的动物中,相对于第14天的血管形态,第42天的深动脉明显变窄。相比之下,在用ENPP1-Fc治疗的动物中,在第14天与第42天之间,观察到深动脉形态几乎没有明显变化。类似地,如通过OCT测量的,在用媒剂对照治疗的动物中,相对于第14天的血管形态,在第42天的深动脉内观察到明显的内膜增厚。相比之下,在第14天与第42天之间,在用ENPP1-Fc治疗的动物的深动脉中观察到很少可见的内膜增厚(图5)。

[0694] 表1和表2(如下)总结了治疗组所有深动脉的平均OCT值。

[0695] 表1.

[0696]

	第14天再损伤,深动脉				
	内腔面积(mm^2)	支架面积(mm^2)	新生内膜厚度(mm)	新生内膜面积(mm^2)	狭窄面积%
ENPP1-Fc	12.10±1.09	14.59±1.24	0.19±0.04	2.49±0.52	17±3
对照	10.82±1.06	13.60±0.82	0.23±0.04	2.78±0.40	21±4

[0697] 表2.

[0698]

	第42天终止，深动脉				
	内腔面积（mm^2）	支架面积（mm^2）	新生内膜厚度（mm）	新生内膜面积（mm^2）	狭窄面积%
ENPP1-Fc	12.95 ± 0.70	16.47 ± 0.89	0.27 ± 0.08	3.52 ± 1.07	21 ± 5
对照	9.51 ± 2.24	14.60 ± 1.40	0.45 ± 0.16	5.10 ± 1.34	35 ± 11

[0699] 如表中所阐述的，与媒剂对照组相比，用ENPP1-Fc治疗的动物的深动脉在第42天具有更高的内腔面积。两组支架面积相似。相对于媒剂对照动物，用ENPP1-Fc治疗的动物在第42天的新生内膜厚度和新生内膜面积也有所减少。另外，与媒剂对照组相比，用ENPP1-Fc治疗的动物的狭窄面积百分比显著降低(参见图6)。这些数据表明，ENPP1多肽尤其可用于抑制与外周血管的损伤和/或外周动脉相关的内膜增厚：

[0700] 实例10：ENPP3-Fc融合蛋白在支架内再狭窄模型中的功效

[0701] 在外周血管损伤的大型动物模型中评估了ENPP3-Fc融合蛋白的功效，特别是在家(约克郡)猪外周血管系统的支架内再狭窄病变中。评估了ENPP3-Fc融合蛋白的治疗效果，以评估其抑制先前受伤且支架化外周动脉的约克郡猪血管成形术后狭窄的能力。

[0702] 在每只动物中创建四个外周动脉部位以诱导新生内膜应答；在四条动脉(双侧深动脉和股浅动脉)中各选择一个部位。

[0703] 在第0天，在第一剂量的ENPP3-Fc或仅媒剂对照前10天，以及在重复损伤前14天，所有靶部位都受到损伤，以建立支架内再狭窄模型。使用定量血管性血管造影术(QVA)绘制四个外周动脉部位，以选择治疗部位和正确尺寸的球囊和支架。损伤是通过用标准的血管成形术球囊导管在靶标130％的过度拉伸下对动脉进行过度拉伸造成的；进行三次充气。损伤后立即展开裸金属支架。外周支架是可自膨胀的，目标是约120％的过度拉伸。

[0704] ENPP3-Fc处理将从第10天开始全身性启动，并且每4天皮下给药一次，直到终止。在第14天，通过血管造影术和光学相干断层扫描(OCT)评估所有血管。然后让先前受伤的和支架化的动脉部位经历再损伤事件，所述再损伤事件由以下组成：动脉过度拉伸，标准血管成形术球囊导管在与最初支架植入前损伤相同的压力/直径(基线参考直径的130％)下进行单次充气。再损伤干预后，还记录了选定外周部位的最终术后血管造影术和OCT。

[0705] 在第14天再损伤事件后四周，动脉将经受血管造影术和血管内成像(OCT)的重复成像。处理过的外周节段将被移出并储存在10％中性缓冲福尔马林中。

[0706] 实例11：ENPP1或ENPP1-Fc融合蛋白在MMD小鼠模型中的功效

[0707] 烟雾病是一种脑血管病症，其特征在于颅内颈动脉的进行性狭窄，导致出血性和缺血性中风两者，通过ICA的血流受到限制，最终导致皮层下区域出现类似“烟雾”(日语中为moyamoya)的新血管。本实例的目的是评估ENPP1-Fc融合蛋白或ENPP1在治疗MMD小鼠模型中的功效。ENPP1-Fc融合蛋白或ENPP1的治疗效果是关于抑制MMD中血管平滑肌细胞增殖和减少或预防脑闭塞的能力来评估的。

[0708] MMD表型的产生

[0709] 从杰克逊实验室(Jackson Laboratories)获得的C57Bl/6雄性小鼠(5周至6周龄)用氯胺酮和甲苯噻嗪的混合物使用重量比麻醉。小鼠麻醉后，对其颈部区域剃毛，并且将小鼠置于仰卧位，其头部、前爪和尾部受到约束(图8)。在小鼠处于仰卧位的情况下，用酒精和必妥碘(betadine)清洁剃毛的区域。从下颌骨到胸骨的角度进行中线切口，暴露气管、颈总

动脉(CCA)和CCA分为颈内动脉和颈外动脉(ICA/ECA)的分叉。牵开器用于保持皮肤和分离的唾液腺不妨碍外科手术区域。为了增加视场,胸锁乳突(SCM)肌和二腹(PBD)肌的后腹部分别暴露在下方和上方。将一对弯钳的尖端轻轻放置在SCM内侧到外侧下方,并且在下方转移一条长度为4±0的缝合线。缝合线环绕SCM并使用胶带固定。对PBD重复此步骤。

[0710] 隔离ICA后,6±0缝合线用作线圈放置的锚。细尖钳用于在一端抓住线圈,并且将其与ICA成一定角度,以便血管插入线圈的最后的横档中。当血管位于线圈的最后的横档中时,线圈反转,使其与ICA平行。使用6±0缝合线,轻轻地围绕线圈旋转血管,以便在线圈的每个横档中放置一定长度的血管。评估血管放置,以确保其不会跳过横档;如果是这样,则将血管展开并重新定位,直到线圈完全包围血管。因此,小鼠的对照和实验子集两者中的MMD表型都是通过遵循Roberts等人讨论的程序诱导的。(Roberts等人,颈内动脉狭窄一种治疗烟雾病综合征的新型外科手术模型,《公共科学图书馆·综合》2018;13(1):e0191312)。

[0711] MMD模型小鼠(n=5)的对照子集用tris缓冲盐水处理,并且MMD小鼠(n=5)的实验子集在MMD表型诱导后用ENPP1或ENPP1-Fc处理,以确定ENPP1或ENPP1-Fc对MMD小鼠脑中血管平滑肌细胞增殖和脑闭塞的影响。ENPP1或ENPP1-Fc处理(每天皮下注射10mg/kg体重的ENPP1或ENPP1-Fc)在实验小鼠组中通过如上所述的外科手术诱导MMD表型后开始,并且继续施用ENPP1或ENPP1-Fc,持续28天,直到采集脑动脉。

[0712] 类似地,对照小鼠组在通过如所描述的外科手术诱导MMD表型后用pH 7.4的Tris缓冲盐水处理,每天通过皮下注射施用Tris缓冲盐水,并且持续28天,直到采集脑动脉。然后用PBS中的4%多聚甲醛固定患有MMD的对照和实验组小鼠的动脉,进行形态分析。

[0713] 脑血管的可视化

[0714] 为了可视化脑血管,每组的所有动物都灌注荧光染料Di I((Li等人,用亲脂性碳花菁染料DiI直接标记和可视化血管(Direct labeling and visualization of blood vessels with lipophilic carbocyanine dye DiI).《自然实验室指南(Nat Protoc.)》2008;3(11):1703±8)。使用灌注泵(设置为1毫升/分钟)对小鼠进行经心灌注,以灌注(室温)5ml的PBS,随后立即灌注10ml的Di I工作溶液,并且然后灌注10ml的10%缓冲福尔马林。脑被小心地从颅骨中取出,以确保韦利斯氏环(CoW)保持完整。

[0715] 然后将提取的脑在4℃下用10%缓冲福尔马林固定过夜。然后将脑转移到PBS中,在4℃下长期保存并避光。使用1X显微镜(Nikon Eclipse E800/Nikon DS-Ril)对荧光标记的脑进行成像。皮质血管系统的图像被用来检查吻合,并且CoW的图像被用于测量血管直径。使用Nikon NES Analysis软件进行图像分析,以测量血管直径(μm)。

[0716] 直径测量是从床突上段颈内动脉分叉处约20μm处、脑中动脉的M1段和脑前动脉的A1段进行的。吻合分析通过计数同侧和对侧半球两者的ACA与MCA之间的吻合数量(放在放大图像上每个连接点上的圆圈)进行。通过测量同侧和对侧两者的分叉点附近的每条血管的宽度来检查ICA、ACA和MCA血管的直径,以确定实验组与对照组之间的大小是否存在差异。

[0717] 形态分析

[0718] 为对照组和实验组两者收集脑动脉(如MCA、ACA和ICA)的连续切片(每个切片5μm)。5-μm厚的冷冻主动脉切片(Microtom,HM 5000)通过使用弹性van Gieson染色(德国卡

尔斯鲁厄的Roth公司)进行染色。使用了ImageJ软件测量外部弹性膜、内部弹性膜和内腔边缘的圆周。之后,使用ImageJ(斐济版本1.51p,美国国立卫生研究院)测量新生内膜和内侧区域,两名研究人员对处理方案不知情。两个分析的参数的比率用作内腔阻塞的度量。计算了中层面积、内膜面积和内膜/中层比率(I/M比率)。(参见图2)。

[0719] 使用学生t检验(针对平均值的未配对双样品检验)进行统计分析。多个组的比较使用单向ANOVA,之后用GraphPad Prism软件版本7进行邦费罗尼后测试。概率值$p<0.05$被认为是显著的。形态测定分析显示,具有MMD表型的对照未经处理的小鼠出现血管病变、闭塞和变窄,伴有高度的血管内腔阻塞。

[0720] 在MMD表型诱导后用ENPP1或ENPP1-Fc处理的实验小鼠中,将内膜增生程度与未接受ENPP1或ENPP1-Fc的对照小鼠进行比较。来自具有MMD表型的未经处理的对照小鼠的脑动脉的定量分析预期显示出显著增加的新生内膜增殖,并且这也与外科手术后28天或之后ENPP1或ENPP1-Fc处理的小鼠进行了比较。预期对照小鼠表现出动脉内膜增厚,并且这与处理的小鼠进行了比较。相应地,也比较了对照和处理的小鼠的I/M比率。

[0721] 实例12:ENPP1或ENPP1-Fc的预防作用

[0722] 修改实例11中所描述的相同实验,以通过在MMD表型诱导前一周向实验组施用ENPP1或ENPP1-Fc来确定ENPP1或ENPP1-Fc在预防或减少血管平滑肌增殖与脑闭塞方面的预防作用,如图7所示。同样,在MMD表型诱导前一周向对照组施用Tris缓冲盐水。然后,在外科手术后用10mg/kg剂量的ENPP1或ENPP1-Fc处理实验组,并且在外科手术后用Tris缓冲盐水处理对照组,重复上述过程。

[0723] 形态分析预期表明,与对照小鼠相比,接受皮下ENPP1或ENPP1-Fc的具有MMD表型的实验小鼠的内膜面积预期会显著减少,而外部内膜与内部内膜之间的中层面积保持恒定。与媒剂处理的对照小鼠相比,ENPP1或ENPP1-Fc处理的实验小鼠的I/M比率预期会降低。在MMD表型诱导之前预防性处理ENPP1或ENPP1-Fc预期会通过降低VSMC增殖水平而产生保护作用。

[0724] 实例13:ENPP3或ENPP3-Fc融合蛋白在MMD小鼠模型中的功效

[0725] 烟雾病是一种脑血管病症,其特征在于颅内颈动脉的进行性狭窄,导致出血性和缺血性中风两者,通过ICA的血流受到限制,最终导致皮层下区域出现类似“烟雾”(日语中为moyamoya)的新血管。本实例的目的是评估ENPP3-Fc融合蛋白或ENPP3在治疗MMD小鼠模型中的功效。ENPP3-Fc融合蛋白或ENPP3的治疗效果是关于抑制MMD中血管平滑肌细胞增殖和减少或预防脑闭塞的能力来评估的。

[0726] MMD表型的产生

[0727] 从杰克逊实验室获得的C57Bl/6雄性小鼠(5周至6周龄)用氯胺酮和甲苯噻嗪的混合物使用重量比麻醉。小鼠麻醉后,对其颈部区域剃毛,并且将小鼠置于仰卧位,其头部、前爪和尾部受到约束(图8)。在小鼠处于仰卧位的情况下,用酒精和必妥碘(betadine)清洁剃毛的区域。从下颌骨到胸骨的角度进行中线切口,暴露气管、颈总动脉(CCA)和CCA分为颈内动脉和颈外动脉(ICA/ECA)的分叉。牵开器用于保持皮肤和分离的唾液腺不妨碍外科手术区域。为了增加视场,胸锁乳突(SCM)肌和二腹(PBD)肌的后腹部分别暴露在下方和上方。将一对弯钳的尖端轻轻放置在SCM内侧到外侧下方,并且在下方转移一条长度为4±0的缝合线。缝合线环绕SCM并使用胶带固定。对PBD重复此步骤。

[0728] 隔离ICA后,6±0缝合线用作线圈放置的锚。细尖钳用于在一端抓住线圈,并且将其与ICA成一定角度,以便血管插入线圈的最后的横档中。当血管位于线圈的最后的横档中时,线圈反转,使其与ICA平行。使用6±0缝合线,轻轻地围绕线圈旋转血管,以便在线圈的每个横档中放置一定长度的血管。评估血管放置,以确保其不会跳过横档;如果是这样,则将血管展开并重新定位,直到线圈完全包围血管。因此,小鼠的对照和实验子集两者中的MMD表型都是通过遵循Roberts等人讨论的程序诱导的。(Roberts等人,颈内动脉狭窄一种治疗烟雾病综合征的新型外科手术模型,《公共科学图书馆·综合》2018;13(1):e0191312)。

[0729] MMD模型小鼠(n=5)的对照子集用tris缓冲盐水处理,并且MMD小鼠(n=5)的实验子集在MMD表型诱导后用ENPP3-Fc或ENPP3处理,以确定ENPP3-Fc或ENPP3对MMD小鼠脑中血管平滑肌细胞增殖和脑闭塞的影响。ENPP3-Fc处理(每天皮下注射10mg/kg体重的ENPP3或ENPP3-Fc)在实验小鼠组中通过如上所述的外科手术诱导MMD表型后开始,并且继续施用ENPP3-Fc或ENPP3,持续28天,直到采集脑动脉。

[0730] 类似地,对照小鼠组在通过如所描述的外科手术诱导MMD表型后用pH 7.4的Tris缓冲盐水处理,每天通过皮下注射施用Tris缓冲盐水,并且持续28天,直到采集脑动脉。然后用PBS中的4%多聚甲醛固定患有MMD的对照和实验组小鼠的动脉,进行形态分析。

