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(54)发明名称

用于治疗外周动脉疾病的组合物和方法

(57)摘要

本公开提供了通过施用外核苷酸焦磷酸酯酶磷酸二酯酶-1(ENPP1)药剂或外核苷酸焦磷酸酯酶磷酸二酯酶-3(ENPP3)治疗受试者的外周动脉疾病的组合物和方法。

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1.一种用于治疗患有外周动脉疾病的受试者的方法,所述方法包括:向所述受试者施用有效量的ENPP1药剂,从而治疗所述受试者的所述外周动脉疾病。

2.一种用于减少和/或预防患有外周动脉疾病的受试者的外周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,从而减少和/或预防所述受试者的所述外周动脉中所述血管平滑肌细胞增殖的进展。

3.根据权利要求1或2所述的方法,其中所述受试者患有III期、IV期或IV期、III级外周动脉疾病。

4.一种用于抑制或减缓受试者的III期外周动脉疾病向IV期外周动脉疾病进展的方法,所述方法包括:向所述受试者施用有效量的ENPP1药剂,从而抑制和/或减缓所述受试者的III期外周动脉疾病向IV期外周动脉疾病进展。

5.根据权利要求1至4中任一项所述的方法,其中所述受试者患有常见的股动脉疾病。

6.根据权利要求1至4中任一项所述的方法,其中所述受试者患有股腘疾病。

7.根据权利要求1至4中任一项所述的方法,其中所述受试者患有胫腓疾病。

8.一种用于减少和/或预防需要在外周动脉上进行外科手术的受试者的所述外周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外周动脉疾病,所述方法包括:向所述受试者施用有效量的ENPP1药剂,从而减少和/或预防所述受试者的所述外周动脉的外科手术部位处所述外周动脉中血管平滑肌细胞增殖的进展。

9.根据权利要求8所述的方法,其中在所述外科手术之前、期间和/或之后施用所述药剂。

10.根据权利要求8或9所述的方法,其中所述外科手术包括放置支架。

11.根据权利要求1至10中任一项所述的方法,其中所述受试者不患有ENPP1缺乏症。

12.根据权利要求1至11中任一项所述的方法,其中所述ENPP1药剂包括ENPP1多肽。

13.根据权利要求1至11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。

14.根据权利要求1至11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。

15.根据权利要求12至14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。

16.根据权利要求12至14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。

17.根据权利要求12至14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。

18.根据权利要求12至14中任一项所述的方法,其中所述ENPP1多肽包括异源蛋白。

19.根据权利要求18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。

20.根据权利要求18或19所述的方法,其中所述异源蛋白为免疫球蛋白分子的Fc区。

21.根据权利要求20所述的方法,其中所述免疫球蛋白分子为IgG1分子。

22.根据权利要求18或19所述的方法,其中所述异源蛋白为白蛋白分子。

23.根据权利要求18至22中任一项所述的方法,其中所述异源蛋白为到所述ENPP1多肽

的羧基末端。

24.根据权利要求18至23中任一项所述的方法，其中所述ENPP1药剂包括接头。

25.根据权利要求24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。

26.根据权利要求24或25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。

27.根据权利要求1至26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。

28.根据权利要求1至26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。

29.根据权利要求1至28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、患有胆固醇或甘油三酯水平升高、患有糖尿病、患有肾病或肥胖。

30.一种用于减少和/或预防在外周动脉中经历支架放置的受试者的所述外周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，从而减少和/或预防所述外周动脉中血管平滑肌细胞增殖的进展。

31.根据权利要求30所述的方法，其中在支架放置之前、期间和/或之后施用所述药剂。

32.一种用于治疗患有外周动脉疾病的受试者的方法，所述方法包括：向所述受试者施用有效量的ENPP3药剂，从而治疗所述受试者的所述外周动脉疾病。

33.一种用于减少和/或预防患有外周动脉疾病的受试者的外周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ENPP3药剂，从而减少和/或预防所述受试者的所述外周动脉中所述血管平滑肌细胞增殖的进展。

34.根据权利要求32或33所述的方法，其中所述受试者患有III期、IV期或IV期、III级外周动脉疾病。

35.一种用于抑制或减缓受试者的III期外周动脉疾病向IV期外周动脉疾病进展的方法，所述方法包括：向所述受试者施用有效量的ENPP3药剂，从而抑制和/或减缓所述受试者的III期外周动脉疾病向IV期外周动脉疾病进展。

36.根据权利要求32至35中任一项所述的方法，其中所述受试者患有常见的股动脉疾病。

37.根据权利要求32至35中任一项所述的方法，其中所述受试者患有股腘疾病。

38.根据权利要求32至35中任一项所述的方法，其中所述受试者患有胫腓疾病。

39.一种用于减少和/或预防需要在外周动脉上进行外科手术的受试者的所述外周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外周动脉疾病，所述方法包括：向所述受试者施用有效量的ENPP1药剂，从而减少和/或预防所述受试者的所述外周动脉的外科手术部位处所述外周动脉中血管平滑肌细胞增殖的进展。

40.根据权利要求39所述的方法，其中在所述外科手术之前、期间和/或之后施用所述药剂。

41.根据权利要求39或40所述的方法，其中所述外科手术包括放置支架。

42.根据权利要求32至41中任一项所述的方法，其中所述受试者不患有ENPP1缺乏症。

43.根据权利要求32至42中任一项所述的方法，其中所述ENPP3药剂包括ENPP3多肽。

44.根据权利要求32至42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。

45.根据权利要求32至42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。

46.根据权利要求32至45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。

47.根据权利要求32至45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。

48.根据权利要求32至45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。

49.根据权利要求32至45中任一项所述的方法，其中所述ENPP3多肽包括异源蛋白。

50.根据权利要求49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。

51.根据权利要求49或50所述的方法，其中所述异源蛋白为免疫球蛋白分子的Fc区。

52.根据权利要求51所述的方法，其中所述免疫球蛋白分子为IgG1分子。

53.根据权利要求49或50所述的方法，其中所述异源蛋白为白蛋白分子。

54.根据权利要求49至53中任一项所述的方法，其中所述异源蛋白为到所述ENPP3多肽的羧基末端。

55.根据权利要求49至53中任一项所述的方法，其中所述ENPP3药剂包括接头。

56.根据权利要求55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。

57.根据权利要求55或56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。

58.根据权利要求32至57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。

59.根据权利要求32至57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。

60.根据权利要求32至59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、患有胆固醇或甘油三酯水平升高、患有糖尿病、患有肾病或肥胖。

61.一种用于减少和/或预防在外周动脉中经历支架放置的受试者的所述外周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ENPP3药剂，从而减少和/或预防所述外周动脉中血管平滑肌细胞增殖的进展。

62.根据权利要求30所述的方法，其中在支架放置之前、期间和/或之后施用所述ENPP3药剂。

63.一种涂覆支架，其包括：

血管支架；以及

所述支架上的涂层，所述涂层包括ENPP1药剂；以及

所述ENPP1药剂的载体，

其中所述涂层被配置成使所述ENPP1药剂以每天1μg/ml至10μg/ml的速率从所述支架

释放。

64.根据权利要求63所述的涂覆支架,基于所述涂层的总重量,所述ENPP1药剂的量介于1wt%与50wt%之间。

65.根据权利要求64所述的涂覆支架,其中所述ENPP1药剂选自由以下组成的组:ENPP1、ENPP1-Fc、ENPP1-白蛋白和ENPP1 mRNA。

66.根据权利要求63所述的涂覆支架,其中所述载体与所述ENPP1药剂无反应性。

67.根据权利要求63所述的涂覆支架,其中所述载体包括与所述ENPP1药剂物理结合的聚合物载体。

68.根据权利要求63所述的涂覆支架,其中所述载体包括与所述ENPP1药剂化学结合的聚合物载体。

69.根据权利要求63所述的涂覆支架,其中所述载体包括聚合物可生物降解载体。

70.根据权利要求63所述的涂覆支架,其中所述载体包括非聚合物载体。

71.根据权利要求70所述的涂覆支架,其中所述非聚合物载体选自由以下组成的组:维生素E、维生素E乙酸酯、维生素E琥珀酸酯、油酸、花生油和棉籽油。

72.根据权利要求63所述的涂覆支架,其中所述载体在体温下为液体。

73.根据权利要求63所述的涂覆支架,其中所述载体在体温下为固体。

74.一种涂覆支架,其包括:

血管支架;以及

所述支架上的涂层,所述涂层包括ENPP3药剂;以及

所述ENPP3药剂的载体,

其中所述涂层被配置成使所述ENPP3药剂以每天1μg/ml至10μg/ml的速率从所述支架释放。

75.根据权利要求74所述的涂覆支架,基于所述涂层的总重量,所述ENPP3药剂的量介于1wt%与50wt%之间。

76.根据权利要求75所述的涂覆支架,其中所述ENPP3药剂选自由以下组成的组:ENPP3、ENPP3-Fc、ENPP3-白蛋白和ENPP3 mRNA。

77.根据权利要求74所述的涂覆支架,其中所述载体与所述ENPP3药剂无反应性。

78.根据权利要求74所述的涂覆支架,其中所述载体包括与所述ENPP3药剂物理结合的聚合物载体。

79.根据权利要求74所述的涂覆支架,其中所述载体包括与所述ENPP3药剂化学结合的聚合物载体。

80.根据权利要求74所述的涂覆支架,其中所述载体包括聚合物可生物降解载体。

81.根据权利要求74所述的涂覆支架,其中所述载体包括非聚合物载体。

82.根据权利要求74所述的涂覆支架,其中所述非聚合物载体选自由以下组成的组:维生素E、维生素E乙酸酯、维生素E琥珀酸酯、油酸、花生油和棉籽油。

83.根据权利要求74所述的涂覆支架,其中所述载体在体温下为液体。

84.根据权利要求74所述的涂覆支架,其中所述载体在体温下为固体。

85.一种用于治疗患有外周动脉疾病的受试者的方法,所述方法包括:将涂覆有ENPP1药剂的动脉支架植入所述受试者的动脉中,其中所述植入的支架被配置成以有效量释放所

述ENPP1药剂,从而治疗所述受试者的所述外周动脉疾病。

86.一种用于减少和/或预防患有外周动脉疾病的受试者的外周动脉中血管平滑肌细胞增殖的进展的方法,所述方法包括:将涂覆有ENPP1药剂的动脉支架植入所述受试者的动脉中,其中所述植入的支架被配置成以有效量释放所述ENPP1药剂,从而减少和/或预防所述受试者的所述外周动脉中所述血管平滑肌细胞增殖的进展。

87.根据权利要求85或86所述的方法,其中所述受试者患有III期、IV期或IV期、III级外周动脉疾病。

88.一种用于抑制或减缓受试者的III期外周动脉疾病向IV期外周动脉疾病进展的方法,所述方法包括:将涂覆有ENPP1药剂的动脉支架植入所述受试者的动脉中,其中所述植入的支架被配置成以有效量释放所述ENPP1药剂,从而抑制和/或减缓所述受试者的III期外周动脉疾病向IV期外周动脉疾病进展。

89.根据权利要求85至88中任一项所述的方法,其中所述受试者患有常见的股动脉疾病。

90.根据权利要求85至88中任一项所述的方法,其中所述受试者患有股腘疾病。

91.根据权利要求85至88中任一项所述的方法,其中所述受试者患有胫腓疾病。

92.一种用于减少和/或预防患有需要在外周动脉上进行外科手术的病状的受试者的所述外周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外周动脉疾病,所述方法包括:将涂覆有ENPP1药剂的动脉支架植入所述受试者的动脉中,其中所述植入的支架被配置成以有效量释放所述ENPP1药剂,从而减少和/或预防所述受试者的所述外周动脉的外科手术部位处的所述外周动脉中血管平滑肌细胞增殖的进展。

93.根据权利要求92所述的方法,其中在所述外科手术之前、期间和/或之后施用所述药剂。

94.根据权利要求92或93所述的方法,其中所述需要外科手术的病状是由于先前在所述动脉中放置非洗脱式动脉支架而引起的。

95.根据权利要求92或93所述的方法,其中所述需要的病状是由于先前在所述动脉中放置洗脱式动脉支架而引起的,所述洗脱式动脉支架洗脱除了所述ENPP1药剂之外的治疗剂。