[0731] 脑血管的可视化

[0732] 为了可视化脑血管,每组的所有动物都灌注荧光染料Di I((Li等人,用亲脂性碳花菁染料DiI直接标记和可视化血管.《自然实验室指南》2008;3(11):1703±8)。使用灌注泵(设置为1毫升/分钟)对小鼠进行经心灌注,以灌注(室温)5ml的PBS,随后立即灌注10ml的Di I工作溶液,并且然后灌注10ml的10%缓冲福尔马林。脑被小心地从颅骨中取出,以确保韦利斯氏环(CoW)保持完整。

[0733] 然后将提取的脑在4℃下用10%缓冲福尔马林固定过夜。然后将脑转移到PBS中,在4℃下长期保存并避光。使用1X显微镜(Nikon Eclipse E800/Nikon DS-Ril)对荧光标记的脑进行成像。皮质血管系统的图像被用来检查吻合,并且CoW的图像被用于测量血管直径。使用Nikon NES Analysis软件进行图像分析,以测量血管直径(μm)。

[0734] 直径测量是从床突上段颈内动脉分叉处约20μm处、脑中动脉的M1段和脑前动脉的A1段进行的。吻合分析通过计数同侧和对侧半球两者的ACA与MCA之间的吻合数量(放在放大图像上每个连接点上的圆圈)进行。通过测量同侧和对侧两者的分叉点附近的每条血管的宽度来检查ICA、ACA和MCA血管的直径,以确定实验组与对照组之间的大小是否存在差异。

[0735] 具有MMD表型的对照小鼠的远端ICA和近端ACA的测量结果预期在外科手术后血管直径会严重变窄,并且这与ENPP3或ENPP3-Fc处理的具有MMD表型的小鼠的血管直径进行了比较。

[0736] 形态分析

[0737] 为对照组和实验组两者收集脑动脉(如MCA、ACA和ICA)的连续切片(每个切片5μm)。5-μm厚的冷冻主动脉切片(Microtom,HM 5000)通过使用弹性van Gieson染色(德国卡尔斯鲁厄的Roth公司)进行染色。使用了ImageJ软件测量外部弹性膜、内部弹性膜和内腔边缘的圆周。之后,使用ImageJ(斐济版本1.51p,美国国立卫生研究院)测量新生内膜和内侧

区域,两名研究人员对处理方案不知情。两个分析的参数的比率用作内腔阻塞的度量。计算了中层面积、内膜面积和内膜/中层比率(I/M比率)。(参见图2)。

[0738] 使用学生t检验(针对平均值的未配对双样品检验)进行统计分析。多个组的比较使用单向ANOVA,之后用GraphPad Prism软件版本7进行邦费罗尼后测试。概率值$p<0.05$被认为是显著的。形态测定分析显示,具有MMD表型的对照未经处理的小鼠出现血管病变、闭塞和变窄,伴有高度的血管内腔阻塞。

[0739] 在MMD表型诱导后用ENPP3或ENPP3-Fc处理的实验小鼠中,将内膜增生程度与未接受ENPP3或ENPP3-Fc的对照小鼠进行比较。来自具有MMD表型的未经处理的对照小鼠的脑动脉的定量分析预期显示出显著增加的新生内膜增殖,并且这也与外科手术后28天或之后ENPP3或ENPP3-Fc处理的小鼠进行了比较。预期对照小鼠表现出动脉内膜增厚,并且这与处理的小鼠进行了比较。相应地,也比较了对照和处理的小鼠的I/M比率。

[0740] 实例14:ENPP3或ENPP3-Fc的预防作用

[0741] 修改实例13中所描述的相同实验,以通过在MMD表型诱导前一周向实验组施用ENPP3或ENPP3-Fc来确定ENPP3或ENPP3-Fc在预防或减少血管平滑肌增殖与脑闭塞方面的预防作用,如图7所示。同样,在MMD表型诱导前一周向对照组施用Tris缓冲盐水。然后,在外科手术后用10mg/kg剂量的ENPP3或ENPP3-Fc处理实验组,并且在外科手术后用Tris缓冲盐水处理对照组,重复上述过程。

[0742] 形态分析预期表明,与对照小鼠相比,接受皮下ENPP3或ENPP3-Fc的具有MMD表型的实验小鼠的内膜面积预期会显著减少,而外部内膜与内部内膜之间的中层面积保持恒定。与媒剂处理的对照小鼠相比,ENPP3或ENPP3-Fc处理的实验小鼠的I/M比率预期会降低。在MMD表型诱导之前预防性处理ENPP3或ENPP3-Fc预期会通过降低VSMC增殖水平而产生保护作用。

[0743] 实例15:ENPP1或ENPP1-Fc融合蛋白在AV瘘衰竭的小鼠模型中的功效

[0744] ENPP1或ENPP1-Fc融合蛋白的功效在动静脉瘘衰竭的小鼠模型中进行评估,例如以下中所描述的:Wong等人,(2014)《血管外科杂志(J Vasc Surg)》59:192-201。在雄性C57b16小鼠的颈外静脉与颈总动脉之间建立单侧AVF。小鼠分为四个队列:(1)在建立AVF之前和之后用ENPP1-Fc融合蛋白或ENPP1接受慢性皮下处理的小鼠;(2)在建立AVF之前和之后接受皮下媒剂对照处理的小鼠;(3)在AVF建立后开始用ENPP1-Fc融合蛋白或ENPP1进行慢性皮下处理的小鼠;以及(4)在AVF建立后接受皮下媒剂对照处理的小鼠。

[0745] 随着时间的推移,对小鼠进行跟踪,并且在不同的时间点(如AVF建立后的一周、两周和/或三周)实施安乐死。对AVF部位或其近端的血管切片进行组织学分析。

[0746] 预计与接受媒剂对照的小鼠相比,用ENPP1-Fc融合蛋白处理的小鼠的AVF邻近血管中内膜增生的程度将显著降低。

[0747] 实例16:ENPP3或ENPP3-Fc融合蛋白在AV瘘失效的小鼠模型中的功效

[0748] ENPP3-Fc融合蛋白或ENPP3的功效在动静脉瘘衰竭的小鼠模型中进行评估,例如以下中所描述的:Wong等人,(2014)《血管外科杂志》59:192-201。在雄性C57b16小鼠的颈外静脉与颈总动脉之间建立单侧AVF。小鼠分为四个队列:(1)在建立AVF之前和之后用ENPP3-Fc融合蛋白或ENPP3接受慢性皮下处理的小鼠;(2)在建立AVF之前和之后接受皮下媒剂对照处理的小鼠;(3)在AVF建立后开始用ENPP3-Fc融合蛋白或ENPP3进行慢性皮下处理的小

鼠;以及(4)在AVF建立后接受皮下媒剂对照处理的小鼠。

[0749] 随着时间的推移,对小鼠进行跟踪,并且在不同的时间点(如AVF建立后的一周、两周和/或三周)实施安乐死。对AVF部位或其附近的血管切片进行组织学分析。

[0750] 预计与接受媒剂对照的小鼠相比,用ENPP3-Fc融合蛋白处理的小鼠的AVF邻近血管中内膜增生的程度将显著降低。

[0751] 实例17:对患有心脏同种异体移植物血管病的人心脏移植患者的治疗

[0752] 执业医师将一名成人心脏同种异体移植物受体鉴定为患有CAV。受体施用或长期施用包括融合蛋白的药物组合物,所述融合蛋白包括与Fc区融合的可溶性形式的ENPP1。医疗专业人员随着时间的推移监测受体,以停止同种异体移植的心脏的一个或多个血管中不期望的内膜增殖和/或随着时间的推移同种异体移植的心脏中的血管闭塞的部分或完全消退。预期用融合蛋白治疗可阻止或显著减少同种异体移植的心脏的一个或多个血管中不期望的内膜增殖,和/或随着时间的推移部分或完全解决同种异体移植的心脏中的血管闭塞。

[0753] 在另一个实例中,从移植时开始或在移植时前后向心脏同种异体移植物的受体长期施用包括融合蛋白的药物组合物,所述融合蛋白包括与Fc区融合的可溶性形式的ENPP1,以预防、减少同种异体移植的心脏的一个或多个血管中不期望的内膜增殖的发生可能性或减少其程度。医疗专业人员随着时间的推移监测受体的同种异体移植的心脏的一个或多个血管中是否存在不期望的内膜增殖和/或其水平。预期用融合蛋白治疗可阻止或显著减少同种异体移植的心脏的一个或多个血管中不期望的内膜增殖。

[0754] 实例18:患有烟雾病的人的治疗

[0755] 一名人类成年患者被执业医师鉴定为患有烟雾病。受体施用或长期施用包括融合蛋白的药物组合物,所述融合蛋白包括与Fc区融合的可溶性形式的ENPP1。医疗专业人员随着时间的推移监测受体,以停止一个或多个供给脑的血管中不期望的内膜增殖和/或随着时间的推移此类血管闭塞的部分或完全消退。预期用融合蛋白治疗可阻止或显著减少一个或多个血管中不期望的内膜增殖,和/或随着时间的推移部分或完全解决血管闭塞。

[0756] 实例19:接受血液透析分流器的透析患者的治疗

[0757] 血液透析分流器放置在受试者体内时或前后向血液透析患者长期施用包括融合蛋白的药物组合物,所述融合蛋白包括与Fc区融合的可溶性形式的ENPP1,由此预防、减少连接到分流器或涉及分流器的一个或多个血管中不期望的内膜增殖的发生可能性或减少其程度。医疗专业人员随着时间的推移监测受体的一个或多个血管中是否存在不期望的内膜增殖和/或其水平。预期用融合蛋白治疗可阻止或显著减少一个或多个血管中不期望的内膜增殖。

[0758] 通过引用并入

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[0766] 其它实施例在以下权利要求内。

序列表

<110> 依诺兹梅制药公司(Inozyme Pharma, Inc.)

明斯特威斯特法伦威廉大学(Westfaelische Wilhelms-Universitaet Muenster)

<120> 用于治疗同种异体移植物血管病、烟雾病、烟雾病综合征和内膜增殖的组合物和方法

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Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly
305 310 315 320
Met Val Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg
325 330 335
Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser

340 345 350

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

355 360 365

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

370 375 380

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

385 390 395 400

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

405 410 415

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

420 425 430

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

435 440 445

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

450 455 460

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465 470 475 480

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

485 490 495

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

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

515 520 525

Glu Val His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp

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Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe

545 550 555 560

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

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Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr

580 585 590

Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp

595 600 605

Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser

610 615 620

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625 630 635 640

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

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Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser
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Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr
675 680 685
Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg
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Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val
705 710 715 720
Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg
725 730 735
Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His
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Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu
755 760 765
His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr
770 775 780
Asp Asn Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val
785 790 795 800
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865 870 875 880
Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu
885 890 895
Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu
900 905 910
His Ala Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val
915 920 925
Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe
930 935 940
Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu
945 950 955 960
Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe

965 970 975
Leu Gln His Lys Asp Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro
980 985 990
Glu Ala Glu Ala Met Cys Thr Ser Phe Lys Glu Asn Pro Thr Thr Phe
995 1000 1005
Met Gly His Tyr Leu His Glu Val Ala Arg Arg His Pro Tyr Phe
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Pro Lys Leu Asp Gly Val Lys Glu Lys Ala Leu Val Ser Ser Val
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1340 1345 1350
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1355 1360 1365
Glu Thr Tyr Val Pro Lys Glu Phe Lys Ala Glu Thr Phe Thr Phe
1370 1375 1380
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1385 1390 1395
Lys Gln Thr Ala Leu Ala Glu Leu Val Lys His Lys Pro Lys Ala
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35 40 45
Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys Ile Glu
50 55 60
Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu Lys Arg
65 70 75 80
Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp Lys Gly
85 90 95
Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp
100 105 110
Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro Ala Gly
115 120 125
Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe Arg Ala
130 135 140
Glu Tyr Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser Lys Leu
145 150 155 160
Lys Lys Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr
165 170 175
Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu
180 185 190
Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala
195 200 205
Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys
210 215 220
Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly
225 230 235 240
Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro
245 250 255
Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile
260 265 270
Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His
275 280 285
Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr
290 295 300
Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly

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Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser
340 345 350
Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn
355 360 365
Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val
370 375 380
Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu
385 390 395 400
Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe
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Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser
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Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr
580 585 590
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Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys
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Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr
675 680 685
Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg
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Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val
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755 760 765
Ser Cys Ala Lys Glu Val Lys Ser Cys Lys Gly Arg Cys Phe Glu Arg
770 775 780
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785 790 795 800
Cys Cys Leu Asp Tyr Gln Glu Thr Cys Ile Glu Pro Glu His Ile Trp
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Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp Val Glu Glu Pro Cys
850 855 860
Glu Ser Ile Asn Glu Pro Gln Cys Pro Ala Gly Phe Glu Thr Pro Pro
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Trp Gly Gly Leu Leu Pro Val Ile Ser Lys Leu Lys Lys Cys Gly Thr
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Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr Lys Thr Phe Pro Asn
915 920 925
His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly Ile Ile

930 935 940

Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala Ser Phe Ser Leu Lys

945 950 955 960

Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys Gly Glu Pro Ile Trp

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Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly Thr Phe Phe Trp Pro

980 985 990

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

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Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Leu Ala Val Leu

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Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Asn Leu
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1250 1255 1260
Leu Lys Asn Pro Val Tyr Thr Pro Lys His Pro Lys Glu Val His
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1295 1300 1305
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1310 1315 1320
Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn
1325 1330 1335
Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser
1340 1345 1350
Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg
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Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser
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35 40 45
Asp Ser Pro Trp Thr Asn Ile Ser Gly Ser Cys Lys Gly Arg Cys Phe
50 55 60
Glu Leu Gln Glu Ala Gly Pro Pro Asp Cys Arg Cys Asp Asn Leu Cys
65 70 75 80
Lys Ser Tyr Thr Ser Cys Cys His Asp Phe Asp Glu Leu Cys Leu Lys
85 90 95
Thr Ala Arg Gly Trp Glu Cys Thr Lys Asp Arg Cys Gly Glu Val Arg
100 105 110
Asn Glu Glu Asn Ala Cys His Cys Ser Glu Asp Cys Leu Ala Arg Gly
115 120 125
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130 135 140
Val Asp Asp Asp Cys Glu Glu Ile Lys Ala Ala Glu Cys Pro Ala Gly
145 150 155 160
Phe Val Arg Pro Pro Leu Ile Ile Phe Ser Val Asp Gly Phe Arg Ala
165 170 175

Ser Tyr Met Lys Lys Gly Ser Lys Val Met Pro Asn Ile Glu Lys Leu
180 185 190
Arg Ser Cys Gly Thr His Ser Pro Tyr Met Arg Pro Val Tyr Pro Thr
195 200 205
Lys Thr Phe Pro Asn Leu Tyr Thr Leu Ala Thr Gly Leu Tyr Pro Glu
210 215 220
Ser His Gly Ile Val Gly Asn Ser Met Tyr Asp Pro Val Phe Asp Ala
225 230 235 240
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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
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Ile Leu Gln Trp Leu Thr Leu Pro Asp His Glu Arg Pro Ser Val Tyr
290 295 300
Ala Phe Tyr Ser Glu Gln Pro Asp Phe Ser Gly His Lys Tyr Gly Pro
305 310 315 320
Phe Gly Pro Glu Met Thr Asn Pro Leu Arg Glu Ile Asp Lys Ile Val
325 330 335
Gly Gln Leu Met Asp Gly Leu Lys Gln Leu Lys Leu His Arg Cys Val
340 345 350
Asn Val Ile Phe Val Gly Asp His Gly Met Glu Asp Val Thr Cys Asp
355 360 365
Arg Thr Glu Phe Leu Ser Asn Tyr Leu Thr Asn Val Asp Asp Ile Thr
370 375 380
Leu Val Pro Gly Thr Leu Gly Arg Ile Arg Ser Lys Phe Ser Asn Asn
385 390 395 400
Ala Lys Tyr Asp Pro Lys Ala Ile Ile Ala Asn Leu Thr Cys Lys Lys
405 410 415
Pro Asp Gln His Phe Lys Pro Tyr Leu Lys Gln His Leu Pro Lys Arg
420 425 430
Leu His Tyr Ala Asn Asn Arg Arg Ile Glu Asp Ile His Leu Leu Val
435 440 445
Glu Arg Arg Trp His Val Ala Arg Lys Pro Leu Asp Val Tyr Lys Lys
450 455 460
Pro Ser Gly Lys Cys Phe Phe Gln Gly Asp His Gly Phe Asp Asn Lys
465 470 475 480
Val Asn Ser Met Gln Thr Val Phe Val Gly Tyr Gly Ser Thr Phe Lys

485 490 495

Tyr Lys Thr Lys Val Pro Pro Phe Glu Asn Ile Glu Leu Tyr Asn Val

500 505 510

Met Cys Asp Leu Leu Gly Leu Lys Pro Ala Pro Asn Asn Gly Thr His

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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

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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

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

660 665 670

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

675 680 685

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

690 695 700

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

705 710 715 720

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

725 730 735

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

740 745 750

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

755 760 765

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

770 775 780

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

785 790 795 800

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

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

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Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His Leu Leu Lys
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545 550 555 560
Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val Asp His Cys Leu
565 570 575
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580 585 590
Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp Thr Ser Pro
595 600 605
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Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys Asn Ile
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Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser Asp Ser
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Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro Met Tyr Glu Glu
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Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu Leu Ile Lys His
675 680 685
Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile Phe Asp
690 695 700
Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr Lys His
705 710 715 720
Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val Val Leu
725 730 735
Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro Gly Trp
740 745 750
Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn Val Glu
755 760 765
Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu Arg Phe
770 775 780

Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr Gly Leu
785 790 795 800
Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu Gln Leu
805 810 815
Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile
820 825

<210> 7
<211> 875
<212> PRT
<213> 人工序列
<220>
<223> NPP3氨基酸序列
<400> 7

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

His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly Ile Ile
210 215 220
Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser Leu Ser
225 230 235 240
Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro Met Trp
245 250 255
Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe Trp Pro
260 265 270
Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr Met Pro
275 280 285
Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu Leu Lys
290 295 300
Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr Met Tyr
305 310 315 320
Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val Ser Ala
325 330 335
Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala Phe Gly Met Leu
340 345 350
Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn Ile Ile
355 360 365
Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys Met Glu
370 375 380
Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr Met Tyr Glu
385 390 395 400
Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro His Asp Phe Phe
405 410 415
Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg Lys Pro
420 425 430
Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys Arg Leu
435 440 445
His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His Leu Phe Val Asp
450 455 460
Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys Gly Gly
465 470 475 480
Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala Ile Phe
485 490 495
Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu Pro Phe
500 505 510
Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg Ile Gln

515 520 525

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

530 535 540

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

545 550 555 560

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

565 570 575

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

580 585 590

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

595 600 605

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

610 615 620

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

625 630 635 640

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

645 650 655

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

660 665 670

Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys Asn Ile

675 680 685

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

690 695 700

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

705 710 715 720

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

725 730 735

Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile Phe Asp

740 745 750

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

755 760 765

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

770 775 780

Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro Gly Trp

785 790 795 800

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

805 810 815

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

820 825 830

Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr Gly Leu
835 840 845
Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu Gln Leu
850 855 860
Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile
865 870 875

<210> 8
<211> 1073
<212> PRT
<213> 人工序列
<220>
<223> 天青杀素-ENPP3-FC
<220>
<221> SIGNAL
<222> (19)..(20)
<223> 信号序列的切割点
<220>
<221> MISC_FEATURE
<222> (847)..(1073)
<223> 表示Fc序列
<400> 8

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

Leu Tyr Thr Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys Thr
145 150 155 160
Cys Gly Ile His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr
165 170 175
Phe Pro Asn His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser His
180 185 190
Gly Ile Ile Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn Phe
195 200 205
Ser Leu Ser Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly Gln
210 215 220
Pro Met Asn Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr
225 230 235 240
Phe Trp Pro Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser Ile
245 250 255
Tyr Met Pro Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser Thr
260 265 270
Leu Leu Lys Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr
275 280 285
Thr Met Tyr Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly Pro
290 295 300
Val Ser Ala Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala Phe
305 310 315 320
Gly Met Leu Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys Val
325 330 335
Asn Ile Ile Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys Asn
340 345 350
Lys Met Glu Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr
355 360 365
Met Tyr Glu Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro His
370 375 380
Asp Phe Phe Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser Cys
385 390 395 400
Arg Lys Pro Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro
405 410 415
Lys Arg Leu His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His Leu
420 425 430
Phe Val Asp Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr Asn
435 440 445
Cys Gly Gly Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu

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

Pro Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro Thr
770 775 780
Asn Val Glu Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val Glu
785 790 795 800
Glu Arg Phe Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu
805 810 815
Thr Gly Leu Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile
820 825 830
Leu Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile Asp Lys
835 840 845
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
850 855 860
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
865 870 875 880
Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
885 890 895
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
900 905 910
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
915 920 925
Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
930 935 940
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
945 950 955 960
Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
965 970 975
Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
980 985 990
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
995 1000 1005
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
1010 1015 1020
Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
1025 1030 1035
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
1040 1045 1050
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
1055 1060 1065
Leu Ser Pro Gly Lys

1070

<210> 9

<211> 1464

<212> PRT

<213> 人工序列

<220>

<223> 天青杀素-ENPP3-白蛋白

<220>

<221> SIGNAL

<222> (19)..(20)

<223> 信号序列的切割点

<220>

<221> MISC_FEATURE

<222> (847)..(1464)

<223> 表示白蛋白序列

<400> 9

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

180 185 190

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

195 200 205

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

210 215 220

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

225 230 235 240

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

245 250 255

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

260 265 270

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

275 280 285

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

290 295 300

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

305 310 315 320

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

325 330 335

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

340 345 350

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

355 360 365

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

370 375 380

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

385 390 395 400

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

405 410 415

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

420 425 430

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

435 440 445

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

450 455 460

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

465 470 475 480

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

485 490 495

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

805 810 815

Thr Gly Leu Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile
820 825 830

Leu Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile Met Lys
835 840 845

Trp Val Thr Phe Leu Leu Leu Leu Phe Val Ser Gly Ser Ala Phe Ser
850 855 860

Arg Gly Val Phe Arg Arg Glu Ala His Lys Ser Glu Ile Ala His Arg
865 870 875 880

Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala
885 890 895

Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys Leu
900 905 910

Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Ser
915 920 925

Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu
930 935 940

Cys Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys
945 950 955 960

Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys
965 970 975

Asp Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala
980 985 990

Met Cys Thr Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly His Tyr
995 1000 1005

Leu His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
1010 1015 1020

Leu Leu Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys
1025 1030 1035

Cys Ala Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp
1040 1045 1050

Gly Val Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met
1055 1060 1065

Lys Cys Ser Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala
1070 1075 1080

Trp Ala Val Ala Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe
1085 1090 1095

Ala Glu Ile Thr Lys Leu Ala Thr Asp Leu Thr Lys Val Asn Lys
1100 1105 1110

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala
1115 1120 1125
Glu Leu Ala Lys Tyr Met Cys Glu Asn Gln Ala Thr Ile Ser Ser
1130 1135 1140
Lys Leu Gln Thr Cys Cys Asp Lys Pro Leu Leu Lys Lys Ala His
1145 1150 1155
Cys Leu Ser Glu Val Glu His Asp Thr Met Pro Ala Asp Leu Pro
1160 1165 1170
Ala Ile Ala Ala Asp Phe Val Glu Asp Gln Glu Val Cys Lys Asn
1175 1180 1185
Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Thr Phe Leu Tyr Glu
1190 1195 1200
Tyr Ser Arg Arg His Pro Asp Tyr Ser Val Ser Leu Leu Leu Arg
1205 1210 1215
Leu Ala Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys Cys Ala Glu
1220 1225 1230
Ala Asn Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu Phe Gln
1235 1240 1245
Pro Leu Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys Asp
1250 1255 1260
Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu
1265 1270 1275
Val Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu
1280 1285 1290
Val Glu Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys
1295 1300 1305
Thr Leu Pro Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu
1310 1315 1320
Ser Ala Ile Leu Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro
1325 1330 1335
Val Ser Glu His Val Thr Lys Cys Cys Ser Gly Ser Leu Val Glu
1340 1345 1350
Arg Arg Pro Cys Phe Ser Ala Leu Thr Val Asp Glu Thr Tyr Val
1355 1360 1365
Pro Lys Glu Phe Lys Ala Glu Thr Phe Thr Phe His Ser Asp Ile
1370 1375 1380
Cys Thr Leu Pro Glu Lys Glu Lys Gln Ile Lys Lys Gln Thr Ala
1385 1390 1395
Leu Ala Glu Leu Val Lys His Lys Pro Lys Ala Thr Ala Glu Gln

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

<210> 10
<211> 846
<212> PRT
<213> 人工序列
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<223> 天青杀素-ENPP3
<220>
<221> SIGNAL
<222> (19)..(20)
<223> 信号序列的切割点
<400> 10

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

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

Ala Ile Phe Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu Val
465 470 475 480
Glu Pro Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu
485 490 495
Arg Ile Gln Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His
500 505 510
Leu Leu Lys Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val Ser
515 520 525
Lys Phe Ser Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu
530 535 540
Asp Cys Phe Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln Val
545 550 555 560
Asn Gln Met Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val Lys
565 570 575
Val Asn Leu Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val Asp
580 585 590
His Cys Leu Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala
595 600 605
Met Arg Met Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp
610 615 620
Thr Ser Pro Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp Val
625 630 635 640
Arg Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp
645 650 655
Lys Asn Ile Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr
660 665 670
Ser Asp Ser Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro Met
675 680 685
Tyr Glu Glu Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu Leu
690 695 700
Ile Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro
705 710 715 720
Ile Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu Ile
725 730 735
Thr Lys His Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr Phe
740 745 750
Val Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys
755 760 765
Pro Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro Thr

770 775 780

Asn Val Glu Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val Glu
785 790 795 800

Glu Arg Phe Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu
805 810 815

Thr Gly Leu Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile
820 825 830

Leu Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile
835 840 845

<210> 11

<211> 453

<212> PRT

<213> 人工序列

<220>

<223> ENPP4氨基酸序列-野生型

<400> 11

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

Arg Ser Asp Ser Ser Ser Ser Leu Pro Pro Lys Leu Leu Leu Val Ser
20 25 30

Phe Asp Gly Phe Arg Ala Asp Tyr Leu Lys Asn Tyr Glu Phe Pro His
35 40 45

Leu Gln Asn Phe Ile Lys Glu Gly Val Leu Val Glu His Val Lys Asn
50 55 60

Val Phe Ile Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly
65 70 75 80

Leu Tyr Glu Glu Ser His Gly Ile Val Ala Asn Ser Met Tyr Asp Ala
85 90 95

Val Thr Lys Lys His Phe Ser Asp Ser Asn Asp Lys Asp Pro Phe Trp
100 105 110

Trp Asn Glu Ala Val Pro Ile Trp Val Thr Asn Gln Leu Gln Glu Asn
115 120 125

Arg Ser Ser Ala Ala Ala Met Trp Pro Gly Thr Asp Val Pro Ile His
130 135 140

Asp Thr Ile Ser Ser Tyr Phe Met Asn Tyr Asn Ser Ser Val Ser Phe
145 150 155 160

Glu Glu Arg Leu Asn Asn Ile Thr Met Trp Leu Asn Asn Ser Asn Pro
165 170 175

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

180 185 190

His Lys Tyr Gly Pro Glu Asp Lys Glu Asn Met Ser Arg Val Leu Lys

195 200 205

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

210 215 220

Gly Leu Trp Glu Asn Leu Asn Val Ile Ile Thr Ser Asp His Gly Met

225 230 235 240

Thr Gln Cys Ser Gln Asp Arg Leu Ile Asn Leu Asp Ser Cys Ile Asp

245 250 255

His Ser Tyr Tyr Thr Leu Ile Asp Leu Ser Pro Val Ala Ala Ile Leu

260 265 270

Pro Lys Ile Asn Arg Thr Glu Val Tyr Asn Lys Leu Lys Asn Cys Ser

275 280 285

Pro His Met Asn Val Tyr Leu Lys Glu Asp Ile Pro Asn Arg Phe Tyr

290 295 300

Tyr Gln His Asn Asp Arg Ile Gln Pro Ile Ile Leu Val Ala Asp Glu

305 310 315 320

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

325 330 335

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

340 345 350

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

355 360 365

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

370 375 380

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

385 390 395 400

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

405 410 415

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

420 425 430

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

435 440 445

Asp Pro Leu Ile Gly

450

<210> 12

<211> 850

<212> PRT

<213> 人工序列

<220>

<223> ENPP51氨基酸序列

<220>

<221> SIGNAL

<222> (24)..(25)

<223> 信号肽序列的切割点

<400> 12

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

Gly Ile Leu Pro Asp Ile Tyr Lys Val Tyr Asn Gly Ser Val Pro Phe
260 265 270
Glu Glu Arg Ile Leu Ala Val Leu Glu Trp Leu Gln Leu Pro Ser His
275 280 285
Glu Arg Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser
290 295 300
Gly His Ser His Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln
305 310 315 320
Lys Val Asp Arg Leu Val Gly Met Leu Met Asp Gly Leu Lys Asp Leu
325 330 335
Gly Leu Asp Lys Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met
340 345 350
Glu Gln Gly Ser Cys Lys Lys Tyr Val Tyr Leu Asn Lys Tyr Leu Gly
355 360 365
Asp Val Asn Asn Val Lys Val Val Tyr Gly Pro Ala Ala Arg Leu Arg
370 375 380
Pro Thr Asp Val Pro Glu Thr Tyr Tyr Ser Phe Asn Tyr Glu Ala Leu
385 390 395 400
Ala Lys Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Arg Pro Tyr
405 410 415
Leu Lys Pro Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg
420 425 430
Ile Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu
435 440 445
Asn Pro Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp
450 455 460
Asn Leu Phe Ser Asn Met Gln Ala Leu Phe Ile Gly Tyr Gly Pro Ala
465 470 475 480
Phe Lys His Gly Ala Glu Val Asp Ser Phe Glu Asn Ile Glu Val Tyr
485 490 495
Asn Leu Met Cys Asp Leu Leu Gly Leu Ile Pro Ala Pro Asn Asn Gly
500 505 510
Ser His Gly Ser Leu Asn His Leu Leu Lys Lys Pro Ile Tyr Asn Pro
515 520 525
Ser His Pro Lys Glu Glu Gly Phe Leu Ser Gln Cys Pro Ile Lys Ser
530 535 540
Thr Ser Asn Asp Leu Gly Cys Thr Cys Asp Pro Trp Ile Val Pro Ile
545 550 555 560
Lys Asp Phe Glu Lys Gln Leu Asn Leu Thr Thr Glu Asp Val Asp Asp