96.根据权利要求85至95中任一项所述的方法,其中所述受试者不患有ENPP1缺乏症。

97.根据权利要求85至96中任一项所述的方法,其中所述ENPP1药剂包括ENPP1多肽。

98.根据权利要求85至96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。

99.根据权利要求85至96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。

100.根据权利要求97至99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。

101.根据权利要求97至99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。

102.根据权利要求97至99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。

103.根据权利要求97至99中任一项所述的方法，其中所述ENPP1多肽包括异源蛋白。

104.根据权利要求103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。

105.根据权利要求103或104所述的方法，其中所述异源蛋白为免疫球蛋白分子的Fc区。

106.根据权利要求105所述的方法，其中所述免疫球蛋白分子为IgG1分子。

107.根据权利要求103或104所述的方法，其中所述异源蛋白为白蛋白分子。

108.根据权利要求103至107中任一项所述的方法，其中所述异源蛋白为到所述ENPP1多肽的羧基末端。

109.根据权利要求103至108中任一项所述的方法，其中所述ENPP1药剂包括接头。

110.根据权利要求109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。

111.根据权利要求109或110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。

112.根据权利要求85至111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。

113.根据权利要求85至111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。

114.根据权利要求85至113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、患有胆固醇或甘油三酯水平升高、患有糖尿病、患有肾病或肥胖。

115.一种用于治疗患有外周动脉疾病的受试者的方法，所述方法包括：将涂覆有ENPP3药剂的动脉支架植入所述受试者的动脉中，其中所述植入的支架被配置成以有效量释放所述ENPP3药剂，从而治疗所述受试者的所述外周动脉疾病。

116.一种用于减少和/或预防患有外周动脉疾病的受试者的外周动脉中血管平滑肌细胞增殖的进展的方法，所述方法包括：将涂覆有ENPP3药剂的动脉支架植入所述受试者的动脉中，其中所述植入的支架被配置成以有效量释放所述ENPP3药剂，从而减少和/或预防所述受试者的所述外周动脉中所述血管平滑肌细胞增殖的进展。

117.根据权利要求115或116所述的方法，其中所述受试者患有III期、IV期或IV期、III级外周动脉疾病。

118.一种用于抑制或减缓受试者的III期外周动脉疾病向IV期外周动脉疾病进展的方法，所述方法包括：将涂覆有ENPP3药剂的动脉支架植入所述受试者的动脉中，其中所述植入的支架被配置成以有效量释放所述ENPP1药剂，从而抑制和/或减缓所述受试者的III期外周动脉疾病向IV期外周动脉疾病进展。

119.根据权利要求115至118中任一项所述的方法，其中所述受试者患有常见的股动脉疾病。

120.根据权利要求115至118中任一项所述的方法，其中所述受试者患有股腘疾病。

121.根据权利要求115至118中任一项所述的方法其中所述受试者患有胫腓疾病。

122.一种用于减少和/或预防患有需要在外周动脉上进行外科手术的病状的受试者的所述外周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外周动脉疾病，

所述方法包括:将涂覆有ENPP3药剂的动脉支架植入所述受试者的动脉中,其中所述植入的支架被配置成以有效量释放所述ENPP3药剂,从而减少和/或预防所述受试者的所述外周动脉的外科手术部位处的所述外周动脉中血管平滑肌细胞增殖的进展。

123.根据权利要求122所述的方法,其中在所述外科手术之前、期间和/或之后施用所述药剂。

124.根据权利要求122或123所述的方法,其中所述需要外科手术的病状是由于先前在所述动脉中放置非洗脱式动脉支架而引起的。

125.根据权利要求122或123所述的方法,其中所述需要的病状是由于先前在所述动脉中放置洗脱式动脉支架而引起的,所述洗脱式动脉支架洗脱除了所述ENPP3药剂之外的治疗剂。

126.根据权利要求115至125中任一项所述的方法,其中所述受试者不患有ENPP1缺乏症。

127.根据权利要求115至126中任一项所述的方法,其中所述ENPP1药剂包括ENPP3多肽。

128.根据权利要求115至126中任一项所述的方法,其中所述ENPP3药剂包括编码ENPP1多肽的核酸。

129.根据权利要求115至126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。

130.根据权利要求127至129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。

131.根据权利要求127至129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。

132.根据权利要求127至129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。

133.根据权利要求127至129中任一项所述的方法,其中所述ENPP3多肽包括异源蛋白。

134.根据权利要求133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。

135.根据权利要求133或134所述的方法,其中所述异源蛋白为免疫球蛋白分子的Fc区。

136.根据权利要求135所述的方法,其中所述免疫球蛋白分子为IgG1分子。

137.根据权利要求133或134所述的方法,其中所述异源蛋白为白蛋白分子。

138.根据权利要求133至137中任一项所述的方法,其中所述异源蛋白为到所述ENPP3多肽的羧基末端。

139.根据权利要求133至138中任一项所述的方法,其中所述ENPP3药剂包括接头。

140.根据权利要求139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。

141.根据权利要求139或140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。

142.根据权利要求115至141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。

143.根据权利要求115至141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。

144.根据权利要求115至143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、患有胆固醇或甘油三酯水平升高、患有糖尿病、患有肾病或肥胖。

145.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。

146.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。

147.根据权利要求63至73中任一项所述的涂覆支架,其中所述ENPP1药剂包括保留酶促活性的ENPP1变体。

148.根据权利要求74至84中任一项所述的涂覆支架,其中所述ENPP3药剂包括保留酶促活性的ENPP3变体。

用于治疗外周动脉疾病的组合物和方法

技术领域

[0001] 本公开涉及治疗血管疾病的组合物和方法。

[0002] 相关申请交叉引用

[0003] 本申请要求于2020年5月27日提交的美国申请第63/030,840号的优先权,所述美国申请的内容在此通过引用以其整体并入。

[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5月27日的所述ASCII副本被命名为4427-10202_sequence_ST25.txt并且大小为340千字节。

背景技术

[0006] 外周动脉疾病(PAD)是一种常见的病症,由动脉粥样硬化引起,其特征在于下肢动脉狭窄和/或阻塞,导致肌肉灌注和氧合降低。有症状的PAD患者出现间歇性跛行(IC)症状,这是指由于运动引起的缺血,在运动过程中四肢肌肉出现疲劳、不适或疼痛。PAD是进行性的,并且可导致坏死、坏疽和需要截肢。由于PAD的复杂性和多因素起源,以及肌肉适应性应答的差异,PAD的确切病理生理机制仍在很大程度上未知。

发明内容

[0007] 本公开至少部分基于令人惊讶的发现,即ENPP1多肽抑制了哺乳动物外周动脉创伤后血管平滑肌细胞的不期望的增殖。如工作实例中所描述的,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(Yorkshire swine)血管成形术后狭窄的能力。与载体对照相比,用ENPP1-Fc蛋白治疗的动物在支架化深动脉中显示出明显较低的内膜增厚,这表明ENPP1在抑制和/或预防受损外周动脉内膜增厚和/或增殖方面具有治疗效用。

[0008] 因此,一方面,本公开涉及一种用于治疗患有外周动脉疾病的受试者的方法,所述方法包括:向所述受试者施用有效量的ENPP1药剂,从而治疗所述受试者的所述外周动脉疾病。

[0009] 本公开包含一种用于减少和/或预防受试者的外周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,从而减少和/或者预防所述受试者的所述外周动脉中所述血管平滑肌细胞增殖的进展。

[0010] 在本文所述的任何方法的一些实施例中,所述受试者患有III期、IV期或IV期、III级外周动脉疾病。

[0011] 本公开还包含一种用于抑制或减缓受试者的III期外周动脉疾病向IV期外周动脉疾病进展的方法,所述方法包括:向所述受试者施用有效量的ENPP1药剂,从而抑制和/或减缓所述受试者的III期外周动脉疾病向IV期外周动脉疾病进展。

[0012] 在本文所述的任何方法的一些实施例中,所述受试者患有常见的股动脉疾病。

[0013] 在本文所述的任何方法的一些实施例中,所述受试者患有股腘疾病。

[0014] 在本文所述的任何方法的一些实施例中,所述受试者患有胫腓疾病。

[0015] 本公开还涉及一种用于减少和/或预防在所述外周动脉上经历外科手术的受试者的外周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,从而减少和/或预防所述受试者的所述外周动脉的外科手术部位处所述外周动脉中血管平滑肌细胞增殖的进展。

[0016] 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。

[0017] 在本文所述的任何方法的一些实施例中,所述外科手术包括放置支架。

[0018] 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。

[0019] 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。

[0020] 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。

[0021] 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。

[0022] 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。

[0023] 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。

[0024] 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。

[0025] 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。

[0026] 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。

[0027] 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。

[0028] 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。

[0029] 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。

[0030] 在本文所述的方法中的任何方法的一些实施例中,所述异源蛋白为到所述ENPP1多肽的羧基末端。

[0031] 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。

[0032] 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。

[0033] 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。

[0034] 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。

[0035] 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。

[0036] 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、患有胆固醇或甘油三酯水平升高、患有糖尿病、患有肾病或肥胖。

[0037] 另一方面，本公开还包含一种用于减少和/或预防在外周动脉中经历支架放置的受试者的所述外周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，从而减少和/或预防所述外周动脉中血管平滑肌细胞增殖的进展。

[0038] 另一方面，本公开的特征在于一种用于减少和/或预防在外周动脉中经历支架放置的受试者的所述外周动脉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，从而减少和/或预防所述外周动脉中的狭窄或再狭窄。

[0039] 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/或之后施用所述药剂。

[0040] 另一方面，本公开的特征在于一种用于治疗患有外周动脉疾病的受试者的方法，所述方法包括：向所述受试者施用有效量的ENPP3药剂，从而治疗所述受试者的所述外周动脉疾病。

[0041] 在又另一方面，本公开的特征在于一种用于减少和/或预防患有外周动脉疾病的受试者的外周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ENPP3药剂，从而减少和/或者预防所述受试者的所述外周动脉中所述血管平滑肌细胞增殖的进展。

[0042] 在本文所述的任何方法的一些实施例中，所述受试者患有III期、IV期或IV期、III级外周动脉疾病。

[0043] 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III期外周动脉疾病向IV期外周动脉疾病进展的方法，所述方法包括：向所述受试者施用有效量的ENPP3药剂，从而抑制和/或减缓所述受试者的III期外周动脉疾病向IV期外周动脉疾病进展。

[0044] 在本文所述的任何方法的一些实施例中，所述受试者患有常见的股动脉疾病。

[0045] 在本文所述的任何方法的一些实施例中，所述受试者患有股腘疾病。

[0046] 在本文所述的任何方法的一些实施例中，所述受试者患有胫腓疾病。

[0047] 另一方面，本公开的特征在于一种用于减少和/或预防在外周动脉上需要外科手术的受试者的所述外周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外周动脉疾病，所述方法包括：向所述受试者施用有效量的ENPP3药剂，从而减少和/或预防所述受试者的所述外周动脉的外科手术部位处所述外周动脉中血管平滑肌细胞增殖的进展。

[0048] 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。

[0049] 在本文所述的任何方法的一些实施例中，所述外科手术包括放置支架。

[0050] 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。

[0051] 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。

[0052] 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。

[0053] 在本文所述的方法中的任何方法的一些实施例中,所述ENPP3药剂包括编码ENPP3多肽的核酸。

[0054] 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。

[0055] 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。

[0056] 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。

[0057] 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

[0058] 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。

[0059] 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。

[0060] 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。

[0061] 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。

[0062] 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。

[0063] 在本文所述的方法中的任何方法的一些实施例中,所述异源蛋白为到所述ENPP3多肽的羧基末端。

[0064] 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。

[0065] 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。

[0066] 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。

[0067] 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。

[0068] 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。

[0069] 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、患有胆固醇或甘油三酯水平升高、患有糖尿病、患有肾病或肥胖。

[0070] 在本文所述的任何方法的一些实施例中,所述受试者患有闭塞性外周动脉疾病。

[0071] 另一方面,本公开的特征在于一种用于减少和/或预防在外周动脉中经历支架放置的受试者的所述外周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ENPP3药剂,从而减少和/或预防所述外周动脉中血管平滑肌细胞增殖的进展。

[0072] 另一方面,本公开的特征在于一种用于减少和/或预防在外周动脉中经历支架放

置的受试者的所述外周动脉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,从而减少和/或预防所述外周动脉中的狭窄或再狭窄。

[0073] 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。

[0074] 在又另一方面,本公开的特征在于一种涂覆支架,其包括:血管支架;以及所述支架上的涂层,所述涂层包括ENPP1药剂;以及所述ENPP1药剂的载体,其中所述涂层被配置成使所述ENPP1药剂以每天1μug/ml至10μug/ml的速率从所述支架释放。

[0075] 在本文所述的支架中的任何支架的一些实施例中,基于所述涂层的总重量,所述ENPP1药剂的量介于1wt%与50wt%之间。

[0076] 在本文所述的支架中的任何支架的一些实施例中,所述ENPP1药剂选自由以下组成的组:ENPP1、ENPP1-Fc、ENPP1-白蛋白和ENPP1mRNA。

[0077] 在本文所述的支架中的任何支架的一些实施例中,所述ENPP1药剂包括保留酶促活性的ENPP1变体。

[0078] 在本文所述的支架中的任何支架的一些实施例中,所述载体与所述ENPP1药剂无反应性。

[0079] 在本文所述的支架中的任何支架的一些实施例中,所述载体包括与所述ENPP1药剂物理结合的聚合物载体。

[0080] 在本文所述的支架中的任何支架的一些实施例中,所述载体包括与所述ENPP1药剂化学结合的聚合物载体。

[0081] 在本文所述的支架中的任何支架的一些实施例中,所述载体包括聚合物可生物降解载体。

[0082] 在本文所述的支架中的任何支架的一些实施例中,所述载体包括非聚合物载体。

[0083] 在本文所述的支架中的任何支架的一些实施例中,所述非聚合物载体选自由以下组成的组:维生素E、维生素E乙酸酯、维生素E琥珀酸酯、油酸、花生油和棉籽油。

[0084] 在本文所述的方法中的任何支架的一些实施例中,所述载体在体温下为液体。

[0085] 在本文所述的方法中的任何支架的一些实施例中,所述载体在体温下为固体。

[0086] 在又另一方面,本公开的特征在于一种涂覆支架,其包括:血管支架;以及所述支架上的涂层,所述涂层包括ENPP3药剂以及所述ENPP3药剂的载体,其中所述涂层被配置成使所述ENPP3药剂以每天1μg/ml至10μg/ml的速率从所述支架释放。

[0087] 在本文所述的支架中的任何支架的一些实施例中,基于所述涂层的总重量,所述ENPP3药剂的量介于1wt%与50wt%之间。

[0088] 在本文所述的支架中的任何支架的一些实施例中,所述ENPP3药剂选自由以下组成的组:ENPP3、ENPP3-Fc、ENPP3-白蛋白和ENPP3mRNA。

[0089] 在本文所述的支架中的任何支架的一些实施例中,所述ENPP3药剂包括保留酶促活性的ENPP3变体。

[0090] 在本文所述的支架中的任何支架的一些实施例中,所述载体与所述ENPP3药剂无反应性。

[0091] 在本文所述的支架中的任何支架的一些实施例中,所述载体包括与所述ENPP3药剂物理结合的聚合物载体。

[0092] 在本文所述的支架中的任何支架的一些实施例中，所述载体包括与所述ENPP3药剂化学结合的聚合物载体。

[0093] 在本文所述的支架中的任何支架的一些实施例中，所述载体包括聚合物可生物降解载体。

[0094] 在本文所述的支架中的任何支架的一些实施例中，所述载体包括非聚合物载体。

[0095] 在本文所述的支架中的任何支架的一些实施例中，所述非聚合物载体选自由以下组成的组：维生素E、维生素E乙酸酯、维生素E琥珀酸酯、油酸、花生油和棉籽油。

[0096] 在本文所述的方法中的任何支架的一些实施例中，所述载体在体温下为液体。

[0097] 在本文所述的方法中的任何支架的一些实施例中，所述载体在体温下为固体。

[0098] 在又另一方面，本公开的特征在于一种用于治疗患有外周动脉疾病的受试者的方法，所述方法包括：将涂覆有ENPP1药剂的动脉支架植入所述受试者动脉中，其中所述植入的支架被配置成以有效量释放所述ENPP1药剂，从而治疗所述受试者的所述外周动脉疾病。

[0099] 在又另一方面，本公开的特征在于一种用于减少和/或预防患有外周动脉疾病的受试者的外周动脉中血管平滑肌细胞增殖的进展的方法，所述方法包括：将涂覆有ENPP1药剂的动脉支架植入所述受试者的动脉中，其中所述植入的支架被配置成以有效量释放所述ENPP1药剂，从而减少和/或预防所述受试者的所述外周动脉中所述血管平滑肌细胞增殖的进展。

[0100] 在本文所述的任何方法的一些实施例中，所述受试者患有III期、IV期或IV期、III级外周动脉疾病。

[0101] 在又另一方面，本公开的特征在于一种用于抑制或减缓受试者的III期外周动脉疾病向IV期外周动脉疾病进展的方法，所述方法包括：将涂覆有ENPP1药剂的动脉支架植入所述受试者的动脉中，其中所述植入的支架被配置成以有效量释放所述ENPP1药剂，从而抑制和/或减缓所述受试者的III期外周动脉疾病向IV期外周动脉疾病进展。

[0102] 在本文所述的任何方法的一些实施例中，所述受试者患有常见的股动脉疾病。

[0103] 在本文所述的任何方法的一些实施例中，所述受试者患有股腘疾病。

[0104] 在本文所述的任何方法的一些实施例中，所述受试者患有胫腓疾病。

[0105] 在又另一方面，本公开的特征在于一种用于减少和/或预防患有需要在外周动脉上进行外科手术的病状的受试者的所述外周动脉中血管平滑肌细胞增殖的进展的方法，其中所处受试者患有外周动脉疾病，所述方法包括：将涂覆有ENPP1药剂的动脉支架植入所述受试者的动脉中，其中所述植入的支架被配置成以有效量释放所述ENPP1药剂，从而减少和/或预防所述受试者的所述外周动脉的外科手术部位处的所述外周动脉中血管平滑肌细胞增殖的进展。

[0106] 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。

[0107] 在本文所述的方法中的任何方法的一些实施例中，所述需要外科手术的病状是由于先前在所述动脉中放置非洗脱式动脉支架而引起的。

[0108] 在本文所述的方法中的任何方法的一些实施例中，所述需要的病状是由于先前在所述动脉中放置洗脱式动脉支架而引起的，所述洗脱式动脉支架洗脱除了所述ENPP1药剂之外的治疗剂。

[0109] 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。

[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药剂包括ENPP1多肽。

[0111] 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。

[0112] 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。

[0113] 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。

[0114] 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。

[0115] 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。

[0116] 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。

[0117] 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。

[0118] 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。

[0119] 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。

[0120] 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。

[0121] 在本文所述的方法中的任何方法的一些实施例中,所述异源蛋白为到所述ENPP1多肽的羧基末端。

[0122] 在本文所述的方法中的任何方法的一些实施例中,所述ENPP1药剂包括接头。

[0123] 在本文所述的方法中的任何方法的一些实施例中,所述ENPP1多肽和所述异源蛋白。

[0124] 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。

[0125] 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。

[0126] 在本文所述的方法中的任何方法的一些实施例中,其中所述ENPP1药剂静脉内施用于所述受试者。

[0127] 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、患有胆固醇或甘油三酯水平升高、患有糖尿病、患有肾病或肥胖。

[0128] 在又另一方面,本公开的特征在于一种用于治疗患有外周动脉疾病的受试者的方法,所述方法包括:将涂覆有ENPP3药剂的动脉支架植入所述受试者动脉中,其中所述植入的支架被配置成以有效量释放所述ENPP3药剂,从而治疗所述受试者的所述外周动脉疾病。

[0129] 在又另一方面,本公开的特征在于一种用于减少和/或预防患有外周动脉疾病的受试者的外周动脉中血管平滑肌细胞增殖的进展的方法,所述方法包括:将涂覆有ENPP3药

剂的动脉支架植入所述受试者的动脉中,其中所述植入的支架被配置成以有效量释放所述ENPP3药剂,从而减少和/或预防所述受试者的所述外周动脉中所述血管平滑肌细胞增殖的进展。

[0130] 在本文所述的任何方法的一些实施例中,所述受试者患有III期、IV期或IV期、III级外周动脉疾病。

[0131] 在又另一方面,本公开的特征在于一种用于抑制或减缓受试者的III期外周动脉疾病向IV期外周动脉疾病进展的方法,所述方法包括:将涂覆有ENPP3药剂的动脉支架植入所述受试者的动脉中,其中所述植入的支架被配置成以有效量释放所述ENPP1药剂,从而抑制和/或减缓所述受试者的III期外周动脉疾病向IV期外周动脉疾病进展。

[0132] 在本文所述的任何方法的一些实施例中,所述受试者患有常见的股动脉疾病。

[0133] 在本文所述的任何方法的一些实施例中,所述受试者患有股腘疾病。

[0134] 在本文所述的任何方法的一些实施例中,所述受试者患有胫腓疾病。

[0135] 在又另一方面,本公开的特征在于一种用于减少和/或预防患有需要在外周动脉上进行外科手术的病状的受试者的所述外周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外周动脉疾病,所述方法包括:将涂覆有ENPP3药剂的动脉支架植入所述受试者的动脉中,其中所述植入的支架被配置成以有效量释放所述ENPP3药剂,从而减少和/或预防所述受试者的所述外周动脉的外科手术部位处的所述外周动脉中血管平滑肌细胞增殖的进展。

[0136] 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。

[0137] 在本文所述的方法中的任何方法的一些实施例中,所述需要外科手术的病状是由于先前在所述动脉中放置非洗脱式动脉支架而引起的。

[0138] 在本文所述的方法中的任何方法的一些实施例中,所述需要的病状是由于先前在所述动脉中放置洗脱式动脉支架而引起的,所述洗脱式动脉支架洗脱除了所述ENPP3药剂之外的治疗剂。

[0139] 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。

[0140] 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ENPP3多肽。

[0141] 在本文描述的任何方法的一些实施例中,ENPP3药剂包括编码ENPP1多肽的核酸。

[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药剂包括病毒载体,所述病毒载体包括编码ENPP3多肽的核酸。

[0143] 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。

[0144] 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。

[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多肽包括SEQ ID NO:7的氨基酸49至875。

[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多肽包括异源蛋白。

[0147] 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。

[0148] 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。

[0149] 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。

[0150] 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。

[0151] 在本文所述的方法中的任何方法的一些实施例中,所述异源蛋白为到所述ENPP3多肽的羧基末端。

[0152] 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。

[0153] 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。

[0154] 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。

[0155] 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。

[0156] 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。

[0157] 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、患有胆固醇或甘油三酯水平升高、患有糖尿病、患有肾病或肥胖。

[0158] 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

[0159] 图1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。

[0160] 图2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。

[0161] 图3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。

[0162] 图4A是在未涂覆支架存在下经历再狭窄的动脉的横截面。内皮12通常用作平滑肌细胞14的层与动脉内腔20之间的固态屏障。内皮12中的小裂口16可以使平滑肌细胞14暴露,所述平滑肌细胞然后可以迁移到动脉内腔20中并且超级增殖成团块18,所述团块可能部分或完全阻塞内腔20,即使在如血管成形术等程序60期间在动脉10中放置了未涂覆支架21以保持动脉内腔20打开也是如此。图4B为含有涂覆支架22的动脉10的横截面。支架具有含有载体和抑制和或防止再狭窄的生物活性化合物,如ENPP1药剂65等的涂层24。通过使用具有此涂层24的支架,可以减少或消除图4A中示出的内皮12中的裂口16。另外,消除或显著

减少了通过平滑肌细胞14的增殖产生的团块18，如图4A所示。

具体实施方式

[0163] 定义

[0164] 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。

[0165] 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。

[0166] 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。

[0167] 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。

[0168] 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。

[0169] 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。

[0170] 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＝7.8s^{-1}。

[0171] 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。

[0172] 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.)