565 570 575
Ile Tyr His Met Thr Val Pro Tyr Gly Arg Pro Arg Ile Leu Leu Lys
580 585 590
Gln His Arg Val Cys Leu Leu Gln Gln Gln Gln Phe Leu Thr Gly Tyr
595 600 605
Ser Leu Asp Leu Leu Met Pro Leu Trp Ala Ser Tyr Thr Phe Leu Ser
610 615 620
Asn Asp Gln Phe Ser Arg Asp Asp Phe Ser Asn Cys Leu Tyr Gln Asp
625 630 635 640
Leu Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Tyr Tyr Lys Ser
645 650 655
Asn Ser Lys Leu Ser Tyr Gly Phe Leu Thr Pro Pro Arg Leu Asn Arg
660 665 670
Val Ser Asn His Ile Tyr Ser Glu Ala Leu Leu Thr Ser Asn Ile Val
675 680 685
Pro Met Tyr Gln Ser Phe Gln Val Ile Trp His Tyr Leu His Asp Thr
690 695 700
Leu Leu Gln Arg Tyr Ala His Glu Arg Asn Gly Ile Asn Val Val Ser
705 710 715 720
Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Tyr Asp Ser Leu Glu
725 730 735
Ile Leu Lys Gln Asn Ser Arg Val Ile Arg Ser Gln Glu Ile Leu Ile
740 745 750
Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Gln Leu Ser Glu
755 760 765
Thr Pro Leu Glu Cys Ser Ala Leu Glu Ser Ser Ala Tyr Ile Leu Pro
770 775 780
His Arg Pro Asp Asn Ile Glu Ser Cys Thr His Gly Lys Arg Glu Ser
785 790 795 800
Ser Trp Val Glu Glu Leu Leu Thr Leu His Arg Ala Arg Val Thr Asp
805 810 815
Val Glu Leu Ile Thr Gly Leu Ser Phe Tyr Gln Asp Arg Gln Glu Ser
820 825 830
Val Ser Glu Leu Leu Arg Leu Lys Thr His Leu Pro Ile Phe Ser Gln
835 840 845
Glu Asp
850
<210> 13
<211> 1474

<212> PRT
<213> 人工序列
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<223> ENPP51-ALB氨基酸序列
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<222> (24)..(25)
<223> 信号序列的切割点
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<222> (857)..(1474)
<223> 表示白蛋白序列
<400> 13

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

Lys Met Asn Ala Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro
210 215 220
Leu Trp Tyr Lys Gly Gln Pro Ile Trp Val Thr Ala Asn His Gln Glu
225 230 235 240
Val Lys Ser Gly Thr Tyr Phe Trp Pro Gly Ser Asp Val Glu Ile Asp
245 250 255
Gly Ile Leu Pro Asp Ile Tyr Lys Val Tyr Asn Gly Ser Val Pro Phe
260 265 270
Glu Glu Arg Ile Leu Ala Val Leu Glu Trp Leu Gln Leu Pro Ser His
275 280 285
Glu Arg Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser
290 295 300
Gly His Ser His Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu Gln
305 310 315 320
Lys Val Asp Arg Leu Val Gly Met Leu Met Asp Gly Leu Lys Asp Leu
325 330 335
Gly Leu Asp Lys Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met
340 345 350
Glu Gln Gly Ser Cys Lys Lys Tyr Val Tyr Leu Asn Lys Tyr Leu Gly
355 360 365
Asp Val Asn Asn Val Lys Val Val Tyr Gly Pro Ala Ala Arg Leu Arg
370 375 380
Pro Thr Asp Val Pro Glu Thr Tyr Tyr Ser Phe Asn Tyr Glu Ala Leu
385 390 395 400
Ala Lys Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Arg Pro Tyr
405 410 415
Leu Lys Pro Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg
420 425 430
Ile Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu
435 440 445
Asn Pro Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp
450 455 460
Asn Leu Phe Ser Asn Met Gln Ala Leu Phe Ile Gly Tyr Gly Pro Ala
465 470 475 480
Phe Lys His Gly Ala Glu Val Asp Ser Phe Glu Asn Ile Glu Val Tyr
485 490 495
Asn Leu Met Cys Asp Leu Leu Gly Leu Ile Pro Ala Pro Asn Asn Gly
500 505 510
Ser His Gly Ser Leu Asn His Leu Leu Lys Lys Pro Ile Tyr Asn Pro

515 520 525

Ser His Pro Lys Glu Glu Gly Phe Leu Ser Gln Cys Pro Ile Lys Ser
530 535 540

Thr Ser Asn Asp Leu Gly Cys Thr Cys Asp Pro Trp Ile Val Pro Ile
545 550 555 560

Lys Asp Phe Glu Lys Gln Leu Asn Leu Thr Thr Glu Asp Val Asp Asp
565 570 575

Ile Tyr His Met Thr Val Pro Tyr Gly Arg Pro Arg Ile Leu Leu Lys
580 585 590

Gln His Arg Val Cys Leu Leu Gln Gln Gln Gln Phe Leu Thr Gly Tyr
595 600 605

Ser Leu Asp Leu Leu Met Pro Leu Trp Ala Ser Tyr Thr Phe Leu Ser
610 615 620

Asn Asp Gln Phe Ser Arg Asp Asp Phe Ser Asn Cys Leu Tyr Gln Asp
625 630 635 640

Leu Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Tyr Tyr Lys Ser
645 650 655

Asn Ser Lys Leu Ser Tyr Gly Phe Leu Thr Pro Pro Arg Leu Asn Arg
660 665 670

Val Ser Asn His Ile Tyr Ser Glu Ala Leu Leu Thr Ser Asn Ile Val
675 680 685

Pro Met Tyr Gln Ser Phe Gln Val Ile Trp His Tyr Leu His Asp Thr
690 695 700

Leu Leu Gln Arg Tyr Ala His Glu Arg Asn Gly Ile Asn Val Val Ser
705 710 715 720

Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Tyr Asp Ser Leu Glu
725 730 735

Ile Leu Lys Gln Asn Ser Arg Val Ile Arg Ser Gln Glu Ile Leu Ile
740 745 750

Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Gln Leu Ser Glu
755 760 765

Thr Pro Leu Glu Cys Ser Ala Leu Glu Ser Ser Ala Tyr Ile Leu Pro
770 775 780

His Arg Pro Asp Asn Ile Glu Ser Cys Thr His Gly Lys Arg Glu Ser
785 790 795 800

Ser Trp Val Glu Glu Leu Leu Thr Leu His Arg Ala Arg Val Thr Asp
805 810 815

Val Glu Leu Ile Thr Gly Leu Ser Phe Tyr Gln Asp Arg Gln Glu Ser
820 825 830

Val Ser Glu Leu Leu Arg Leu Lys Thr His Leu Pro Ile Phe Ser Gln
835 840 845
Glu Asp Gly Gly Ser Gly Gly Ser Met Lys Trp Val Thr Phe Leu Leu
850 855 860
Leu Leu Phe Val Ser Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg
865 870 875 880
Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu
885 890 895
Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln
900 905 910
Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu Val Thr Asp
915 920 925
Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys
930 935 940
Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu
945 950 955 960
Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro
965 970 975
Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Ser Leu
980 985 990
Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met Cys Thr Ser Phe Lys
995 1000 1005
Glu Asn Pro Thr Thr Phe Met Gly His Tyr Leu His Glu Val Ala
1010 1015 1020
Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Tyr Tyr Ala
1025 1030 1035
Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys Ala Glu Ala Asp
1040 1045 1050
Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val Lys Glu Lys
1055 1060 1065
Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys Ser Ser Met
1070 1075 1080
Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
1085 1090 1095
Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr Lys
1100 1105 1110
Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly
1115 1120 1125
Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr

1130 1135 1140

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

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

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

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

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

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

Glu Ala Thr Leu Glu Lys Cys Cys Ala Glu Ala Asn Pro Pro Ala
1235 1240 1245

Cys Tyr Gly Thr Val Leu Ala Glu Phe Gln Pro Leu Val Glu Glu
1250 1255 1260

Pro Lys Asn Leu Val Lys Thr Asn Cys Asp Leu Tyr Glu Lys Leu
1265 1270 1275

Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val Arg Tyr Thr Gln
1280 1285 1290

Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu Ala Ala Arg
1295 1300 1305

Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu Pro Glu Asp
1310 1315 1320

Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile Leu Asn
1325 1330 1335

Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His Val
1340 1345 1350

Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe
1355 1360 1365

Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys
1370 1375 1380

Ala Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu
1385 1390 1395

Lys Glu Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val
1400 1405 1410

Lys His Lys Pro Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met
1415 1420 1425

Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp
1430 1435 1440
Lys Asp Thr Cys Phe Ser Thr Glu Gly Pro Asn Leu Val Thr Arg
1445 1450 1455
Cys Lys Asp Ala Leu Ala Arg Ser Trp Ser His Pro Gln Phe Glu
1460 1465 1470
Lys

<210> 14
<211> 1074
<212> PRT
<213> 人工序列
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<223> 信号序列的切割点
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<222> (848)..(1074)
<223> 表示白蛋白序列
<400> 14

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

130 135 140

Tyr Leu Tyr Thr Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys
145 150 155 160
Thr Cys Gly Ile His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys
165 170 175
Thr Phe Pro Asn His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser
180 185 190
His Gly Ile Ile Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn
195 200 205
Phe Ser Leu Ser Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly
210 215 220
Gln Pro Met Trp Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr
225 230 235 240
Tyr Phe Trp Pro Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser
245 250 255
Ile Tyr Met Pro Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser
260 265 270
Thr Leu Leu Lys Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe
275 280 285
Tyr Thr Met Tyr Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly
290 295 300
Pro Val Ser Ala Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala
305 310 315 320
Phe Gly Met Leu Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys
325 330 335
Val Asn Ile Ile Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys
340 345 350
Asn Lys Met Glu Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe
355 360 365
Tyr Met Tyr Glu Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro
370 375 380
His Asp Phe Phe Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser
385 390 395 400
Cys Arg Lys Pro Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu
405 410 415
Pro Lys Arg Leu His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His
420 425 430
Leu Phe Val Asp Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr
435 440 445

Asn Cys Gly Gly Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met
450 455 460
Glu Ala Ile Phe Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu
465 470 475 480
Val Glu Pro Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu
485 490 495
Leu Arg Ile Gln Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn
500 505 510
His Leu Leu Lys Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val
515 520 525
Ser Lys Phe Ser Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser
530 535 540
Leu Asp Cys Phe Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln
545 550 555 560
Val Asn Gln Met Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val
565 570 575
Lys Val Asn Leu Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val
580 585 590
Asp His Cys Leu Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys
595 600 605
Ala Met Arg Met Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly
610 615 620
Asp Thr Ser Pro Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp
625 630 635 640
Val Arg Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala
645 650 655
Asp Lys Asn Ile Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg
660 665 670
Thr Ser Asp Ser Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro
675 680 685
Met Tyr Glu Glu Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu
690 695 700
Leu Ile Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly
705 710 715 720
Pro Ile Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu
725 730 735
Ile Thr Lys His Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr
740 745 750
Phe Val Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn

755 760 765

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

770 775 780

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

785 790 795 800

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

805 810 815

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

820 825 830

Ile Leu Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile Asp

835 840 845

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly

850 855 860

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

865 870 875 880

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

885 890 895

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

900 905 910

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

915 920 925

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

930 935 940

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

945 950 955 960

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

965 970 975

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

980 985 990

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

995 1000 1005

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

1010 1015 1020

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

1025 1030 1035

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

1040 1045 1050

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

1055 1060 1065

Ser Leu Ser Pro Gly Lys
1070

<210> 15
<211> 1469
<212> PRT
<213> 人工序列
<220>
<223> ENPP5-NPP3-白蛋白序列
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<222> (22)..(23)
<223> 信号肽序列的切割点
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<221> MISC_FEATURE
<222> (848)..(1469)
<223> 表示白蛋白序列
<400> 15

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

Thr Phe Pro Asn His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser
180 185 190
His Gly Ile Ile Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn
195 200 205
Phe Ser Leu Ser Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly
210 215 220
Gln Pro Met Trp Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr
225 230 235 240
Tyr Phe Trp Pro Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser
245 250 255
Ile Tyr Met Pro Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser
260 265 270
Thr Leu Leu Lys Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe
275 280 285
Tyr Thr Met Tyr Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly
290 295 300
Pro Val Ser Ala Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala
305 310 315 320
Phe Gly Met Leu Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys
325 330 335
Val Asn Ile Ile Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys
340 345 350
Asn Lys Met Glu Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe
355 360 365
Tyr Met Tyr Glu Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro
370 375 380
His Asp Phe Phe Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser
385 390 395 400
Cys Arg Lys Pro Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu
405 410 415
Pro Lys Arg Leu His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His
420 425 430
Leu Phe Val Asp Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr
435 440 445
Asn Cys Gly Gly Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met
450 455 460
Glu Ala Ile Phe Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu
465 470 475 480
Val Glu Pro Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu

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

Glu Glu Arg Phe Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu
805 810 815
Leu Thr Gly Leu Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu
820 825 830
Ile Leu Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile Gly
835 840 845
Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Met Lys Trp
850 855 860
Val Thr Phe Leu Leu Leu Leu Phe Val Ser Gly Ser Ala Phe Ser Arg
865 870 875 880
Gly Val Phe Arg Arg Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr
885 890 895
Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe
900 905 910
Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val
915 920 925
Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala
930 935 940
Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys
945 950 955 960
Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys
965 970 975
Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp
980 985 990
Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met
995 1000 1005
Cys Thr Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly His Tyr
1010 1015 1020
Leu His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
1025 1030 1035
Leu Leu Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys
1040 1045 1050
Cys Ala Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp
1055 1060 1065
Gly Val Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met
1070 1075 1080
Lys Cys Ser Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala
1085 1090 1095
Trp Ala Val Ala Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe

1100 1105 1110

Ala Glu Ile Thr Lys Leu Ala Thr Asp Leu Thr Lys Val Asn Lys
1115 1120 1125

Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala
1130 1135 1140

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

Lys Leu Gln Thr Cys Cys Asp Lys Pro Leu Leu Lys Lys Ala His
1160 1165 1170

Cys Leu Ser Glu Val Glu His Asp Thr Met Pro Ala Asp Leu Pro
1175 1180 1185

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

Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Thr Phe Leu Tyr Glu
1205 1210 1215

Tyr Ser Arg Arg His Pro Asp Tyr Ser Val Ser Leu Leu Leu Arg
1220 1225 1230

Leu Ala Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys Cys Ala Glu
1235 1240 1245

Ala Asn Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu Phe Gln
1250 1255 1260

Pro Leu Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys Asp
1265 1270 1275

Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu
1280 1285 1290

Val Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu
1295 1300 1305

Val Glu Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys
1310 1315 1320

Thr Leu Pro Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu
1325 1330 1335

Ser Ala Ile Leu Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro
1340 1345 1350

Val Ser Glu His Val Thr Lys Cys Cys Ser Gly Ser Leu Val Glu
1355 1360 1365

Arg Arg Pro Cys Phe Ser Ala Leu Thr Val Asp Glu Thr Tyr Val
1370 1375 1380

Pro Lys Glu Phe Lys Ala Glu Thr Phe Thr Phe His Ser Asp Ile
1385 1390 1395

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

<210> 16
<211> 23
<212> PRT
<213> 人工序列
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<222> (23)..(23)
<223> X可以是任何氨基酸
<400> 16
Met Thr Ser Lys Phe Leu Leu Val Ser Phe Ile Leu Ala Ala Leu Ser
1 5 10 15
Leu Ser Thr Thr Phe Ser Xaa
20

<210> 17
<211> 1079
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<223> ENPP51-Fc
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<223> 信号肽序列的切割点
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<223> 表示Fc序列