[0173] 如本文所使用的,术语“PPi”是指无机焦磷酸酯。

[0174] 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。

[0175] 如本文所使用的,术语“ENPP1前体蛋白”是指其信号肽序列位于ENPP1N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。

[0176] 如本文所使用的,术语“ENPP3前体蛋白”是指其信号肽序列位于ENPP3N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。

[0177] 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)。

[0178] 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。

[0179] 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。

[0180] 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。

[0181] 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。

[0182] 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。

[0183] 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。

[0184] ENPP1或ENPP3的“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。

[0185] 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。

[0186] 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。

[0187] 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)。

[0188] 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。

[0189] 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。

[0190] 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。

[0191] 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。

[0192] 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。

[0193] 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。

[0194] 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。

[0195] 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。

[0196] 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。

[0197] 如本文所定义的,短语“血管创伤”是指对血管,即,动脉或静脉的损伤,所述动脉将血液载送到末端或器官,所述静脉使血液返回到心脏。血管损伤还可能是由非侵入性程序,如血管旁路外科手术造成的。

[0198] 如本文所定义的,短语“意外创伤”是指如动脉等血管受到钝性损伤或穿透性损伤,所述钝性损伤发生在血管由于施加物理力而被挤压或拉伸时,穿透性损伤发生在血管被刺穿、撕裂或切断时。钝性损伤发生在物理改变期间,如拳击,并且穿透性损伤是由于如刀或枪弹伤等尖锐物体发生的。创伤或损伤可能是由不同因素造成的,如辐射、病毒感染、

免疫复合物发展和高脂血症。

[0199] 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。

[0200] 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。

[0201] 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。

[0202] 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。

[0203] 如本文所用，术语“消融”是指身体部位或组织或其功能的去除或破坏。消融可以通过外科手术、激素、药物、射频、热来进行。

[0204] 如本文所用，短语“减少或预防肌内膜增生”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。

[0205] 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。

[0206] 如本文所用，术语“支架”是指放置在血管、管或导管内以帮助愈合或缓解阻塞或防止通道变窄的管状支撑件。支架总体上包括由金属(例如:不锈钢、钴合金、镍-钛合金、锰合金、钼合金、铂合金、钨合金)或聚合物(例如:硅酮)制成的可膨胀网格线圈。

[0207] 如本文所用，术语“血管支架”是指放置在哺乳动物的动脉或静脉内以帮助愈合或缓解阻塞或防止动脉通道变窄的管状支撑件。

[0208] 如本文所用，术语“涂覆支架”或“洗脱式支架”是指涂覆有治疗分子，如蛋白质、化学化合物或核酸的支架，所述治疗分子在植入部位处从支架表面(内部或外部)逐渐洗脱，由此提供治疗性缓解。如ENPP1药剂或ENPP3药剂等治疗分子可以直接与金属支架键合，并且一些治疗分子与基质聚合物键合，所述基质聚合物充当药物储库以确保展开期间的药物保留和在支架上的均匀分布。涂覆在支架上的聚合物的类型、组成和设计指示药物在原位植入之后的几周或几个月的时间段内的持续时间释放的洗脱动力学。涂层材料可以分类为有机物质对无机物质、生物可蚀性物质对非生物可蚀性物质以及合成物质对天然存在的物质。

[0209] 如本文所用，术语“涂层”是指包括聚合物载体的组合物，所述聚合物载体与ENPP1药剂或ENPP3药剂结合使用以涂覆支架。涂层可以以包括悬浮在聚合物基质中的ENPP1药剂或ENPP3药剂的喷雾或干燥膜的形式施涂。聚合物载体的量足以提供聚合物基质或对ENPP1药剂或ENPP3药剂的支撑。聚合物优选地与ENPP1药剂或ENPP3药剂无反应性，即当两者混合时不发生化学反应。

[0210] 如本文所用,术语“溶剂”是根据其最广泛公认的定义而定义的,并且包含载体(聚合物)和ENPP1药剂或ENPP3药剂在其中可以在室温或20℃至40℃下完全或部分溶解以形成涂层组合物的任何材料。无菌双蒸馏水是优选溶剂。

[0211] 如本文所用,术语“损伤部位”是指脉管系统中血流或脊髓流体由于脂质、胆固醇、钙和各种类型的细胞,如平滑肌细胞和血小板的累积而受限的区。损伤部位通常通过使用心脏插管来鉴定。在心脏插管期间,通过塑料导引器套(插入到手臂或腿部的血管中的短、中空管)插入被称为导管的长、窄的管。在X射线机的辅助下,引导导管穿过血管到达冠状动脉。通过导管注入造影材料并且随着造影材料移动穿过心脏腔、瓣和主血管产生x射线图像(冠状血管造影)。造影材料的数字照片用于鉴定冠状动脉中变窄或阻塞的部位。可以进行被称为血管内超声(IVUS)和血流储备分数(FFR)的额外成像程序以及在一些情况下心脏插管以获得血管壁的详细图像。

[0212] 如本文所用,“植入物的位点”是指ENPP1或ENPP3涂覆的支架植入在脉管系统中的区。本发明的涂覆支架可以放置在组织损伤部位的中心处,紧邻组织损伤部位,或者位于距组织损伤部位的中心的任一侧200μm内。

[0213] 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。

[0214] 如本文所用,术语“钝力创伤”是指通过撞击、损伤或身体攻击或高速撞击对身体部位造成的身体创伤。钝性创伤可能导致挫伤、擦伤、裂伤和/或骨折。

[0215] 如本文所用,术语“非外科手术组织损伤”或“穿透性创伤”是指在如射弹或刀等物体进入身体组织从而产生开放伤口时发生的对身体部位的创伤。

[0216] 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。

[0217] 如本文所用,术语“外周动脉疾病”(PAD)是指服务于腿、胃、手臂和头部的外周动脉变窄。(在这种情况下,“外周”是指远离心脏,在身体的外部区域。)PAD最常影响腿部动脉。PAD的发生通常是由于动脉粥样硬化,即胆固醇和脂肪沉积(斑块)的堆积,这会使血液流向手臂、腿和脚的动脉变窄或受阻。由于动脉壁中的斑块堆积,细胞的氧气供应也受到限制。PAD涉及下肢的最常见症状是行走或爬楼梯时腿部或臀部肌肉抽筋、疼痛或疲劳。患有外周动脉疾病的患者患冠心病、心脏病或中风的风险较高。如果不治疗,PAD可能导致坏疽和截肢。美国心脏病学会(American College of Cardiology)/《美国心脏协会实践指南(American Heart Association Practice Guidelines)》将PAD的表现分为四类:无症状、跛行、严重肢体缺血和急性肢体缺血(ALI)。至少有两个主要的分类标准是本领域常规用于对PAD严重程度进行分类的标准,Fontaine分类系统和Rutherford分类系统(外周动脉疾病分类系统概述(Overview of Classification Systems in Peripheral Artery Disease),Rulon L.Hardman,《介入放射学研讨会(Semin Intervent Radiol)》2014;31:378-388)

[0218] 如本文所用,术语“跛行”是指下肢(通常是小腿)的疲劳、不适或疼痛,这可通过运

动再现,并且通过休息缓解。

[0219] 如本文所用,术语“严重肢体缺血(CLI)”是指患者经历慢性缺血性静息疼痛、夜间卧痛或可能包含溃疡或坏疽的缺血性皮肤损伤的病状。

[0220] 如本文所用,术语“急性肢体缺血(ALI)”是指肢体灌注突然减少,导致对肢体生存能力造成直接威胁的患者。

[0221] 如本文所用,术语“Fontaine分类系统”是指由Fontaine等人开发的分类系统(Fontaine R,Kim M,Kieny R.外周循环障碍的外科治疗(Surgical treatment of peripheral circulation disorders)[德语].《瑞士化学学报(Helv Chir Acta)》1954;21(5-6):499-533)。此分类系统将患者的临床表现分为四个期。所述系统仅基于临床症状,没有其它诊断测试,并且如下表所示。

[0222]

等级	症状
I期PAD	无症状、不完全血管阻塞
II期PAD	肢体轻度跛行疼痛
IIA期PAD	距离>200m的跛行
IIB期PAD	距离<200m的跛行
III期PAD	静息疼痛,主要在脚上
IV期PAD	肢体坏死和/或坏疽

[0223] 如本文所用,术语“Rutherford分类系统”是指由Rutherford等人开发的分类系统。(Rutherford RB,Flanigan DP,Gupta SK等人处理下肢缺血报告的建议标准(Suggested standards for reports dealing with lower extremity ischemia).《血管外科杂志(J Vasc Surg)》1986;4(1):80-94)。Rutherford系统将PAD分为急性和慢性肢体缺血,强调每种表现都需要不同的治疗算法。Rutherford分类还将患者的临床症状与客观结果相关联,包含多普勒(Doppler)、动脉肱指数(ABI)和脉搏体积记录。

[0224] Rutherford的慢性肢体缺血分类与Fontaine的分类最为相似,增加了客观的无创数据,如跑步机测试。跑步机方案在其它出版物中有很好的描述。(Høyer C,Sandermann J,Petersen LJ.趾肱指数在外周动脉疾病诊断中的应用(The toe-brachial index in the diagnosis of peripheral arterial disease).《血管外科杂志》2013;58(1):231-238)。有或无运动前和运动后ABI的跑步机运动测试有助于区分有运动腿部症状患者的跛行和假性跛行。无法进行跑步机测试的患者可以使用足底弯曲或大腿血压袖带压迫进行类似的压力测试,以导致反应性充血。针对慢性肢体缺血的Rutherford的分类如下表所示。

[0225]

等级	类别	临床描述	客观标准
0	0	无症状——无血流动力学意义的闭塞性疾病	正常跑步机或反应性充血测试
	1	轻度跛行	完成跑步机运动；运动后 AP> 50 mm Hg但至少低于静息值20 mm Hg
I	2	中度跛行	1类与3类之间
	3	重度跛行	无法完成标准跑步机运动，并且运动后 AP< 50 mm Hg
II	4	缺血性静息疼痛	静息 AP < 40 mm Hg，踝关节或跖骨 PVR 平坦或几乎不跳动；TP < 30 mm Hg
III	5	轻度组织损失——不愈合溃疡，局灶性坏疽伴弥漫性足缺血	静息 AP < 60 mm Hg，脚踝或跖骨 PVR 平坦或几乎不跳动；TP < 40 mm Hg
	6	严重的组织损失——延伸到 TM 水平以上，功能性足部不再可挽救	与5类相同

[0226] 缩略语:AP,踝关节压力;PVR,脉搏体积记录;TM,跨跖;TP,脚趾压力。

[0227] 如本文所用,术语“脚趾压力”是指脚趾血压与手臂血压的比较测量

[0228] 如本文所用,术语“脚踝压力”是指小腿血压与手臂血压的比较测量

[0229] 如本文所用,术语“脉搏体积记录”是指无创血管测试,其中使用血压袖带和手持式超声装置(如多普勒或换能器)来获得关于手臂和腿部动脉血流的信息。如本文所用,术语“III期外周动脉疾病”是指如Fontaine分类系统所指示的PAD疾病阶段

[0230] 如本文所用,术语“IV期外周动脉疾病”是指如Fontaine分类系统所分类的PAD疾病阶段

[0231] 如本文所用,术语“IV期、III级外周动脉疾病”是指如Rutherford分类系统所分类的PAD疾病阶段

[0232] 如本文所用,术语“常见的股动脉疾病”是指其中患者的股动脉中发生PAD导致的闭塞的疾病状态。

[0233] 如本文所用,术语“股腘疾病”是指其中患者由于股腘动脉中的PAD而发生阻塞性闭塞的疾病状态。

[0234] 如本文所用,术语“胫腓疾病”是指其中患者由于动脉段(称为胫腓干)中的PAD而发生阻塞性闭塞的疾病状态,所述动脉段位于膝盖下方,远离腘动脉的胫骨前动脉起点,并且靠近胫后动脉和腓动脉的分支点。

[0235] 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。

[0236] 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。

[0237] 如本文所用,术语“血管成形术”是指打开心脏周围堵塞或狭窄的动脉的医疗程序。这是动脉狭窄或堵塞的标准治疗

[0238] “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))

[0239] 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。

[0240] 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。

[0241] 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。

[0242] 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。

[0243] 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。

[0244] 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。

[0245] 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。

[0246] 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

[0247] 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。

[0248] 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。

[0249] 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,商品编号:10006(2015))。

[0250] 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。

[0251] 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。

[0252] 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钙化。

[0253] 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。

[0254] 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大脑病症相关,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。

[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
```

[0282]