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

Ser Gly His Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu
305 310 315 320
Gln Arg Val Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu
325 330 335
Leu Asn Leu His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly
340 345 350
Met Glu Gln Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu
355 360 365
Gly Asp Val Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu
370 375 380
Arg Pro Ser Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly
385 390 395 400
Ile Ala Arg Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro
405 410 415
Tyr Leu Lys His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp
420 425 430
Arg Ile Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala
435 440 445
Leu Asn Pro Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser
450 455 460
Asp Asn Val Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro
465 470 475 480
Gly Phe Lys His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val
485 490 495
Tyr Asn Leu Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn
500 505 510
Gly Thr His Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr
515 520 525
Pro Lys His Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr
530 535 540
Arg Asn Pro Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu
545 550 555 560
Pro Ile Glu Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu
565 570 575
Lys Ile Ile Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu
580 585 590
Gln Lys Glu Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser
595 600 605
Gly Tyr Ser Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val

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

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

<210> 18
<211> 1082
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<223> ENPP71-Fc氨基酸序列
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<222> (22)..(23)
<223> 信号肽序列的切割点
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<222> (856)..(1082)
<223> 表示Fc序列
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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 Gly Leu Lys Pro Ser Cys Ala Lys Glu Val
20 25 30

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

340 345 350

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

355 360 365

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

370 375 380

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

385 390 395 400

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

405 410 415

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

420 425 430

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

435 440 445

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

450 455 460

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

465 470 475 480

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

485 490 495

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

500 505 510

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

515 520 525

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

530 535 540

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

545 550 555 560

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

565 570 575

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

580 585 590

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

595 600 605

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

610 615 620

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

625 630 635 640

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

645 650 655

Lys Asn Asn Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu
660 665 670
Asn Lys Asn Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn
675 680 685
Ile Val Pro Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His
690 695 700
Asp Thr Leu Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val
705 710 715 720
Val Ser Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser
725 730 735
Leu Glu Asn Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile
740 745 750
Leu Ile Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr
755 760 765
Ser Gln Thr Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile
770 775 780
Leu Pro His Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His
785 790 795 800
Asp Ser Ser Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile
805 810 815
Thr Asp Val Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys
820 825 830
Glu Pro Val Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe
835 840 845
Ser Gln Glu Asp Leu Ile Asn Asp Lys Thr His Thr Cys Pro Pro Cys
850 855 860
Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
865 870 875 880
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
885 890 895
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
900 905 910
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
915 920 925
Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
930 935 940
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
945 950 955 960
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly

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

<210> 19
<211> 849
<212> PRT
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<220>
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<222> (22)..(23)
<223> 信号肽序列的切割点
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20 25 30
Lys Gly Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala
35 40 45
Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys
50 55 60
Ile Glu Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu
65 70 75 80
Lys Arg Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp
85 90 95
Lys Gly Asp Cys Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys

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

His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu
420 425 430
Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro
435 440 445
Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val
450 455 460
Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys
465 470 475 480
His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu
485 490 495
Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His
500 505 510
Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His
515 520 525
Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro
530 535 540
Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu
545 550 555 560
Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile
565 570 575
Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu
580 585 590
Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser
595 600 605
Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn
610 615 620
Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe
625 630 635 640
Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn
645 650 655
Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn
660 665 670
Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro
675 680 685
Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu
690 695 700
Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly
705 710 715 720
Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn

725 730 735
Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro
740 745 750
Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr
755 760 765
Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His
770 775 780
Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser
785 790 795 800
Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val
805 810 815
Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val
820 825 830
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35 40 45
Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys
50 55 60

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

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

Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu
690 695 700
Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly
705 710 715 720
Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn
725 730 735
Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro
740 745 750
Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr
755 760 765
Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His
770 775 780
Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser
785 790 795 800
Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val
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820 825 830
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835 840 845
Asp Leu Ile Asn Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
850 855 860
Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
865 870 875 880
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
885 890 895
Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
900 905 910
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
915 920 925
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
930 935 940
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
945 950 955 960
Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
965 970 975
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
980 985 990
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp

995 1000 1005

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
1010 1015 1020

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
1025 1030 1035

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
1040 1045 1050

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

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20 25 30

Lys Gly Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala
35 40 45

Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys
50 55 60

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

Lys Arg Leu Thr Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp
85 90 95

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

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

His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu
420 425 430
Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro
435 440 445
Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val
450 455 460
Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys
465 470 475 480
His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu
485 490 495
Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His
500 505 510
Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His
515 520 525
Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro
530 535 540
Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu
545 550 555 560
Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile
565 570 575
Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu
580 585 590
Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser
595 600 605
Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn
610 615 620
Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe
625 630 635 640
Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn
645 650 655
Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn
660 665 670
Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro
675 680 685
Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu
690 695 700
Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly
705 710 715 720
Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn

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

Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys Ala Glu Ala Asp
1040 1045 1050
Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val Lys Glu Lys
1055 1060 1065
Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys Ser Ser Met
1070 1075 1080
Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg
1085 1090 1095
Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr Lys
1100 1105 1110
Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly
1115 1120 1125
Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr
1130 1135 1140
Met Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys
1145 1150 1155
Cys Asp Lys Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val
1160 1165 1170
Glu His Asp Thr Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp
1175 1180 1185
Phe Val Glu Asp Gln Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys
1190 1195 1200
Asp Val Phe Leu Gly Thr Phe Leu Tyr Glu Tyr Ser Arg Arg His
1205 1210 1215
Pro Asp Tyr Ser Val Ser Leu Leu Leu Arg Leu Ala Lys Lys Tyr
1220 1225 1230
Glu Ala Thr Leu Glu Lys Cys Cys Ala Glu Ala Asn Pro Pro Ala
1235 1240 1245
Cys Tyr Gly Thr Val Leu Ala Glu Phe Gln Pro Leu Val Glu Glu
1250 1255 1260
Pro Lys Asn Leu Val Lys Thr Asn Cys Asp Leu Tyr Glu Lys Leu
1265 1270 1275
Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val Arg Tyr Thr Gln
1280 1285 1290
Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu Ala Ala Arg
1295 1300 1305
Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu Pro Glu Asp
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Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile Leu Asn

1325 1330 1335
Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His Val
1340 1345 1350
Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe
1355 1360 1365
Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys
1370 1375 1380
Ala Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu
1385 1390 1395
Lys Glu Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val
1400 1405 1410
Lys His Lys Pro Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met
1415 1420 1425
Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp
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35 40 45
Arg Gly Asp Cys Cys Trp Asp Phe Glu Asp Thr Cys Val Glu Ser Thr
50 55 60
Arg Ile Trp Met Cys Asn Lys Phe Arg Cys Gly Glu Arg Leu Glu Ala
65 70 75 80
Ser Leu Cys Ser Cys Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys Cys
85 90 95
Ala Asp Tyr Lys Ser Val Cys Gln Gly Glu Thr Ser Trp Leu Glu Glu
100 105 110
Asn Cys Asp Thr Ala Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp Leu
115 120 125
Pro Pro Val Ile Leu Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr Leu
130 135 140
Tyr Thr Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys Thr Cys
145 150 155 160
Gly Ile His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr Phe
165 170 175
Pro Asn His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly
180 185 190
Ile Ile Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser
195 200 205
Leu Ser Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro
210 215 220
Met Trp Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe
225 230 235 240
Trp Pro Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr
245 250 255
Met Pro Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu
260 265 270
Leu Lys Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr
275 280 285
Met Tyr Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val
290 295 300
Ser Ala Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala Phe Gly
305 310 315 320
Met Leu Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn
325 330 335
Ile Ile Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys

340 345 350

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

355 360 365

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

370 375 380

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

385 390 395 400

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

405 410 415

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

420 425 430

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

435 440 445

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

450 455 460

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

465 470 475 480

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

485 490 495

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

500 505 510

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

515 520 525

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

530 535 540

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

545 550 555 560

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

565 570 575

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

580 585 590

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

595 600 605

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

610 615 620

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

625 630 635 640

Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys

645 650 655

Asn Ile Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser
660 665 670
Asp Ser Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro Met Tyr
675 680 685
Glu Glu Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu Leu Ile
690 695 700
Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile
705 710 715 720
Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr
725 730 735
Lys His Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val
740 745 750
Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro
755 760 765
Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn
770 775 780
Val Glu Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu
785 790 795 800
Arg Phe Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr
805 810 815
Gly Leu Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu
820 825 830
Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile Asp Lys Thr
835 840 845
His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
850 855 860
Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
865 870 875 880
Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
885 890 895
Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
900 905 910
Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
915 920 925
Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
930 935 940
Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
945 950 955 960
Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu

965 970 975
Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
980 985 990
Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
995 1000 1005
Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
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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
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Ser Pro Gly Lys
1070

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Cys Lys Gly Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp
35 40 45
Ala Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr
50 55 60
Cys Ile Glu Pro Glu His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly

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

Ser Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala
385 390 395 400
Arg Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu
405 410 415
Lys His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile
420 425 430
Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn
435 440 445
Pro Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn
450 455 460
Val Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe
465 470 475 480
Lys His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn
485 490 495
Leu Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr
500 505 510
His Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys
515 520 525
His Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn
530 535 540
Pro Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile
545 550 555 560
Glu Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile
565 570 575
Ile Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys
580 585 590
Glu Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr
595 600 605
Ser Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg
610 615 620
Asn Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp
625 630 635 640
Phe Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn
645 650 655
Asn Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys
660 665 670
Asn Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val
675 680 685
Pro Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr

690 695 700

Leu Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser
705 710 715 720

Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu
725 730 735

Asn Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile
740 745 750

Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln
755 760 765

Thr Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro
770 775 780

His Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His Asp Ser
785 790 795 800

Ser Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp
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Val Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro
820 825 830

Val Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln
835 840 845

Glu Asp Gly Gly Ser Gly Gly Ser Met Lys Trp Val Thr Phe Leu Leu
850 855 860

Leu Leu Phe Val Ser Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg
865 870 875 880

Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu
885 890 895

Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln
900 905 910

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

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

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

Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro
965 970 975

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Ser Leu
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Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met Cys Thr Ser Phe Lys
995 1000 1005

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1340 1345 1350
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Arg Gly Asp Cys Cys Trp Asp Phe Glu Asp Thr Cys Val Glu Ser Thr
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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

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

Lys Pro Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys
405 410 415
Arg Leu His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His Leu Phe
420 425 430
Val Asp Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys
435 440 445
Gly Gly Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala
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Pro Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg
485 490 495
Ile Gln Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His Leu
500 505 510
Leu Lys Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys
515 520 525
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530 535 540
Cys Phe Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn
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Gln Met Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val
565 570 575
Asn Leu Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val Asp His
580 585 590
Cys Leu Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala Met
595 600 605
Arg Met Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp Thr
610 615 620
Ser Pro Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp Val Arg
625 630 635 640
Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys
645 650 655
Asn Ile Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser
660 665 670
Asp Ser Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro Met Tyr
675 680 685
Glu Glu Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu Leu Ile
690 695 700
Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile

705 710 715 720
Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr
725 730 735
Lys His Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val
740 745 750
Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro
755 760 765
Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn
770 775 780
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Arg Phe Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr
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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
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885 890 895
Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln
900 905 910
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915 920 925
Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn
930 935 940
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Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys
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Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn
980 985 990
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995 1000 1005
Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly His Tyr Leu His
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Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val Arg
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Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu
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Glu His Val Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg
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Glu Phe Lys Ala Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr
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Glu Leu Val Lys His Lys Pro Lys Ala Thr Ala Glu Gln Leu Lys
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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

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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

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Ser Ala Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala Phe Gly

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Ile Ile Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys
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Tyr Glu Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro His Asp
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565 570 575
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580 585 590
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595 600 605
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Ser Pro Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp Val Arg
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645 650 655
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675 680 685
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690 695 700
Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile
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Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr
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755 760 765
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Thr Leu Glu Lys Cys Cys Ala Glu Ala Asn Pro Pro Ala Cys Tyr

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

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

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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
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Gly Glu Lys Ser Trp Val Glu Glu Pro Cys Glu Ser Ile Asn Glu Pro
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Gln Cys Pro Ala Gly Phe Glu Thr Pro Pro Thr Leu Leu Phe Ser Leu
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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
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210 215 220
Pro Glu Trp Tyr Lys Gly Glu Pro Ile Trp Val Thr Ala Lys Tyr Gln
225 230 235 240
Gly Leu Lys Ser Gly Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile
245 250 255

Asn Gly Ile Phe Pro Asp Ile Tyr Lys Met Tyr Asn Gly Ser Val Pro
260 265 270
Phe Glu Glu Arg Ile Leu Ala Val Leu Gln Trp Leu Gln Leu Pro Lys
275 280 285
Asp Glu Arg Pro His Phe Tyr Thr Leu Tyr Leu Glu Glu Pro Asp Ser
290 295 300
Ser Gly His Ser Tyr Gly Pro Val Ser Ser Glu Val Ile Lys Ala Leu
305 310 315 320
Gln Arg Val Asp Gly Met Val Gly Met Leu Met Asp Gly Leu Lys Glu
325 330 335
Leu Asn Leu His Arg Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly
340 345 350
Met Glu Gln Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu
355 360 365
Gly Asp Val Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu
370 375 380
Arg Pro Ser Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly
385 390 395 400
Ile Ala Arg Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro
405 410 415
Tyr Leu Lys His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp
420 425 430
Arg Ile Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala
435 440 445
Leu Asn Pro Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser
450 455 460
Asp Asn Val Phe Ser Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro
465 470 475 480
Gly Phe Lys His Gly Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val
485 490 495
Tyr Asn Leu Met Cys Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn
500 505 510
Gly Thr His Gly Ser Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr
515 520 525
Pro Lys His Pro Lys Glu Val His Pro Leu Val Gln Cys Pro Phe Thr
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Arg Asn Pro Arg Asp Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu
545 550 555 560
Pro Ile Glu Asp Phe Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu

565 570 575
Lys Ile Ile Lys His Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu
580 585 590
Gln Lys Glu Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser
595 600 605
Gly Tyr Ser Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val
610 615 620
Asp Arg Asn Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr
625 630 635 640
Gln Asp Phe Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr
645 650 655
Lys Asn Asn Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu
660 665 670
Asn Lys Asn Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn
675 680 685
Ile Val Pro Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His
690 695 700
Asp Thr Leu Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val
705 710 715 720
Val Ser Gly Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser
725 730 735
Leu Glu Asn Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile
740 745 750
Leu Ile Pro Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr
755 760 765
Ser Gln Thr Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile
770 775 780
Leu Pro His Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His
785 790 795 800
Asp Ser Ser Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile
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Thr Asp Val Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys
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35 40 45
Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala
50 55 60
Arg Ala Arg Thr Ala Lys Asp Pro Asn Thr Tyr Lys Ile Ile Ser Leu
65 70 75 80
Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly 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
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145 150 155 160
Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp Lys Gly Asp Cys
165 170 175
Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp Val Glu
180 185 190
Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro Ala Gly Phe Glu
195 200 205
Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe Arg Ala Glu Tyr
210 215 220
Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser Lys Leu Lys Lys
225 230 235 240

Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr Lys Thr
245 250 255
Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu Ser His
260 265 270
Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala Ser Phe
275 280 285
Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys Gly Glu
290 295 300
Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly Thr Phe
305 310 315 320
Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro Asp Ile
325 330 335
Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Leu Ala
340 345 350
Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His Phe Tyr
355 360 365
Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr Gly Pro
370 375 380
Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly Met Val
385 390 395 400
Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg Cys Leu
405 410 415
Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser Cys Lys
420 425 430
Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn Ile Lys
435 440 445
Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val Pro Asp
450 455 460
Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu Ser Cys
465 470 475 480
Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe Leu Pro
485 490 495
Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu Thr Phe
500 505 510
Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu Arg Lys
515 520 525
Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser Asn Met
530 535 540
Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys His Gly Ile Glu

545 550 555 560
Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu
565 570 575
Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn
580 585 590
His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His Pro Lys Glu Val
595 600 605
His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp Asn Leu
610 615 620
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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
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690 695 700
Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile Pro Leu
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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
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Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His Cys
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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
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50 55 60
Arg Ala Arg Thr Ala Lys Asp Pro Asn Thr Tyr Lys Ile Ile Ser Leu
65 70 75 80
Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly Phe Thr Ala Gly
85 90 95
Leu Lys Pro Ser Cys Ala Lys Glu Val Lys Ser Cys Lys Gly Arg Cys
100 105 110
Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala Ala Cys Val Glu
115 120 125