```
                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
```

[0283]

Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr Ile
Cys
660 665 670
Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp Ile
Leu
675 680 685
Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser Phe
Ser
690 695 700
Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile Pro
Leu
705 710 715
720
Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val
Ser
725 730 735
Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser Gly
Ile
740 745 750
Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln
Ser
755 760 765
Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys
Tyr
770 775 780
Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val Phe

[0284]

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

[0285] SEQ ID No:2-天青杀素-ENPP1-FC

[0286] MTRLTVLALLAGLLASSRA**APSCAKEVKSCKGRCFERTFGNCRCDAACVELGNCCLDYQETCIEPE
HIWTCNKFRCGEKRLTRSLCACSDDCKDKGDCCINYSSVCQGEKSWVEEPCESINEPQCPAGFETPPT
LLFSLDGFRAEYLHTWGGLLPVISKLKKCGTYTKNMRPVYPTKTFPNHYSIVTGLYPESHGIIDNKMY
DPKMNASFSLKSKEKFNPEWYKGEPIWVTAKYQGLKSGTFFWPGSDVEINGIFPDIYKMYNGSVPFEE
RILAVLQWLQLPKDERPHFYTLYLEEPDSSGHSYGPVSSEVIKALQRVDGMVGMLMDGLKELNLHRCL
NLILISDHGMEQGSCKKYIYLNKYLGDVKNIKVIYGPAARLRPSDVPDKYYSFNYEGIARNLSCREPN
QHFKPYLKHFLPKRLHFAKSDRIEPLTFYLDPQWQLALNPSERKYCGSGFHGSDNVFSNMQALFVGYG
PGFKHGIEADTFENIEVYNLMCDLLNLTPAPNNGTHGSLNHLLKNPVYTPKHPKEVHPLVQCPFTRNP
RDNLGCSCNPSILPIEDFQTQFNLTVAEEKIIKHETLPYGRPRVLQKENTICLLSQHQFMSGYSQDIL
MPLWTSYTVDRNDSFSTEDFSNCLYQDFRIPLSPVHKCSFYKNNTKVSYGFLSPPQLNKNSSGIYSEA
LLTTNIVPMYQSFQVIWRYFHDTLLRKYAEERNGVNVVSGPVFDFDYDGRCDSLENLRQKRRVIRNQE
ILIPTHFFIVLTSCKDTSQTPLHCENLDTLAFILPHRTDNSESCVHGKHDSSWVEELLMLHRARITDV
EHITGLSFYQQRKEPVSDILKLKTHLPTFSQEDLIN**DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM**
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

[0289] MTRLTVLALLAGLLASSRA**APSCAKEVKSCKGRCFERTFGNCRCDAACVELGNCCLDYQETCIEPE
HIWTCNKFRCGEKRLTRSLCACSDDCKDKGDCCINYSSVCQGEKSWVEEPCESINEPQCPAGFETPPT
LLFSLDGFRAEYLHTWGGLLPVISKLKKCGTYTKNMRPVYPTKTFPNHYSIVTGLYPESHGIIDNKMY
DPKMNASFSLKSKEKFNPEWYKGEPIWVTAKYQGLKSGTFFWPGSDVEINGIFPDIYKMYNGSVPFEE
RILAVLQWLQLPKDERPHFYTLYLEEPDSSGHSYGPVSSEVIKALQRVDGMVGMLMDGLKELNLHRCL
NLILISDHGMEQGSCKKYIYLNKYLGDVKNIKVIYGPAARLRPSDVPDKYYSFNYEGIARNLSCREPN
QHFKPYLKHFLPKRLHFAKSDRIEPLTFYLDPQWQLALNPSERKYCGSGFHGSDNVFSNMQALFVGYG
PGFKHGIEADTFENIEVYNLMCDLLNLTPAPNNGTHGSLNHLLKNPVYTPKHPKEVHPLVQCPFTRNP
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
[0292] ILIPTHFFIVLTSCKDTSQTAPSCAKEVKSCKGRCFERTFGNCRCDAACVELGNCCLDYQETCIEPEH
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

```
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
```

[0295]

[0296]

```
225                 230                 235                 240
Thr Phe His Leu Arg Gly Arg Glu Lys Phe Asn His Arg Trp Trp Gly
                245                 250                 255
Gly Gln Pro Leu Trp Ile Thr Ala Thr Lys Gln Gly Val Lys Ala Gly
            260                 265                 270
Thr Phe Phe Trp Ser Val Val Ile Pro His Glu Arg Arg Ile Leu Thr
        275                 280                 285
Ile Leu Gln Trp Leu Thr Leu Pro Asp His Glu Arg Pro Ser Val Tyr
    290                 295                 300
Ala Phe Tyr Ser Glu Gln Pro Asp Phe Ser Gly His Lys Tyr Gly Pro
305                 310                 315                 320
Phe Gly Pro Glu Met Thr Asn Pro Leu Arg Glu Ile Asp Lys Ile Val
                325                 330                 335
Gly Gln Leu Met Asp Gly Leu Lys Gln Leu Lys Leu His Arg Cys Val
            340                 345                 350
Asn Val Ile Phe Val Gly Asp His Gly Met Glu Asp Val Thr Cys Asp
        355                 360                 365
Arg Thr Glu Phe Leu Ser Asn Tyr Leu Thr Asn Val Asp Asp Ile Thr
    370                 375                 380
Leu Val Pro Gly Thr Leu Gly Arg Ile Arg Ser Lys Phe Ser Asn Asn
385                 390                 395                 400
Ala Lys Tyr Asp Pro Lys Ala Ile Ile Ala Asn Leu Thr Cys Lys Lys
                405                 410                 415
Pro Asp Gln His Phe Lys Pro Tyr Leu Lys Gln His Leu Pro Lys Arg
            420                 425                 430
Leu His Tyr Ala Asn Asn Arg Arg Ile Glu Asp Ile His Leu Leu Val
        435                 440                 445
Glu Arg Arg Trp His Val Ala Arg Lys Pro Leu Asp Val Tyr Lys Lys
    450                 455                 460
Pro Ser Gly Lys Cys Phe Phe Gln Gly Asp His Gly Phe Asp Asn Lys
465                 470                 475                 480
Val Asn Ser Met Gln Thr Val Phe Val Gly Tyr Gly Ser Thr Phe Lys
                485                 490                 495
Tyr Lys Thr Lys Val Pro Pro Phe Glu Asn Ile Glu Leu Tyr Asn Val
            500                 505                 510
Met Cys Asp Leu Leu Gly Leu Lys Pro Ala Pro Asn Asn Gly Thr His
        515                 520                 525
Gly Ser Leu Asn His Leu Leu Arg Thr Asn Thr Phe Arg Pro Thr Met
    530                 535                 540
Pro Glu Glu Val Thr Arg Pro Asn Tyr Pro Gly Ile Met Tyr Leu Gln
545                 550                 555                 560
Ser Asp Phe Asp Leu Gly Cys Thr Cys Asp Asp Lys Val Glu Pro Lys
                565                 570                 575
Asn Lys Leu Asp Glu Leu Asn Lys Arg Leu His Thr Lys Gly Ser Thr
            580                 585                 590
Glu Ala Glu Thr Arg Lys Phe Arg Gly Ser Arg Asn Glu Asn Lys Glu
        595                 600                 605
Asn Ile Asn Gly Asn Phe Glu Pro Arg Lys Glu Arg His Leu Leu Tyr
    610                 615                 620
Gly Arg Pro Ala Val Leu Tyr Arg Thr Arg Tyr Asp Ile Leu Tyr His
625                 630                 635                 640
Thr Asp Phe Glu Ser Gly Tyr Ser Glu Ile Phe Leu Met Pro Leu Trp
                645                 650                 655
Thr Ser Tyr Thr Val Ser Lys Gln Ala Glu Val Ser Ser Val Pro Asp
            660                 665                 670
His Leu Thr Ser Cys Val Arg Pro Asp Val Arg Val Ser Pro Ser Phe
```

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

[0297]
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：

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

[0299]
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

[0300]

```
          195                 200                 205
Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe Trp Pro
      210                 215                 220
Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr Met Pro
225                 230                 235                 240
Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu Leu Lys
                245                 250                 255
Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr Met Tyr
            260                 265                 270
Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val Ser Ala
          275                 280                 285
Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala Phe Gly Met Leu
      290                 295                 300
Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn Ile Ile
305                 310                 315                 320
Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys Met Glu
                325                 330                 335
Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr Met Tyr Glu
            340                 345                 350
Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro His Asp Phe Phe
          355                 360                 365
Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg Lys Pro
      370                 375                 380
Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys Arg Leu
385                 390                 395                 400
His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His Leu Phe Val Asp
                405                 410                 415
Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys Gly Gly
            420                 425                 430
Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala Ile Phe
          435                 440                 445
Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu Pro Phe
      450                 455                 460
Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg Ile Gln
465                 470                 475                 480
Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His Leu Leu Lys
                485                 490                 495
Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys Phe Ser
            500                 505                 510
Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu Asp Cys Phe
          515                 520                 525
Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn Gln Met
      530                 535                 540
Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val Asn Leu
545                 550                 555                 560
Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val Asp His Cys Leu
                565                 570                 575
Leu Tyr His Arg Glu Tyr Val Ser Gly Phe Gly Lys Ala Met Arg Met
            580                 585                 590
Pro Met Trp Ser Ser Tyr Thr Val Pro Gln Leu Gly Asp Thr Ser Pro
          595                 600                 605
Leu Pro Pro Thr Val Pro Asp Cys Leu Arg Ala Asp Val Arg Val Pro
      610                 615                 620
Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys Asn Ile
625                 630                 635                 640
Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser Asp Ser
```

[0301]

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

[0302] 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

[0303] SEQ.ID NO:7-NPP3氨基酸序列：

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

[0304] 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

[0305]

```
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

[0306]

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

[0307] SEQ ID No:8-天青杀素-ENPP3-FC

MTRLTVLALLAGLLASSRA**AKQGSCRKKCFDASFRGLENCRCDVACKDRGDCCWDFEDTC
VESTRIWMCNKFRCGETRLEASLCSCSDDCLQRKDCCADYKSVCQGETSWLEENCDTAQQSQCPEGFD
LPPVILFSMDGFRAEYLYTWDTLMPNINKLKTCGIHSKYMRAMYPTKTFPNHYTIVTGLYPESHGIID
NNMYDVNLNKNFSLSSKEQNNPAWWHGQPMNLTAMYQGLKAATYFWPGSEVAINGSFPSIYMPYNGSV
PFEERISTLLKWLDLPKAERPRFYTMYFEEPDSSGHAGGPVSARVIKALQVVDHAFGMLMEGLKQRNL
HNCVNIILLADHGMDQTYCNKMEYMTDYFPRINFFYMYEGPAPRIRAHNIPHDFFSFNSEEIVRNLSC
RKPDQHFKPYLTPDLPKRLHYAKNVRIDKVHLFVDQQWLAVRSKSNTNCGGGNHGYNNEFRSMEAIFL
AHGPSFKEKTEVEPFENIEVYNLMCDLLRIQPAPNNGTHGSLNHLLKVPFYEPSHAEEVSKFSVCGFA

[0308]

NPLPTESLDCFCPHLQNSTQLEQVNQMLNLTQEEITATVKVNLPFGRPRVLQKNVDHCLLYHREYVSG
FGKAMRMPMWSSYTVPQLGDTSPLPPTVPDCLRADVRVPPSESQKCSFYLADKNITHGFLYPPASNRT
SDSQYDALITSNLVPMYEEFRKMWDYFHSVLLIKHATERNGVNVVSGPIFDYNYDGHFDAPDEITKHL
ANTDVPIPTHYFVVLTSCKNKSHTPENCPGWLDVLPFIIPHRPTNVESCPEGKPEALWVEERFTAHIA
RVRDVELLTGLDFYQDKVQPVSEILQLKTYLPTFETTI**DKTHTCPPCPAPELLGGPSVFLFPPKPKDT**
LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[0309] 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。

[0310] SEQ ID No:9-天青杀素-ENPP3-白蛋白

MTRLTVLALLAGLLASSRA**AKQGSCRKKCFDASFRGLENCRCDVACKDRGDCCWDFEDTC
VESTRIWMCNKFRCGETRLEASLCSCSDDCLQRKDCCADYKSVCQGETSWLEENCDTAQQSQCPEGFD
LPPVILFSMDGFRAEYLYTWDTLMPNINKLKTCGIHSKYMRAMYPTKTFPNHYTIVTGLYPESHGIID
NNMYDVNLNKNFSLSSKEQNNPAWWHGQPMNLTAMYQGLKAATYFWPGSEVAINGSFPSIYMPYNGSV