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

435 440 445

Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val Pro Asp
450 455 460

Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu Ser Cys
465 470 475 480

Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe Leu Pro
485 490 495

Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu Thr Phe
500 505 510

Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu Arg Lys
515 520 525

Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser Asn Met
530 535 540

Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys His Gly Ile Glu
545 550 555 560

Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu
565 570 575

Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn
580 585 590

His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His Pro Lys Glu Val
595 600 605

His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp Asn Leu
610 615 620

Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe Gln Thr
625 630 635 640

Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His Glu Thr
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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
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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
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Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln Ser
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Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys Tyr
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Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln Lys
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Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile Thr
885 890 895
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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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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
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Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
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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
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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
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Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala Ala Cys Val Glu
115 120 125

Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys Ile Glu Pro Glu
130 135 140

His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu Lys Arg Leu Thr
145 150 155 160

Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp Lys Gly Asp Cys
165 170 175

Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp Val Glu
180 185 190

Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro Ala Gly Phe Glu
195 200 205

Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe Arg Ala Glu Tyr
210 215 220

Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser Lys Leu Lys Lys
225 230 235 240

Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr Lys Thr
245 250 255

Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu Ser His
260 265 270

Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala Ser Phe
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
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Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val Pro Asp
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Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe Leu Pro
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Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu Arg Lys
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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
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690 695 700
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740 745 750
Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln Ser
755 760 765
Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys Tyr
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885 890 895
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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
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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
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Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys Ser Leu His
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Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met Cys Thr Ser Phe
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Val Glu His Asp Thr Met Pro Ala Asp Leu Pro Ala Ile Ala Ala
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Glu Lys Glu Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu
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35 40 45
Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala
50 55 60
Arg Ala Arg Thr Ala Lys Asp Pro Asn Thr Tyr Lys Ile Ile Ser Leu
65 70 75 80
Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly Phe Thr Ala Lys
85 90 95
Gln Gly Ser Cys Arg Lys Lys Cys Phe Asp Ala Ser Phe Arg Gly Leu
100 105 110
Glu Asn Cys Arg Cys Asp Val Ala Cys Lys Asp Arg Gly Asp Cys Cys
115 120 125
Trp Asp Phe Glu Asp Thr Cys Val Glu Ser Thr Arg Ile Trp Met Cys
130 135 140
Asn Lys Phe Arg Cys Gly Glu Arg Leu Glu Ala Ser Leu Cys Ser Cys
145 150 155 160
Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys Cys Ala Asp Tyr Lys Ser
165 170 175
Val Cys Gln Gly Glu Thr Ser Trp Leu Glu Glu Asn Cys Asp Thr Ala
180 185 190
Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp Leu Pro Pro Val Ile Leu
195 200 205
Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr Leu Tyr Thr Trp Asp Thr
210 215 220
Leu Met Pro Asn Ile Asn Lys Leu Lys Thr Cys Gly Ile His Ser Lys
225 230 235 240

Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Thr
245 250 255
Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Asn
260 265 270
Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser Leu Ser Ser Lys Glu
275 280 285
Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro Met Trp Leu Thr Ala
290 295 300
Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe Trp Pro Gly Ser Glu
305 310 315 320
Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr Met Pro Tyr Asn Gly
325 330 335
Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu Leu Lys Trp Leu Asp
340 345 350
Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr Met Tyr Phe Glu Glu
355 360 365
Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val Ser Ala Arg Val Ile
370 375 380
Lys Ala Leu Gln Val Val Asp His Ala Phe Gly Met Leu Met Glu Gly
385 390 395 400
Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn Ile Ile Leu Leu Ala
405 410 415
Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys Met Glu Tyr Met Thr
420 425 430
Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr Met Tyr Glu Gly Pro Ala
435 440 445
Pro Arg Ile Arg Ala His Asn Ile Pro His Asp Phe Phe Ser Phe Asn
450 455 460
Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg Lys Pro Asp Gln His
465 470 475 480
Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys Arg Leu His Tyr Ala
485 490 495
Lys Asn Val Arg Ile Asp Lys Val His Leu Phe Val Asp Gln Gln Trp
500 505 510
Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys Gly Gly Gly Asn His
515 520 525
Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala Ile Phe Leu Ala His
530 535 540
Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu Pro Phe Glu Asn Ile

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

Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu Arg Phe Thr Ala His
865 870 875 880
Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr Gly Leu Asp Phe Tyr
885 890 895
Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu Gln Leu Lys Thr Tyr
900 905 910
Leu Pro Thr Phe Glu Thr Thr Ile Asp Lys Thr His Thr Cys Pro Pro
915 920 925
Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
930 935 940
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
945 950 955 960
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
965 970 975
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
980 985 990
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
995 1000 1005
Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
1010 1015 1020
Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
1025 1030 1035
Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
1040 1045 1050
Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
1055 1060 1065
Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
1070 1075 1080
Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
1085 1090 1095
Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
1100 1105 1110
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
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Ser Pro Gly Lys
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        35                  40                  45
Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala
    50                  55                  60
Arg Ala Arg Thr Ala Lys Asp Pro Asn Thr Tyr Lys Ile Ile Ser Leu
65                  70                  75                  80
Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly 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
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195 200 205

Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr Leu Tyr Thr Trp Asp Thr
210 215 220

Leu Met Pro Asn Ile Asn Lys Leu Lys Thr Cys Gly Ile His Ser Lys
225 230 235 240

Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr Phe Pro Asn His Tyr Thr
245 250 255

Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly Ile Ile Asp Asn Asn
260 265 270

Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser Leu Ser Ser Lys Glu
275 280 285

Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro Met Trp Leu Thr Ala
290 295 300

Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe Trp Pro Gly Ser Glu
305 310 315 320

Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr Met Pro Tyr Asn Gly
325 330 335

Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu Leu Lys Trp Leu Asp
340 345 350

Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr Met Tyr Phe Glu Glu
355 360 365

Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val Ser Ala Arg Val Ile
370 375 380

Lys Ala Leu Gln Val Val Asp His Ala Phe Gly Met Leu Met Glu Gly
385 390 395 400

Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn Ile Ile Leu Leu Ala
405 410 415

Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys Met Glu Tyr Met Thr
420 425 430

Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr Met Tyr Glu Gly Pro Ala
435 440 445

Pro Arg Ile Arg Ala His Asn Ile Pro His Asp Phe Phe Ser Phe Asn
450 455 460

Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg Lys Pro Asp Gln His
465 470 475 480

Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys Arg Leu His Tyr Ala
485 490 495

Lys Asn Val Arg Ile Asp Lys Val His Leu Phe Val Asp Gln Gln Trp
500 505 510

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

820 825 830

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

835 840 845

Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn Val Glu Ser Cys Pro

850 855 860

Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu Arg Phe Thr Ala His

865 870 875 880

Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr Gly Leu Asp Phe Tyr

885 890 895

Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu Gln Leu Lys Thr Tyr

900 905 910

Leu Pro Thr Phe Glu Thr Thr Ile Gly Gly Gly Ser Gly Gly Gly Gly

915 920 925

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

930 935 940

Phe Val Ser Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg Glu Ala

945 950 955 960

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

965 970 975

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

980 985 990

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

995 1000 1005

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

1010 1015 1020

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

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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
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Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys
1145 1150 1155
Ser Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala
1160 1165 1170
Val Ala Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu
1175 1180 1185
Ile Thr Lys Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys
1190 1195 1200
Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu
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Ala Lys Tyr Met Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu
1220 1225 1230
Gln Thr Cys Cys Asp Lys Pro Leu Leu Lys Lys Ala His Cys Leu
1235 1240 1245
Ser Glu Val Glu His Asp Thr Met Pro Ala Asp Leu Pro Ala Ile
1250 1255 1260
Ala Ala Asp Phe Val Glu Asp Gln Glu Val Cys Lys Asn Tyr Ala
1265 1270 1275
Glu Ala Lys Asp Val Phe Leu Gly Thr Phe Leu Tyr Glu Tyr Ser
1280 1285 1290
Arg Arg His Pro Asp Tyr Ser Val Ser Leu Leu Leu Arg Leu Ala
1295 1300 1305
Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys Cys Ala Glu Ala Asn
1310 1315 1320
Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu Phe Gln Pro Leu
1325 1330 1335
Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys Asp Leu Tyr
1340 1345 1350
Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val Arg
1355 1360 1365
Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu
1370 1375 1380
Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu
1385 1390 1395
Pro Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala
1400 1405 1410
Ile Leu Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser

1415 1420 1425
Glu His Val Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg
1430 1435 1440
Pro Cys Phe Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys
1445 1450 1455
Glu Phe Lys Ala Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr
1460 1465 1470
Leu Pro Glu Lys Glu Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala
1475 1480 1485
Glu Leu Val Lys His Lys Pro Lys Ala Thr Ala Glu Gln Leu Lys
1490 1495 1500
Thr Val Met Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys Cys Lys
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Val Thr Arg Cys Lys Asp Ala Leu Ala
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Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala Ser
35 40 45
Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala
50 55 60
Arg Ala Arg Thr Ala Lys Asp Pro Asn Thr Tyr Lys Ile Ile Ser Leu
65 70 75 80
Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly Phe Thr Ala Gly
85 90 95
Leu Lys

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            20                  25                  30
Ser Arg Gly Val Phe Arg Arg Glu Ala His Lys Ser Glu Ile Ala His
        35                  40                  45
Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile
    50                  55                  60
Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys
65                  70                  75                  80
Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu
                85                  90                  95
Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys
            100                 105                 110
Leu Cys Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala Asp
        115                 120                 125
Cys Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His
    130                 135                 140
Lys Asp Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala Glu
145                 150                 155                 160
Ala Met Cys Thr Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly His
                165                 170                 175
Tyr Leu His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
            180                 185                 190
Leu Leu Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys
        195                 200                 205
Ala Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val
    210                 215                 220
Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys Ser
225                 230                 235                 240
Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala
                245                 250                 255
Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr Lys
            260                 265                 270
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Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly Asp
275 280 285
Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met Cys
290 295 300
Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys Cys Asp Lys
305 310 315 320
Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val Glu His Asp Thr
325 330 335
Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp Phe Val Glu Asp Gln
340 345 350
Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Thr
355 360 365
Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Asp Tyr Ser Val Ser Leu
370 375 380
Leu Leu Arg Leu Ala Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys Cys
385 390 395 400
Ala Glu Ala Asn Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu Phe
405 410 415
Gln Pro Leu Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys Asp
420 425 430
Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val
435 440 445
Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu
450 455 460
Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu Pro
465 470 475 480
Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile Leu
485 490 495
Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His Val
500 505 510
Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe Ser
515 520 525
Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys Ala Glu
530 535 540
Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu Lys Glu Lys
545 550 555 560
Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val Lys His Lys Pro
565 570 575
Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met Asp Asp Phe Ala Gln

580 585 590
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35 40 45
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65 70 75 80
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85 90 95
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
100 105 110
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
115 120 125
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
130 135 140
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145 150 155 160
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
165 170 175
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
180 185 190
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
195 200 205
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser

210 215 220

Pro Gly Lys

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<211> 618

<212> PRT

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<223> 白蛋白序列

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

225 230 235 240
Ala Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr
245 250 255
Lys Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly
260 265 270
Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met
275 280 285
Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys Cys Asp
290 295 300
Lys Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val Glu His Asp
305 310 315 320
Thr Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp Phe Val Glu Asp
325 330 335
Gln Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350
Thr Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Asp Tyr Ser Val Ser
355 360 365
Leu Leu Leu Arg Leu Ala Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys
370 375 380
Cys Ala Glu Ala Asn Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu
385 390 395 400
Phe Gln Pro Leu Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys
405 410 415
Asp Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu
420 425 430
Val Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445
Glu Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu
450 455 460
Pro Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile
465 470 475 480
Leu Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His
485 490 495
Val Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe
500 505 510
Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys Ala
515 520 525
Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu Lys Glu
530 535 540

Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val Lys His Lys
545 550 555 560
Pro Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met Asp Asp Phe Ala
565 570 575
Gln Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp Lys Asp Thr Cys Phe
580 585 590
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Arg Ser Trp Ser His Pro Gln Phe Glu Lys
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Ala Pro Gly Ala
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Ala Pro Gly Ala Gly Ala
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<212> PRT
<213> 人工序列
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<223> 信号序列ENPP1-2-1
<400> 39

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

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<212> PRT
<213> 人工序列
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<400> 40

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

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<400> 41

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

1 5 10 15
Leu Ser Thr Thr Phe Ser
20
<210> 42
<211> 19
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<223> 信号序列-天青杀素
<400> 42
Met Thr Arg Leu Thr Val Leu Ala Leu Leu Ala Gly Leu Leu Ala Ser
1 5 10 15
Ser Arg Ala
<210> 43
<211> 15
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<223> 列表的特征部分,氨基酸1至15中的任何一项或所有可以存在或不存在
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Arg Arg Arg Arg Arg Arg Arg Arg Arg Arg Arg Arg Arg Arg Arg
1 5 10 15
<210> 44
<211> 16
<212> PRT
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<400> 44
Asp Ser Ser Ser Glu Glu Lys Phe Leu Arg Arg Ile Gly Arg Phe Gly
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<211> 12
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<223> 接头
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Glu Glu Glu Glu Glu Glu Glu Pro Arg Gly Asp Thr
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<210> 46
<211> 12
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<400> 46
Ala Pro Trp His Leu Ser Ser Gln Tyr Ser Arg Thr
1 5 10
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Ser Thr Leu Pro Ile Pro His Glu Phe Ser Arg Glu
1 5 10
<210> 48
<211> 12
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<213> 人工序列
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<400> 48
Val Thr Lys His Leu Asn Gln Ile Ser Gln Ser Tyr
1 5 10
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<213> 人工序列

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<223> 接头

<400> 50

Gly Gly Ser Gly Gly Ser
1 5

<210> 51

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<212> PRT

<213> 人工序列

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<223> 接头

<400> 51

Arg Ser Gly Ser Gly Gly Ser
1 5

<210> 52

<211> 15

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<211> 15
<212> PRT
<213> 人工序列
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<400> 54
Val Ile Met Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5 10 15
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<211> 14
<212> PRT
<213> 人工序列
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<223> 接头
<400> 55
Ile Met Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5 10
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<211> 13
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<223> 接头
<400> 56
Met Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5 10
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<400> 57
Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys

1 5 10

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<223> 接头

<400> 58

Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys

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<211> 10

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<213> 人工序列

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<223> 接头

<400> 59

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1 5 10

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<211> 9

<212> PRT

<213> 人工序列

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<223> 接头

<400> 60

Leu Gly Leu Gly Leu Gly Leu Arg Lys

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<211> 8

<212> PRT

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<223> 接头

<400> 61

Gly Leu Gly Leu Gly Leu Arg Lys

1 5

<210> 62

<211> 7

<212> PRT
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<400> 62
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<211> 6
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<400> 63
Gly Leu Gly Leu Arg Lys
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Leu Gly Leu Arg Lys
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<223> 接头
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1 5 10 15
<210> 67
<211> 15
<212> PRT
<213> 人工序列
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<211> 50
<212> PRT
<213> 人工序列
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<223> 接头
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<223> 氨基酸6至50可以存在或不存在于从位置6处开始的5(GGGGS)组中
<400> 68
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1 5 10 15
Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
20 25 30
Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
35 40 45
Gly Ser
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<210> 69
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<212> DNA

<213> 人工序列

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<223> ENPP3核苷酸序列

<400> 69

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gcatcattta gaggactgga gaactgccgg tgtgatgtgg catgtaaaga ccgaggtgat 240
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gaagaaaact gtgacacagc ccagcagtct cagtgcccag aagggtttga cctgccacca 480
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attttgcaac taaagacata tttaccaaca tttgaaacca ctatt 2625

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<223> ENPP1核苷酸序列
<400> 70

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<211> 3255
<212> DNA
<213> 人工序列
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<223> 天青杀素-ENPP1-FC核苷酸序列
<400> 71

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<211> 3219
<212> DNA
<213> 人工序列
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<223> 天青杀素-ENPP3-FC核苷酸序列
<400> 72

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cagctgggcg acaccagccc cctgcccccc accgtgcccg actgcctgag agccgacgtg 1920
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cacggcttcc tgtacccccc cgccagcaac agaaccagcg acagccagta cgacgccctg 2040
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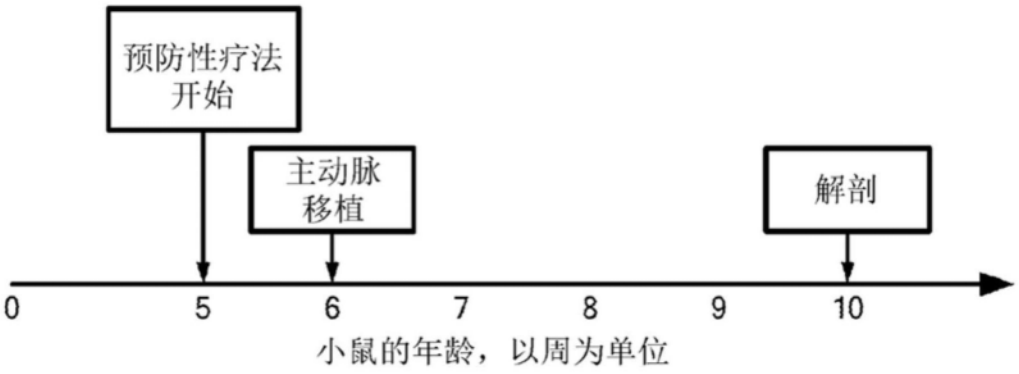

预防性疗法
开始
主动脉
移植
解剖
0
5
6
7
8
9
10
小鼠的年龄，以周为单位

图1

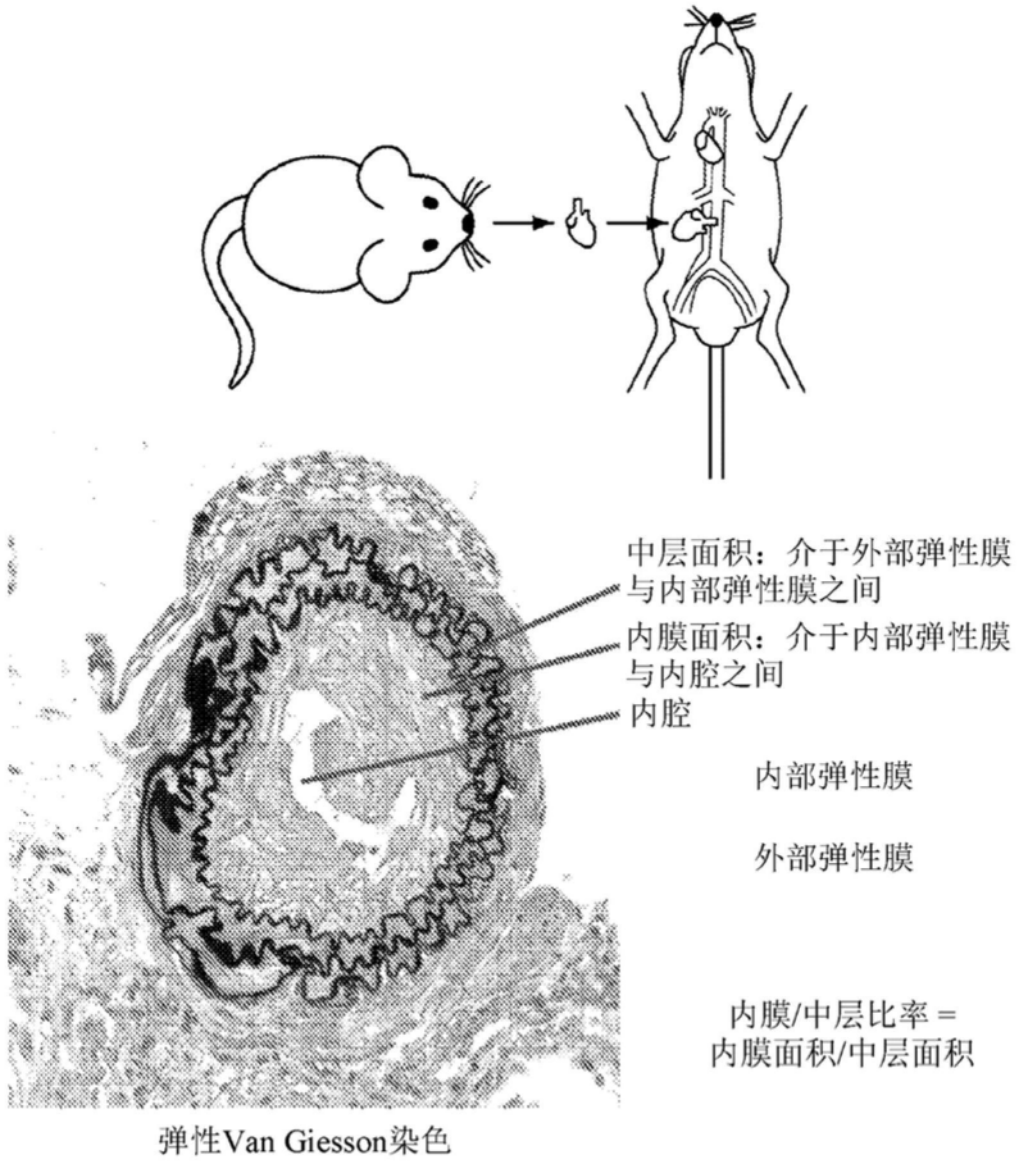

中层面积：介于外部弹性膜
与内部弹性膜之间
内膜面积：介于内部弹性膜
与内腔之间
内腔
内部弹性膜
外部弹性膜
内膜/中层比率＝
内膜面积/中层面积
弹性Van Giesson染色