PFEERISTLLKWLDLPKAERPRFYTMYFEEPDSSGHAGGPVSARVIKALQVVDHAFGMLMEGLKQRNL
HNCVNIILLADHGMDQTYCNKMEYMTDYFPRINFFYMYEGPAPRIRAHNIPHDFFSFNSEEIVRNLSC
RKPDQHFKPYLTPDLPKRLHYAKNVRIDKVHLFVDQQWLAVRSKSNTNCGGGNHGYNNEFRSMEAIFL
AHGPSFKEKTEVEPFENIEVYNLMCDLLRIQPAPNNGTHGSLNHLLKVPFYEPSHAEEVSKFSVCGFA
NPLPTESLDCFCPHLQNSTQLEQVNQMLNLTQEEITATVKVNLPFGRPRVLQKNVDHCLLYHREYVSG
FGKAMRMPMWSSYTVPQLGDTSPLPPTVPDCLRADVRVPPSESQKCSFYLADKNITHGFLYPPASNRT
[0311] SDSQYDALITSNLVPMYEEFRKMWDYFHSVLLIKHATERNGVNVVSGPIFDYNYDGHFDAPDEITKHL
ANTDVPIPTHYFVVLTSCKNKSHTPENCPGWLDVLPFIIPHRPTNVESCPEGKPEALWVEERFTAHIA
RVRDVELLTGLDFYQDKVQPVSEILQLKTYLPTFETTI**MKWVTFLLLLFVSGSAFSRGVFRREAHKSE**
IAHRYNDLGEQHFKGLVLIAFSQYLQKCSYDEHAKLVQEVTDFAKTCVADESAANCDKSLHTLFGDKL
CAIPNLRENYGELADCCTKQEPERNECFLQHKDDNPSLPPFERPEAEAMCTSFKENPTTFMGHYLHEV
ARRHPYFYAPELLYYAEQYNEILTQCCAEADKESCLTPKLDGVKEKALVSSVRQRMKCSSMQKFGERA
FKAWAVARLSQTFPNADFAEITKLATDLTKVNKECCHGDLLECADDRAELAKYMCENQATISSKLQTC
CDKPLLKKAHCLSEVEHDTMPADLPAIAADFVEDQEVCKNYAEAKDVFLGTFLYEYSRRHPDYSVSLL
LRLAKKYEATLEKCCAEANPPACYGTVLAEFQPLVEEPKNLVKTNCDLYEKLGEYGFQNAILVRYTQK
APQVSTPTLVEAARNLGRVGTKCCTLPEDQRLPCVEDYLSAILNRVCLLHEKTPVSEHVTKCCSGSLV
ERRPCFSALTVDETYVPKEFKAETFTFHSDICTLPEKEKQIKKQTALAELVKHKPKATAEQLKTVMDD
FAQFLDTCCKAADKDTCFSTEGPNLVTRCKDALARSWSHPQFEK

[0312] 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。

[0313] SEQ ID No:10-天青杀素-ENPP3

MTRLTVLALLAGLLASSRA**AKQGSCRKKCFDASFRGLENCRCDVACKDRGDCCWDFEDTC
VESTRIWMCNKFRCGETRLEASLCSCSDDCLQRKDCCADYKSVCQGETSWLEENCDTAQQSQCPEGFD
LPPVILFSMDGFRAEYLYTWDTLMPNINKLKTCGIHSKYMRAMYPTKTFPNHYTIVTGLYPESHGIID
NNMYDVNLNKNFSLSSKEQNNPAWWHGQPMNLTAMYQGLKAATYFWPGSEVAINGSFPSIYMPYNGSV
PFEERISTLLKWLDLPKAERPRFYTMYFEEPDSSGHAGGPVSARVIKALQVVDHAFGMLMEGLKQRNL
HNCVNIILLADHGMDQTYCNKMEYMTDYFPRINFFYMYEGPAPRIRAHNIPHDFFSFNSEEIVRNLSC
[0314] RKPDQHFKPYLTPDLPKRLHYAKNVRIDKVHLFVDQQWLAVRSKSNTNCGGGNHGYNNEFRSMEAIFL
AHGPSFKEKTEVEPFENIEVYNLMCDLLRIQPAPNNGTHGSLNHLLKVPFYEPSHAEEVSKFSVCGFA
NPLPTESLDCFCPHLQNSTQLEQVNQMLNLTQEEITATVKVNLPFGRPRVLQKNVDHCLLYHREYVSG
FGKAMRMPMWSSYTVPQLGDTSPLPPTVPDCLRADVRVPPSESQKCSFYLADKNITHGFLYPPASNRT
SDSQYDALITSNLVPMYEEFRKMWDYFHSVLLIKHATERNGVNVVSGPIFDYNYDGHFDAPDEITKHL
ANTDVPIPTHYFVVLTSCKNKSHTPENCPGWLDVLPFIIPHRPTNVESCPEGKPEALWVEERFTAHIA
RVRDVELLTGLDFYQDKVQPVSEILQLKTYLPTFETTI

[0315] 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。

[0316] 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
[0317] 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
```

[0318] 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
```

[0319]

[0320] SEQ.ID NO:12-ENPP51氨基酸序列

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

[0321]

```
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
```

[0322]

```
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
```

[0323]

```
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
```

[0324]

[0325] 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

[0326] 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
```

[0327]

```
                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
[0328] 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
```

[0329]

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
[0330] 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
```

[0331]

```
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
```

[0332]

```
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
```

[0333] 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

[0334] 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
```

[0335]

```
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
```

[0336]

```
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
```

[0337]

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
[0338]
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

[0339]

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

[0340] 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

[0341] 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

[0342]

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
[0343] 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
```

[0344]

```
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
[0345] 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

[0346]

```
                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
```

[0347]

[0348] 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

[0349] 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
     1               5                   10                  15
     Leu Ser Thr Thr Phe Ser Xaa
                 20
```

[0350]

[0351] 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
```

[0352]

```
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
```

[0353]

```
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
```

[0354]

```
                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
[0355]
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

[0356]

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

[0357] 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

[0358] SEQ.ID NO:18-ENPP71-Fc氨基酸序列

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

[0359]

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
```

[0360]

[0361]

```
                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
[0362]
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
```

[0363]

[0364] 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

[0365] SEQ.ID NO:19-ENPP71(缺乏NPP1N末端GLK)氨基酸序列:

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

[0366]

```
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
```

[0367]

[0368] 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

[0369] 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
```

[0370]

[0371] 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

[0372] SEQ.ID NO:20-ENPP71(缺乏NPP1N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
```

[0373]

```
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
```

[0374]

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
[0375] 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
[0376] 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
[0377]    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
```

[0378] 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

[0379] SEQ.ID NO:21-ENPP71(缺乏NPP1N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
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
```

[0380]

```
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
```

[0381]

```
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

[0382] Thr

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

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

[0383]

```
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
```

[0384]

```
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
```

[0385] 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

[0386] 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
```

[0387]

```
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
[0388] 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
```

[0389]

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
[0390] 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

[0391]

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

[0392] 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

[0393] 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

[0394]

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
[0395]
                    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
```

[0396]

[0397]

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

[0398]

```
          945                 950                 955
960
Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu
Pro
                    965                 970                 975
Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Ser
Leu
                980                 985                 990
Pro Pro Phe Glu Arg Pro Glu Ala  Glu Ala Met Cys Thr  Ser Phe
Lys
          995                1000                1005
Glu Asn  Pro Thr Thr Phe Met  Gly His Tyr Leu His  Glu Val Ala
     1010                1015                1020
Arg Arg  His Pro Tyr Phe Tyr  Ala Pro Glu Leu Leu  Tyr Tyr Ala
     1025                1030                1035
Glu Gln  Tyr Asn Glu Ile Leu  Thr Gln Cys Cys Ala  Glu Ala Asp
     1040                1045                1050
Lys Glu  Ser Cys Leu Thr Pro  Lys Leu Asp Gly Val  Lys Glu Lys
     1055                1060                1065
Ala Leu  Val Ser Ser Val Arg  Gln Arg Met Lys Cys  Ser Ser Met
     1070                1075                1080
Gln Lys  Phe Gly Glu Arg Ala  Phe Lys Ala Trp Ala  Val Ala Arg
     1085                1090                1095
Leu Ser  Gln Thr Phe Pro Asn  Ala Asp Phe Ala Glu  Ile Thr Lys
     1100                1105                1110
Leu Ala  Thr Asp Leu Thr Lys  Val Asn Lys Glu Cys  Cys His Gly
     1115                1120                1125
Asp Leu  Leu Glu Cys Ala Asp  Asp Arg Ala Glu Leu  Ala Lys Tyr
     1130                1135                1140
Met Cys  Glu Asn Gln Ala Thr  Ile Ser Ser Lys Leu  Gln Thr Cys
     1145                1150                1155
Cys Asp  Lys Pro Leu Leu Lys  Lys Ala His Cys Leu  Ser Glu Val
     1160                1165                1170
Glu His  Asp Thr Met Pro Ala  Asp Leu Pro Ala Ile  Ala Ala Asp
     1175                1180                1185
Phe Val  Glu Asp Gln Glu Val  Cys Lys Asn Tyr Ala  Glu Ala Lys
     1190                1195                1200
Asp Val  Phe Leu Gly Thr Phe  Leu Tyr Glu Tyr Ser  Arg Arg His
     1205                1210                1215
Pro Asp  Tyr Ser Val Ser Leu  Leu Leu Arg Leu Ala  Lys Lys Tyr
     1220                1225                1230
Glu Ala  Thr Leu Glu Lys Cys  Cys Ala Glu Ala Asn  Pro Pro Ala
     1235                1240                1245
Cys Tyr  Gly Thr Val Leu Ala  Glu Phe Gln Pro Leu  Val Glu Glu
     1250                1255                1260
Pro Lys  Asn Leu Val Lys Thr  Asn Cys Asp Leu Tyr  Glu Lys Leu
     1265                1270                1275
Gly Glu  Tyr Gly Phe Gln Asn  Ala Ile Leu Val Arg  Tyr Thr Gln
     1280                1285                1290
Lys Ala  Pro Gln Val Ser Thr  Pro Thr Leu Val Glu  Ala Ala Arg
     1295                1300                1305
Asn Leu  Gly Arg Val Gly Thr  Lys Cys Cys Thr Leu  Pro Glu Asp
     1310                1315                1320
Gln Arg  Leu Pro Cys Val Glu  Asp Tyr Leu Ser Ala  Ile Leu Asn
     1325                1330                1335
Arg Val  Cys Leu Leu His Glu  Lys Thr Pro Val Ser  Glu His Val
```

```
          1340                1345                1350
Thr Lys  Cys Cys Ser Gly Ser  Leu Val Glu Arg Arg  Pro Cys Phe
          1355                1360                1365
Ser Ala  Leu Thr Val Asp Glu  Thr Tyr Val Pro Lys  Glu Phe Lys
          1370                1375                1380
Ala Glu  Thr Phe Thr Phe His  Ser Asp Ile Cys Thr  Leu
          1385                1390                1395
```

[0399]

[0400] 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

[0401] SEQ.ID NO:24-ENPP7-NPP3-白蛋白

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

[0402]

[0403]

```
                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

[0404]

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

[0405]

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

```
     1055                1060                1065
Lys Glu  Lys Ala Leu Val Ser  Ser Val Arg Gln Arg  Met Lys Cys
     1070                1075                1080
Ser Ser  Met Gln Lys Phe Gly  Glu Arg Ala Phe Lys  Ala Trp Ala
     1085                1090                1095
Val Ala  Arg Leu Ser Gln Thr  Phe Pro Asn Ala Asp  Phe Ala Glu
     1100                1105                1110
Ile Thr  Lys Leu Ala Thr Asp  Leu Thr Lys Val Asn  Lys Glu Cys
     1115                1120                1125
Cys His  Gly Asp Leu Leu Glu  Cys Ala Asp Asp Arg  Ala Glu Leu
     1130                1135                1140
Ala Lys  Tyr Met Cys Glu Asn  Gln Ala Thr Ile Ser  Ser Lys Leu
     1145                1150                1155
Gln Thr  Cys Cys Asp Lys Pro  Leu Leu Lys Lys Ala  His Cys Leu
     1160                1165                1170
Ser Glu  Val Glu His Asp Thr  Met Pro Ala Asp Leu  Pro Ala Ile
     1175                1180                1185
Ala Ala  Asp Phe Val Glu Asp  Gln Glu Val Cys Lys  Asn Tyr Ala
     1190                1195                1200
Glu Ala  Lys Asp Val Phe Leu  Gly Thr Phe Leu Tyr  Glu Tyr Ser
     1205                1210                1215
Arg Arg  His Pro Asp Tyr Ser  Val Ser Leu Leu Leu  Arg Leu Ala
     1220                1225                1230
Lys Lys  Tyr Glu Ala Thr Leu  Glu Lys Cys Cys Ala  Glu Ala Asn
     1235                1240                1245
Pro Pro  Ala Cys Tyr Gly Thr  Val Leu Ala Glu Phe  Gln Pro Leu
     1250                1255                1260
Val Glu  Glu Pro Lys Asn Leu  Val Lys Thr Asn Cys  Asp Leu Tyr
     1265                1270                1275
Glu Lys  Leu Gly Glu Tyr Gly  Phe Gln Asn Ala Ile  Leu Val Arg
     1280                1285                1290
Tyr Thr  Gln Lys Ala Pro Gln  Val Ser Thr Pro Thr  Leu Val Glu
     1295                1300                1305
Ala Ala  Arg Asn Leu Gly Arg  Val Gly Thr Lys Cys  Cys Thr Leu
     1310                1315                1320
Pro Glu  Asp Gln Arg Leu Pro  Cys Val Glu Asp Tyr  Leu Ser Ala
     1325                1330                1335
Ile Leu  Asn Arg Val Cys Leu  Leu His Glu Lys Thr  Pro Val Ser
     1340                1345                1350
Glu His  Val Thr Lys Cys Cys  Ser Gly Ser Leu Val  Glu Arg Arg
     1355                1360                1365
Pro Cys  Phe Ser Ala Leu Thr  Val Asp Glu Thr Tyr  Val Pro Lys
     1370                1375                1380
Glu Phe  Lys Ala Glu Thr Phe  Thr Phe His Ser Asp  Ile Cys Thr
     1385                1390                1395
Leu Pro  Glu Lys Glu Lys Gln  Ile Lys Lys Gln Thr  Ala Leu Ala
     1400                1405                1410
Glu Leu  Val Lys His Lys Pro  Lys Ala Thr Ala Glu  Gln Leu Lys
     1415                1420                1425
Thr Val  Met Asp Asp Phe Ala  Gln Phe Leu Asp Thr  Cys Cys Lys
     1430                1435                1440
Ala Ala  Asp Lys Asp Thr Cys  Phe Ser Thr Glu Gly  Pro Asn Leu
     1445                1450                1455
Val Thr  Arg Cys Lys Asp Ala  Leu Ala
     1460                1465
```

[0406]

[0407] 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

[0408] SEQ.ID NO:25-ENPP7-ENPP3-白蛋白

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

[0409]

```
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
```

[0410]

```
                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
```

[0411]

[0412]

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

```
     1115                1120                1125
Phe Gly  Glu Arg Ala Phe Lys  Ala Trp Ala Val Ala  Arg Leu Ser
     1130                1135                1140
Gln Thr  Phe Pro Asn Ala Asp  Phe Ala Glu Ile Thr  Lys Leu Ala
     1145                1150                1155
Thr Asp  Leu Thr Lys Val Asn  Lys Glu Cys Cys His  Gly Asp Leu
     1160                1165                1170
Leu Glu  Cys Ala Asp Asp Arg  Ala Glu Leu Ala Lys  Tyr Met Cys
     1175                1180                1185
Glu Asn  Gln Ala Thr Ile Ser  Ser Lys Leu Gln Thr  Cys Cys Asp
     1190                1195                1200
Lys Pro  Leu Leu Lys Lys Ala  His Cys Leu Ser Glu  Val Glu His
     1205                1210                1215
Asp Thr  Met Pro Ala Asp Leu  Pro Ala Ile Ala Ala  Asp Phe Val
     1220                1225                1230
Glu Asp  Gln Glu Val Cys Lys  Asn Tyr Ala Glu Ala  Lys Asp Val
     1235                1240                1245
Phe Leu  Gly Thr Phe Leu Tyr  Glu Tyr Ser Arg Arg  His Pro Asp
     1250                1255                1260
Tyr Ser  Val Ser Leu Leu Leu  Arg Leu Ala Lys Lys  Tyr Glu Ala
     1265                1270                1275
Thr Leu  Glu Lys Cys Cys Ala  Glu Ala Asn Pro Pro  Ala Cys Tyr
     1280                1285                1290
Gly Thr  Val Leu Ala Glu Phe  Gln Pro Leu Val Glu  Glu Pro Lys
     1295                1300                1305
Asn Leu  Val Lys Thr Asn Cys  Asp Leu Tyr Glu Lys  Leu Gly Glu
     1310                1315                1320
Tyr Gly  Phe Gln Asn Ala Ile  Leu Val Arg Tyr Thr  Gln Lys Ala
     1325                1330                1335
Pro Gln  Val Ser Thr Pro Thr  Leu Val Glu Ala Ala  Arg Asn Leu
     1340                1345                1350
Gly Arg  Val Gly Thr Lys Cys  Cys Thr Leu Pro Glu  Asp Gln Arg
     1355                1360                1365
Leu Pro  Cys Val Glu Asp Tyr  Leu Ser Ala Ile Leu  Asn Arg Val
     1370                1375                1380
Cys Leu  Leu His Glu Lys Thr  Pro Val Ser Glu His  Val Thr Lys
     1385                1390                1395
Cys Cys  Ser Gly Ser Leu Val  Glu Arg Arg Pro Cys  Phe Ser Ala
     1400                1405                1410
Leu Thr  Val Asp Glu Thr Tyr  Val Pro Lys Glu Phe  Lys Ala Glu
     1415                1420                1425
Thr Phe  Thr Phe His Ser Asp  Ile Cys Thr Leu Pro  Glu Lys Glu
     1430                1435                1440
Lys Gln  Ile Lys Lys Gln Thr  Ala Leu Ala Glu Leu  Val Lys His
     1445                1450                1455
Lys Pro  Lys Ala Thr Ala Glu  Gln Leu Lys Thr Val  Met Asp Asp
     1460                1465                1470
Phe Ala  Gln Phe Leu Asp Thr  Cys Cys Lys Ala Ala  Asp Lys Asp
     1475                1480                1485
Thr Cys  Phe Ser Thr Glu Gly  Pro Asn Leu Val Thr  Arg Cys Lys
     1490                1495                1500
Asp Ala  Leu Ala
     1505
```

[0413]

[0414] 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

[0415] 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
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
```

[0416]

[0417]

```
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
```

[0418]

[0419]

```
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
```

[0420] 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

[0421] SEQ.ID NO:27-ENPP121氨基酸序列

[0422]

```
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
```

[0423]

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

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

[0424]

```
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
```

[0425]

[0426] 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

[0427] 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
```

[0428]

```
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
```

[0429]

```
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
```

[0430]

```
His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp Asn
Leu
 610                 615                 620
Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe Gln
Thr
625                 630                 635
640
Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His Glu
Thr
                645                 650                 655
Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr Ile
Cys
            660                 665                 670
Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp Ile
Leu
        675                 680                 685
Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser Phe
Ser
 690                 695                 700
Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile Pro
Leu
705                 710                 715
720
Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val
Ser
                725                 730                 735
Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser Gly
Ile
            740                 745                 750
Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln
Ser
        755                 760                 765
Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys
Tyr
 770                 775                 780
Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val Phe
Asp
785                 790                 795
800
Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln
Lys
                805                 810                 815
Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe
Phe
            820                 825                 830
Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His
Cys
        835                 840                 845
Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp
Asn
 850                 855                 860
Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu
Glu
865                 870                 875
880
```

[0431]

Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile
Thr
885 890 895
Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile
Leu
900 905 910
Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp Leu Ile
Asn
915 920 925
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
Gly
930 935 940
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
Met
945 950 955
960
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
His
965 970 975
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
Val
980 985 990

[0432]
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

[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Fc序列

[0434] 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
[0435] 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
[0436]
      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

[0437]

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

[0438]

Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val Ser
725 730 735
Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser Gly Ile
740 745 750
Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln Ser
755 760 765
Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys Tyr
770 775 780
Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val Phe Asp
785 790 795 800
Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln Lys
805 810 815
Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe Phe
820 825 830
Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His Cys
835 840 845
Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp Asn

```
                850                 855                 860
Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu
Glu
865                 870                 875
880
Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile
Thr
                    885                 890                 895
Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile
Leu
            900                 905                 910
Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp Arg Ser
Gly
        915                 920                 925
Ser Gly Gly Ser Met Lys Trp Val Thr Phe Leu Leu Leu Leu Phe
Val
    930                 935                 940
Ser Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg Glu Ala His
Lys
945                 950                 955
960
Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe
Lys
                    965                 970                 975
Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser
Tyr
            980                 985                 990
Asp Glu His Ala Lys Leu Val Gln  Glu Val Thr Asp Phe  Ala Lys
Thr
        995                 1000                1005
Cys Val  Ala Asp Glu Ser Ala  Ala Asn Cys Asp Lys  Ser Leu His
    1010                1015                1020
Thr Leu  Phe Gly Asp Lys Leu  Cys Ala Ile Pro Asn  Leu Arg Glu
    1025                1030                1035
Asn Tyr  Gly Glu Leu Ala Asp  Cys Cys Thr Lys Gln  Glu Pro Glu
    1040                1045                1050
Arg Asn  Glu Cys Phe Leu Gln  His Lys Asp Asp Asn  Pro Ser Leu
    1055                1060                1065
Pro Pro  Phe Glu Arg Pro Glu  Ala Glu Ala Met Cys  Thr Ser Phe
    1070                1075                1080
Lys Glu  Asn Pro Thr Thr Phe  Met Gly His Tyr Leu  His Glu Val
    1085                1090                1095
Ala Arg  Arg His Pro Tyr Phe  Tyr Ala Pro Glu Leu  Leu Tyr Tyr
    1100                1105                1110
Ala Glu  Gln Tyr Asn Glu Ile  Leu Thr Gln Cys Cys  Ala Glu Ala
    1115                1120                1125
Asp Lys  Glu Ser Cys Leu Thr  Pro Lys Leu Asp Gly  Val Lys Glu
    1130                1135                1140
Lys Ala  Leu Val Ser Ser Val  Arg Gln Arg Met Lys  Cys Ser Ser
    1145                1150                1155
Met Gln  Lys Phe Gly Glu Arg  Ala Phe Lys Ala Trp  Ala Val Ala
    1160                1165                1170
Arg Leu  Ser Gln Thr Phe Pro  Asn Ala Asp Phe Ala  Glu Ile Thr
    1175                1180                1185
Lys Leu  Ala Thr Asp Leu Thr  Lys Val Asn Lys Glu  Cys Cys His
    1190                1195                1200
```

[0439]

[0440]

```
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
```

[0441] 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

[0442] SEQ.ID NO:30-ENPP121-NPP3-Fc序列

[0443]

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

```
Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro Met Trp Leu Thr
Ala
 290                 295                 300
Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe Trp Pro Gly Ser
Glu
305                 310                 315
320
Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr Met Pro Tyr Asn
Gly
                325                 330                 335
Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu Leu Lys Trp Leu
Asp
            340                 345                 350
Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr Met Tyr Phe Glu
Glu
        355                 360                 365
Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val Ser Ala Arg Val
Ile
 370                 375                 380
Lys Ala Leu Gln Val Val Asp His Ala Phe Gly Met Leu Met Glu
Gly
385                 390                 395
400
Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn Ile Ile Leu Leu
Ala
                405                 410                 415
Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys Met Glu Tyr Met
[0444] 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
[0445]
      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
[0446]                  965                 970                 975
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
Arg
                980                 985                 990
Glu Glu Gln Tyr Asn Ser Thr Tyr  Arg Val Val Ser Val  Leu Thr
Val
                995                 1000                1005
Leu His  Gln Asp Trp Leu Asn  Gly Lys Glu Tyr Lys  Cys Lys Val
    1010                1015                1020
Ser Asn  Lys Ala Leu Pro Ala  Pro Ile Glu Lys Thr  Ile Ser Lys
    1025                1030                1035
Ala Lys  Gly Gln Pro Arg Glu  Pro Gln Val Tyr Thr  Leu Pro Pro
    1040                1045                1050
Ser Arg  Glu Glu Met Thr Lys  Asn Gln Val Ser Leu  Thr Cys Leu
    1055                1060                1065
Val Lys  Gly Phe Tyr Pro Ser  Asp Ile Ala Val Glu  Trp Glu Ser
    1070                1075                1080
Asn Gly  Gln Pro Glu Asn Asn  Tyr Lys Thr Thr Pro  Pro Val Leu
    1085                1090                1095
Asp Ser  Asp Gly Ser Phe Phe  Leu Tyr Ser Lys Leu  Thr Val Asp
    1100                1105                1110
Lys Ser  Arg Trp Gln Gln Gly  Asn Val Phe Ser Cys  Ser Val Met
    1115                1120                1125
His Glu  Ala Leu His Asn His  Tyr Thr Gln Lys Ser  Leu Ser Leu
    1130                1135                1140
Ser Pro  Gly Lys
    1145
```

[0447] 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

[0448] SEQ.ID NO:31-ENPP121-NPP3-白蛋白序列