图2

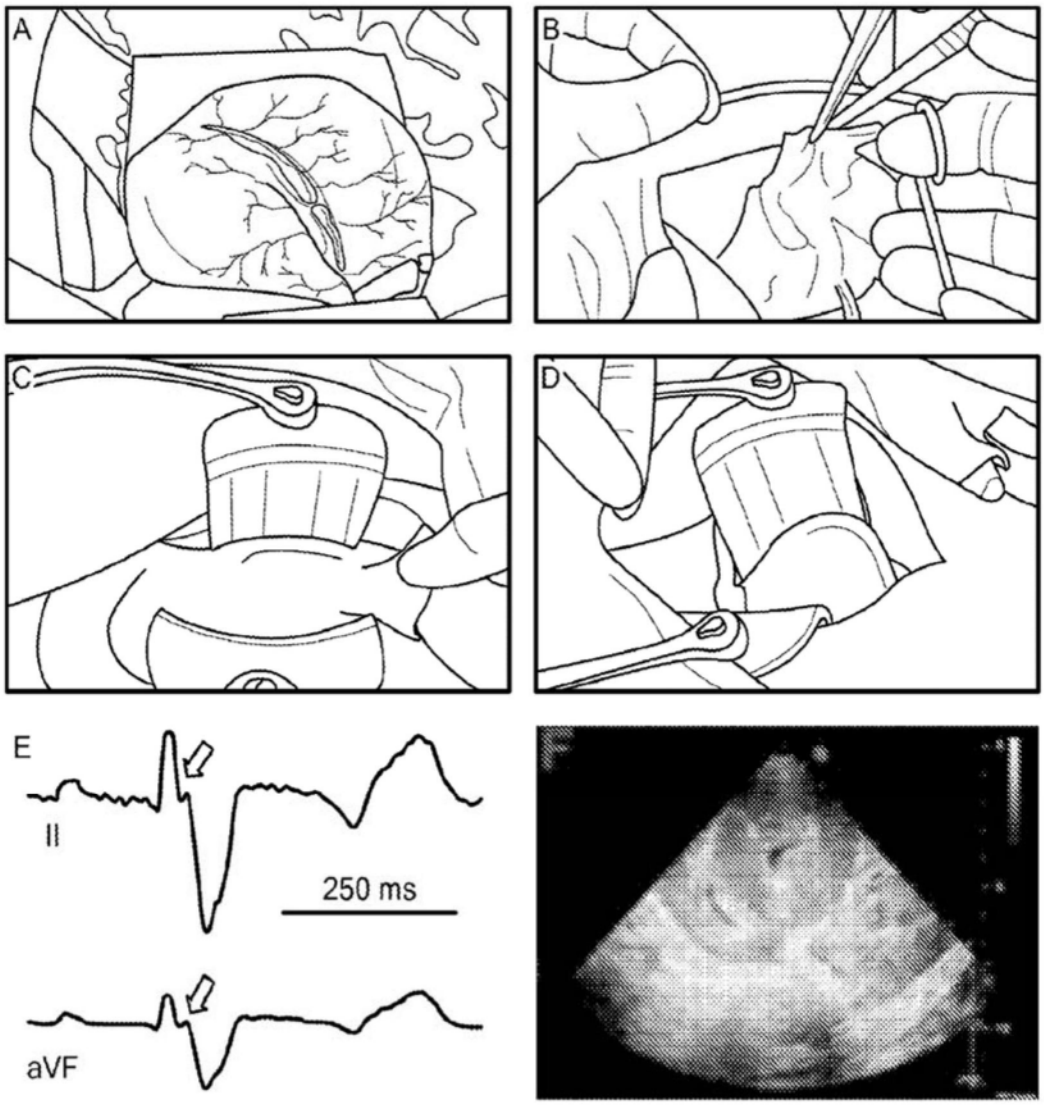


图3

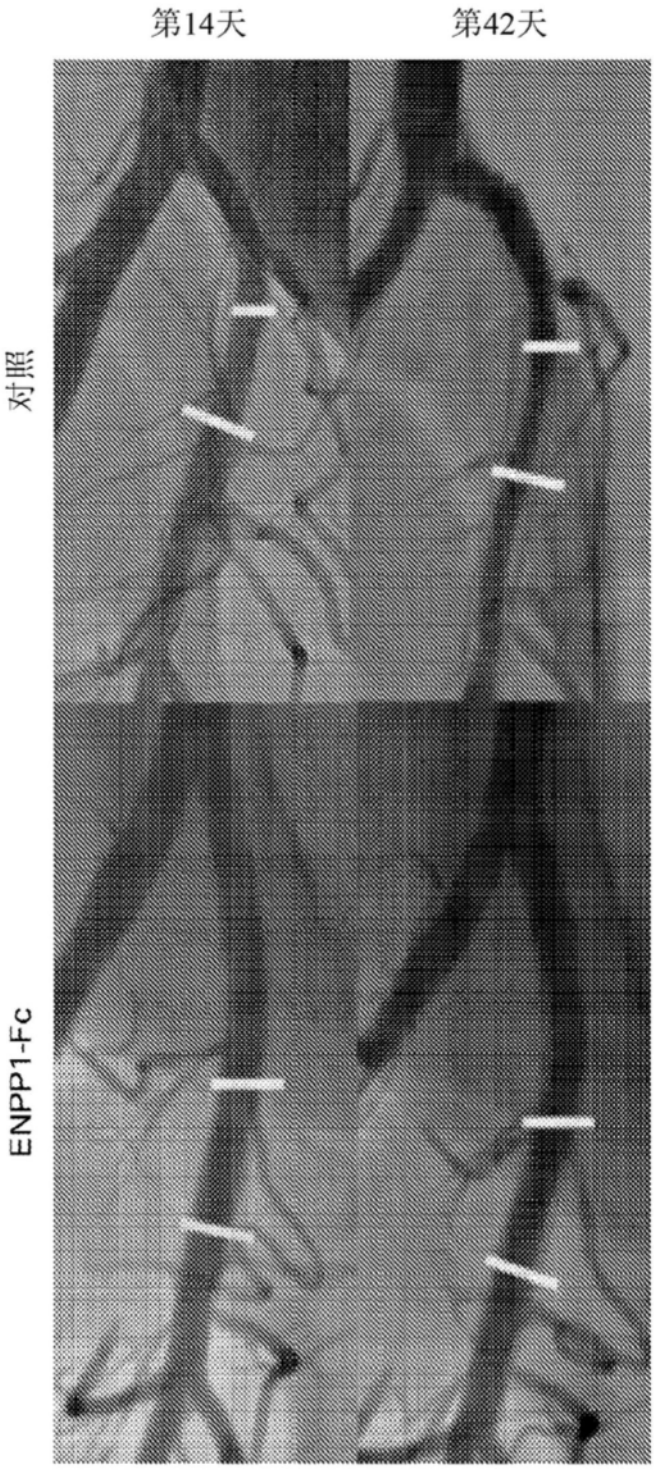


图4

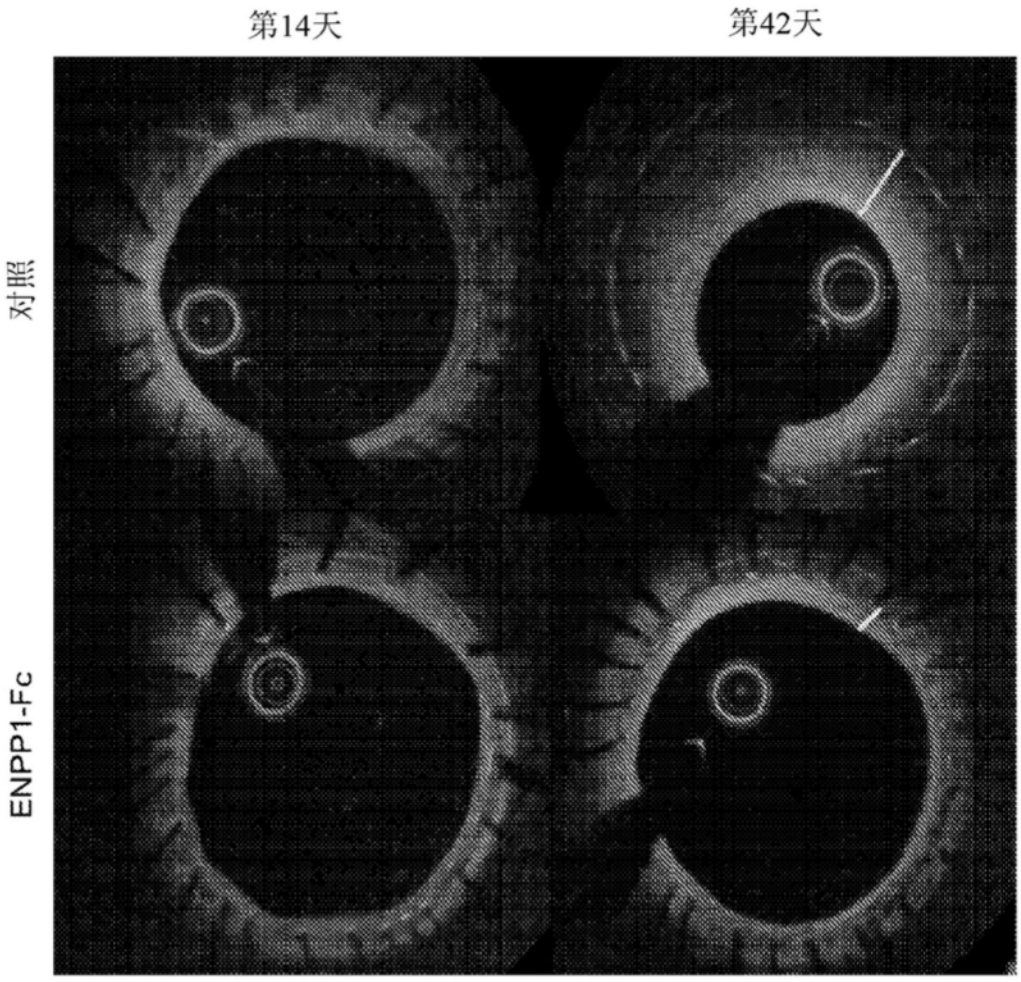


图5

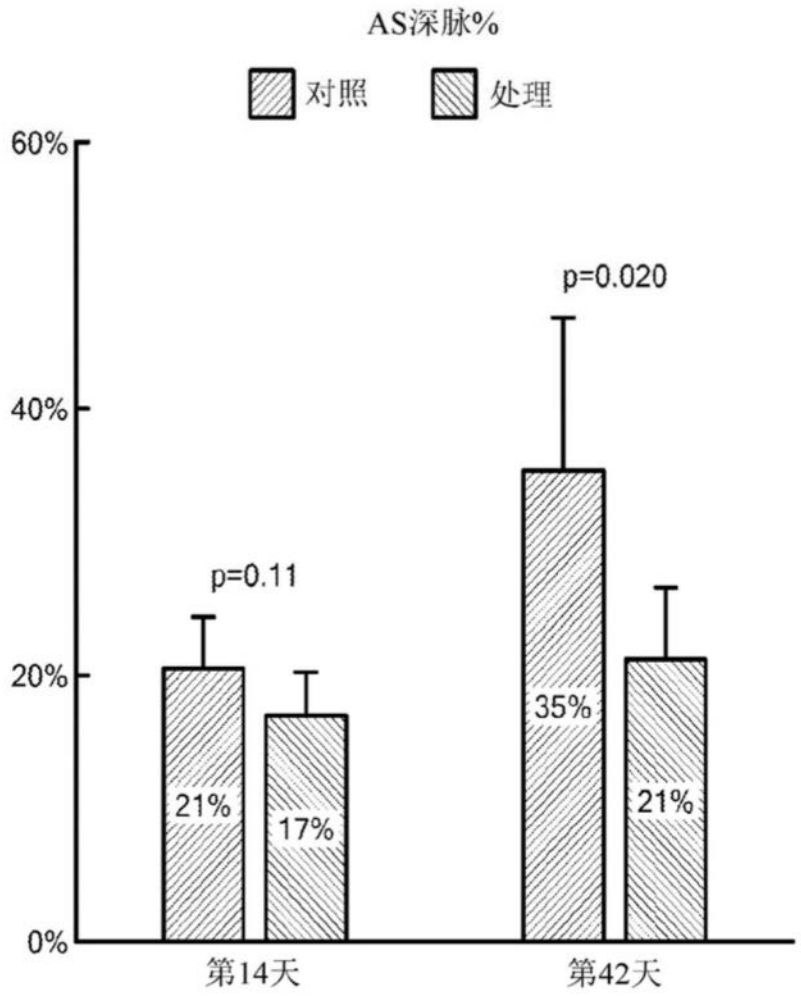

AS深脉%
对照
处理
60%
40%
20%
0%
p=0.11
p=0.020
21%
17%
35%
21%
第14天
第42天

图6

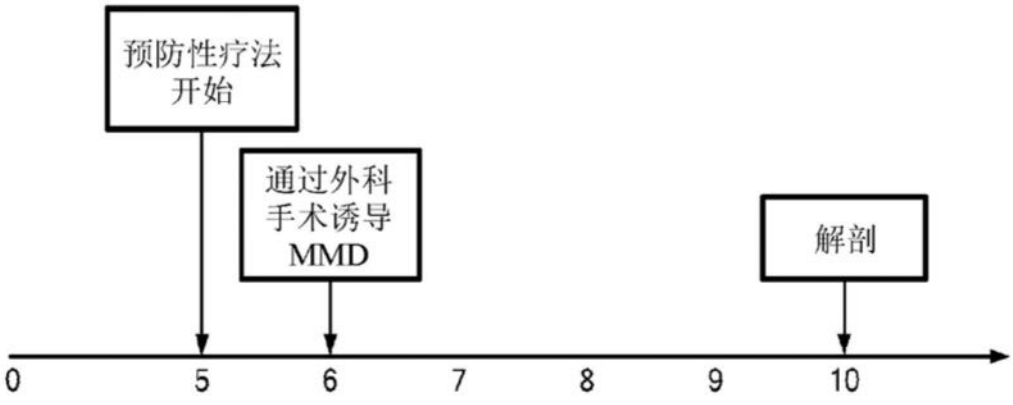

预防性疗法
开始
通过外科
手术诱导
MMD
解剖
0
5
6
7
8
9
10

图7

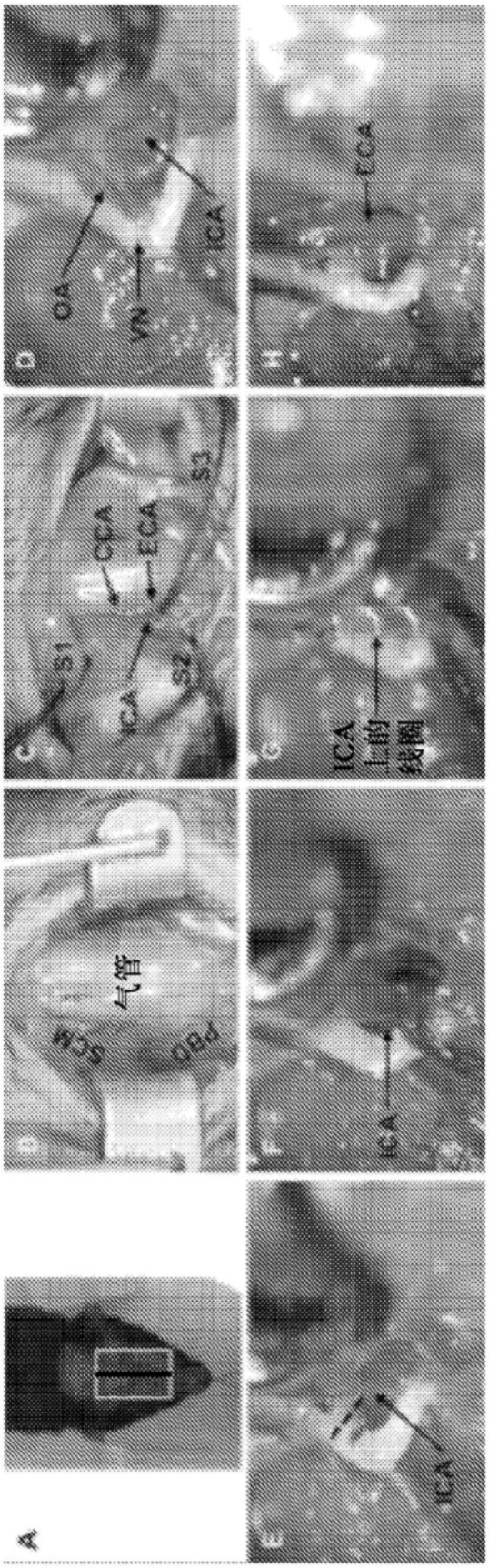

A
B
SCM
气管
PSD
C
S1
CCA
ECA
ICA
S2
S3
D
OA
VN
ICA
E
ICA
F
ICA
G
ICA
上的
线圈
H
ECA

图8

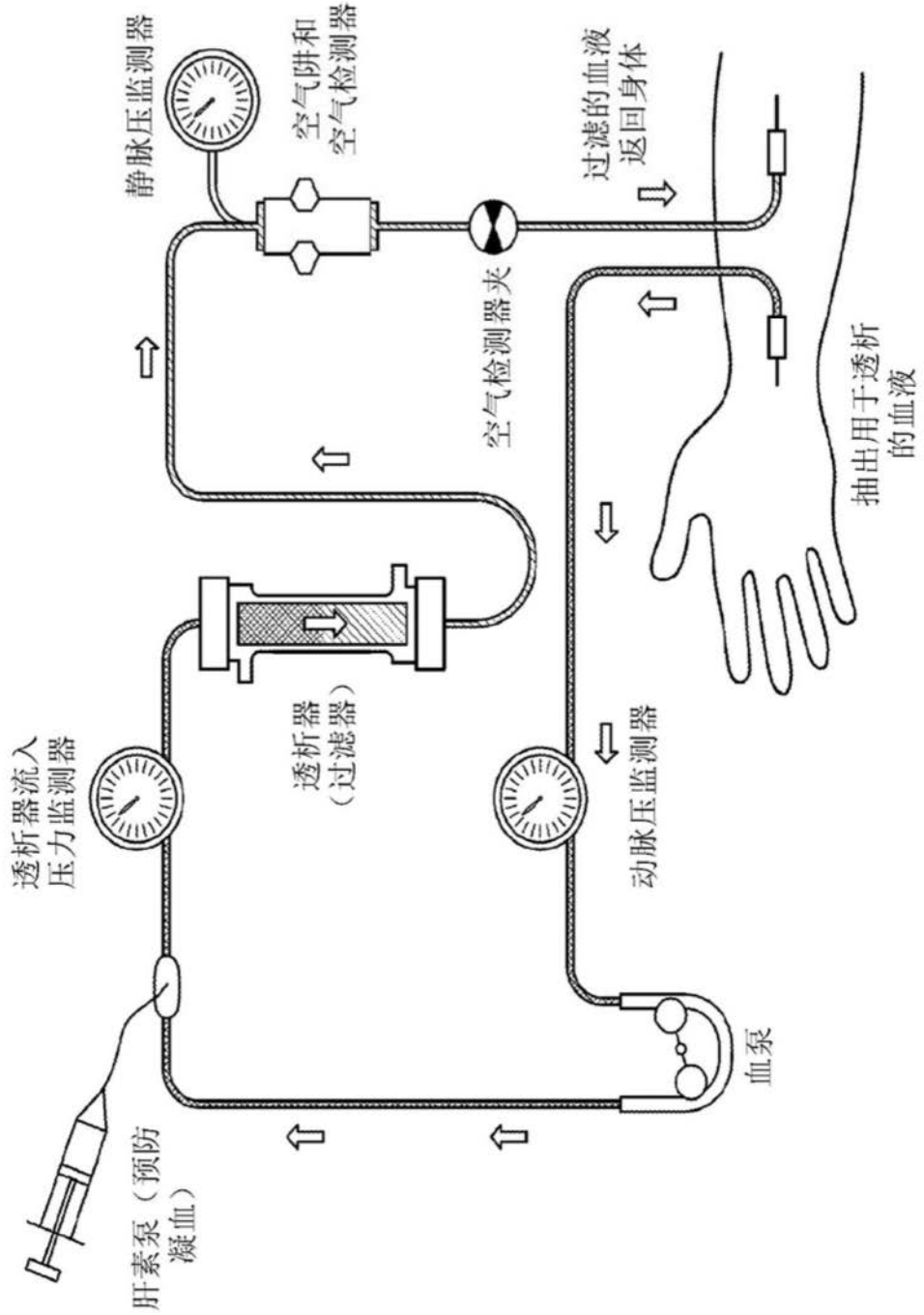

静脉压监测器
空气阱和
空气检测器
过滤的血液
返回身体
空气检测器夹
抽出用于透析
的血液
透析器流入
压力监测器
透析器
（过滤器）
动脉压监测器
血泵
肝素泵（预防
凝血）

图9

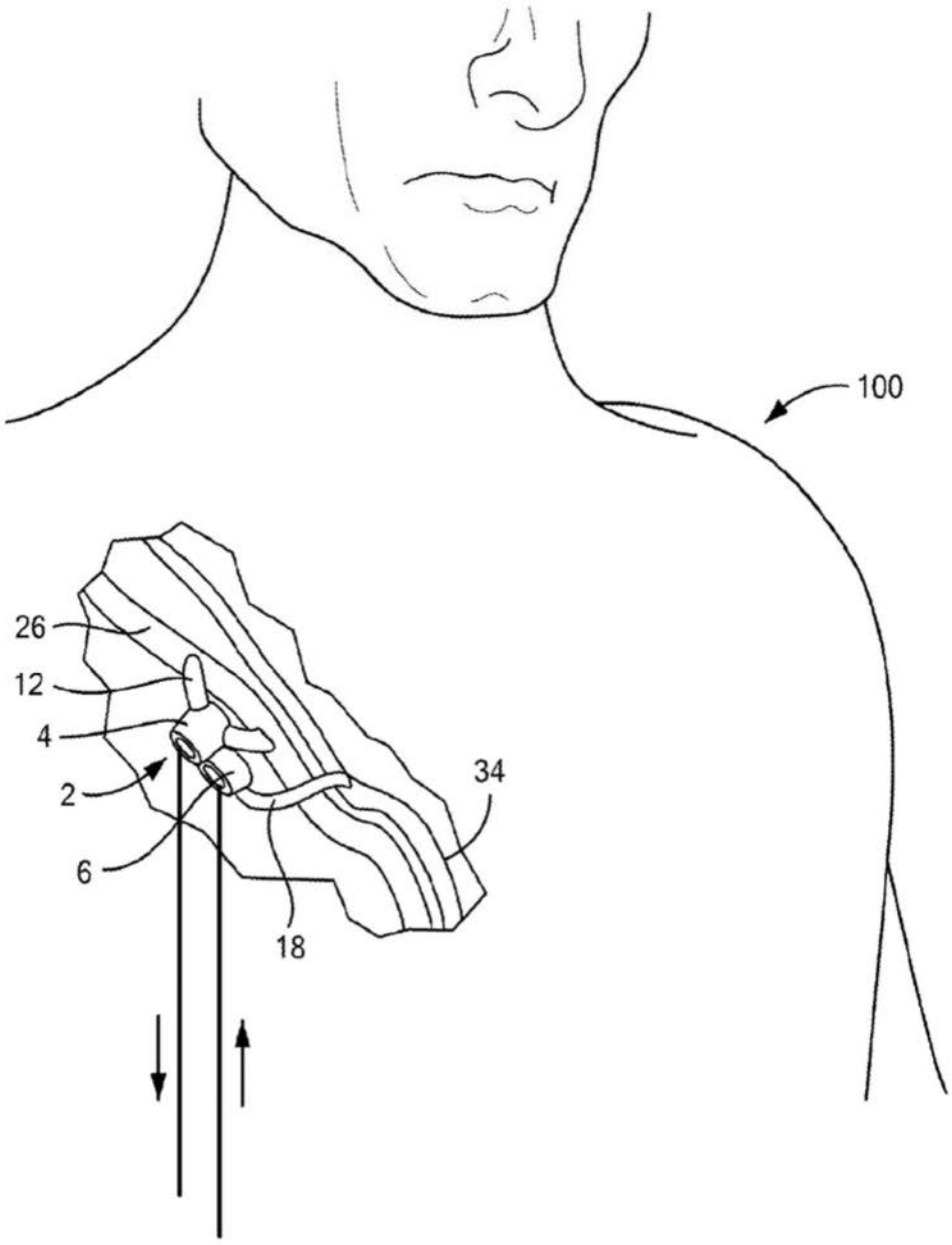


图10