```
      Met Glu Arg Asp Gly Cys Ala Gly Gly Gly Ser Arg Gly Gly Glu
Gly
      1               5                   10                  15
      Gly Arg Ala Pro Arg Glu Gly Pro Ala Gly Asn Gly Arg Asp Arg
Gly
                  20                  25                  30
      Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala
Ser
              35                  40                  45
      Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala
Ala
          50                  55                  60
      Arg Ala Arg Thr Ala Lys Asp Pro Asn Thr Tyr Lys Ile Ile Ser
Leu
      65                  70                  75
      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
[0449]            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
[0450]
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
```

[0451]

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

[0452]

Phe Val Ser Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg Glu Ala
945 950 955 960
His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His
965 970 975
Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys
980 985 990
Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu Val Thr Asp Phe Ala
995 1000 1005
Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys Ser
1010 1015 1020
Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu
1025 1030 1035
Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu
1040 1045 1050
Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro
1055 1060 1065
Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met Cys Thr
1070 1075 1080
Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly His Tyr Leu His
1085 1090 1095
Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu
1100 1105 1110
Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys Ala

[0453]

```
     1115                1120                1125
Glu Ala  Asp Lys Glu Ser Cys  Leu Thr Pro Lys Leu  Asp Gly Val
     1130                1135                1140
Lys Glu  Lys Ala Leu Val Ser  Ser Val Arg Gln Arg  Met Lys Cys
     1145                1150                1155
Ser Ser  Met Gln Lys Phe Gly  Glu Arg Ala Phe Lys  Ala Trp Ala
     1160                1165                1170
Val Ala  Arg Leu Ser Gln Thr  Phe Pro Asn Ala Asp  Phe Ala Glu
     1175                1180                1185
Ile Thr  Lys Leu Ala Thr Asp  Leu Thr Lys Val Asn  Lys Glu Cys
     1190                1195                1200
Cys His  Gly Asp Leu Leu Glu  Cys Ala Asp Asp Arg  Ala Glu Leu
     1205                1210                1215
Ala Lys  Tyr Met Cys Glu Asn  Gln Ala Thr Ile Ser  Ser Lys Leu
     1220                1225                1230
Gln Thr  Cys Cys Asp Lys Pro  Leu Leu Lys Lys Ala  His Cys Leu
     1235                1240                1245
Ser Glu  Val Glu His Asp Thr  Met Pro Ala Asp Leu  Pro Ala Ile
     1250                1255                1260
Ala Ala  Asp Phe Val Glu Asp  Gln Glu Val Cys Lys  Asn Tyr Ala
     1265                1270                1275
Glu Ala  Lys Asp Val Phe Leu  Gly Thr Phe Leu Tyr  Glu Tyr Ser
     1280                1285                1290
Arg Arg  His Pro Asp Tyr Ser  Val Ser Leu Leu Leu  Arg Leu Ala
     1295                1300                1305
Lys Lys  Tyr Glu Ala Thr Leu  Glu Lys Cys Cys Ala  Glu Ala Asn
     1310                1315                1320
Pro Pro  Ala Cys Tyr Gly Thr  Val Leu Ala Glu Phe  Gln Pro Leu
     1325                1330                1335
Val Glu  Glu Pro Lys Asn Leu  Val Lys Thr Asn Cys  Asp Leu Tyr
     1340                1345                1350
Glu Lys  Leu Gly Glu Tyr Gly  Phe Gln Asn Ala Ile  Leu Val Arg
     1355                1360                1365
Tyr Thr  Gln Lys Ala Pro Gln  Val Ser Thr Pro Thr  Leu Val Glu
     1370                1375                1380
Ala Ala  Arg Asn Leu Gly Arg  Val Gly Thr Lys Cys  Cys Thr Leu
     1385                1390                1395
Pro Glu  Asp Gln Arg Leu Pro  Cys Val Glu Asp Tyr  Leu Ser Ala
     1400                1405                1410
Ile Leu  Asn Arg Val Cys Leu  Leu His Glu Lys Thr  Pro Val Ser
     1415                1420                1425
Glu His  Val Thr Lys Cys Cys  Ser Gly Ser Leu Val  Glu Arg Arg
     1430                1435                1440
Pro Cys  Phe Ser Ala Leu Thr  Val Asp Glu Thr Tyr  Val Pro Lys
     1445                1450                1455
Glu Phe  Lys Ala Glu Thr Phe  Thr Phe His Ser Asp  Ile Cys Thr
     1460                1465                1470
Leu Pro  Glu Lys Glu Lys Gln  Ile Lys Lys Gln Thr  Ala Leu Ala
     1475                1480                1485
Glu Leu  Val Lys His Lys Pro  Lys Ala Thr Ala Glu  Gln Leu Lys
     1490                1495                1500
Thr Val  Met Asp Asp Phe Ala  Gln Phe Leu Asp Thr  Cys Cys Lys
     1505                1510                1515
Ala Ala  Asp Lys Asp Thr Cys  Phe Ser Thr Glu Gly  Pro Asn Leu
     1520                1525                1530
Val Thr  Arg Cys Lys Asp Ala  Leu Ala
```

[0454]

```
     1535                1540
```

[0455] 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

[0456] SEQ.ID NO:32-ENPP121GLK蛋白输出信号序列

```
      Met Glu Arg Asp Gly Cys Ala Gly Gly Gly Ser Arg Gly Gly Glu
Gly
      1               5                   10                  15
      Gly Arg Ala Pro Arg Glu Gly Pro Ala Gly Asn Gly Arg Asp Arg
Gly
                  20                  25                  30
      Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala
Ser
              35                  40                  45
[0457]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
```

[0458] 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
[0459]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
```

[0460]

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

385 390 395
400
Ala Glu Ala Asn Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu
Phe
405 410 415
Gln Pro Leu Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys
Asp
420 425 430
Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu
Val
435 440 445
Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val
Glu
450 455 460
Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu
Pro
465 470 475
480
Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile
Leu
485 490 495
Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His
[0461] 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

[0462] 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
[0463] 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
```

[0464]

[0465] 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
```

[0466]

```
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
```

[0467]

```
                    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
```

[0468]

```
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
```

[0469] SEQ.ID NO:36-ENPP2信号肽

Leu Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly

[0470] 1 5 10 15

Phe Thr Ala

[0471] 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

[0472] 1 5 10 15

Ala Pro Gly Ala

20

[0473] 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

[0474] 1 5 10 15

Ala Pro Gly Ala Gly Ala

20

[0475] 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

[0476] 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

[0477] SEQ.ID NO:40-exENPP3

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

[0478] 1 5 10 15

Lys

[0479] 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

[0480] 1 5 10 15

Leu Ser Thr Thr Phe Ser

20

[0481] 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

[0482]

Ser Arg Ala

[0483] SEQ.ID NO:43-接头

[0484] Asp Ser Ser

[0485] SEQ.ID NO:44-接头

[0486] Glu Ser Ser

[0487] SEQ.ID NO:45-接头

[0488] Arg Gln Gln

[0489] SEQ.ID NO:46-接头

[0490] Lys Arg

[0491] SEQ.ID NO:47-接头

[0492] $(Arg)_m$; m=0-15

[0493] SEQ.ID NO:48-接头

[0494] Asp Ser Ser Ser Glu Glu Lys Phe Leu Arg Arg Ile Gly Arg Phe Gly

[0495] SEQ.ID NO:49-接头

[0496] Glu Glu Glu Glu Glu Glu Glu Pro Arg Gly Asp Thr

1 5 10

[0497] SEQ.ID NO:50-接头

[0498] Ala Pro Trp His Leu Ser Ser Gln Tyr Ser Arg Thr

1 5 10

[0499] SEQ.ID NO:51-接头

[0500] Ser Thr Leu Pro Ile Pro His Glu Phe Ser Arg Glu

1 5 10

[0501] SEQ.ID NO:52-接头

[0502] Val Thr Lys His Leu Asn Gln Ile Ser Gln Ser Tyr

1 5 10

[0503] SEQ.ID NO:53-接头

[0504] $(Glu)_m$; m=1-15

[0505] SEQ.ID NO:54-接头

[0506] Leu Ile Asn

[0507] SEQ.ID NO:55-接头

[0508] Gly Gly Ser Gly Gly Ser

1 5

[0509] SEQ.ID NO:56-接头

[0510] Arg Ser Gly Ser Gly Gly Ser

1 5

[0511] SEQ.ID NO:57-接头

[0512] $(Asp)_m$; m=1-15

1

[0513] SEQ.ID NO:58-接头

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

[0514]

1 5 10 15

[0515] SEQ.ID NO:59-接头

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

[0516]

1 5 10 15

[0517] SEQ.ID NO:60-接头

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

[0518]

1 5 10

[0519] SEQ.ID NO:61-接头

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

[0520]

1 5 10

[0521] SEQ.ID NO:62-接头

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

[0522]

1 5 10

[0523] SEQ.ID NO:63-接头

Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys

[0524]

1 5 10

[0525] SEQ.ID NO:64-接头

Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys

[0526]

1 5 10

[0527] SEQ.ID NO:65-接头

Leu Gly Leu Gly Leu Gly Leu Arg Lys

[0528]

1 5

[0529] SEQ.ID NO:66-接头

Gly Leu Gly Leu Gly Leu Arg Lys

[0530]

1 5

[0531] SEQ.ID NO:67-接头

Leu Gly Leu Gly Leu Arg Lys

[0532]

1 5

[0533] SEQ.ID NO:68-接头

Gly Leu Gly Leu Arg Lys

[0534]

1 5

[0535] SEQ.ID NO:69-接头

Leu Gly Leu Arg Lys

[0536]

1 5

[0537] SEQ.ID NO:70-接头

Gly Leu Arg Lys

[0538]

1

[0539] SEQ.ID NO:71-接头

Leu Arg Lys

[0540]

1

[0541] SEQ.ID NO:72-接头

Arg Lys

[0542]

1

[0543] SEQ.ID NO:73-接头

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

[0544]

1

[0545] SEQ.ID NO:74-接头

[0546] D_m; m=1-15

[0547] SEQ.ID NO:75-接头

[0548] $(GGGGS)_n$; n=1-10

[0549] SEQ.ID NO:76-ENPP3核苷酸序列

```
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
```

[0550]

[0551]

```
acactgttaa aatggctgga cctgcccaaa gctgaaagac ccaggtttta taccatgtat      960
tttgaagaac ctgattcctc tggacatgca ggtggaccag tcagtgccag agtaattaaa     1020
gccttacagg tagtagatca tgcttttggg atgttgatgg aaggcctgaa gcagcggaat     1080
ttgcacaact gtgtcaatat catccttctg gctgaccatg gaatggacca gacttattgt     1140
aacaagatgg aatacatgac tgattatttt cccagaataa acttcttcta catgtacgaa     1200
gggcctgccc cccgcatccg agctcataat atacctcatg actttttag ttttaattct      1260
gaggaaattg ttagaaacct cagttgccga aaacctgatc agcatttcaa gccctatttg     1320
actcctgatt tgccaaagcg actgcactat gccaagaacg tcagaatcga caaagttcat     1380
ctctttgtgg atcaacagtg gctggctgtt aggagtaaat caaatacaaa ttgtggagga     1440
ggcaaccatg gttataacaa tgagtttagg agcatggagg ctatctttct ggcacatgga     1500
cccagtttta aagagaagac tgaagttgaa ccatttgaaa atattgaagt ctataaccta     1560
atgtgtgatc ttctacgcat tcaaccagca ccaaacaatg gaacccatgg tagtttaaac     1620
catcttctga aggtgccttt ttatgagcca tcccatgcag aggaggtgtc aaagttttct     1680
gtttgtggct ttgctaatcc attgcccaca gagtctcttg actgtttctg ccctcaccta     1740
caaaatagta ctcagctgga acaagtgaat cagatgctaa atctcaccca agaagaaata     1800
acagcaacag tgaaagtaaa tttgccattt gggaggccta gggtactgca gaagaacgtg     1860
gaccactgtc tcctttacca cagggaatat gtcagtggat ttggaaaagc tatgaggatg     1920
cccatgtgga gttcatacac agtcccccag ttgggagaca catcgcctct gcctcccact     1980
gtcccagact gtctgcgggc tgatgtcagg gttcctcctt ctgagagcca aaaatgttcc     2040

ttctatttag cagacaagaa tatcacccac ggcttcctct atcctcctgc cagcaataga     2100
acatcagata gccaatatga tgctttaatt actagcaatt tggtacctat gtatgaagaa     2160
ttcagaaaaa tgtgggacta cttccacagt gttcttctta taaaacatgc cacagaaaga     2220
aatggagtaa atgtggttag tggaccaata tttgattata attatgatgg ccattttgat     2280
gctccagatg aaattaccaa acatttagcc aacactgatg ttcccatccc aacacactac     2340
tttgtggtgc tgaccagttg taaaaacaag agccacacac cggaaaactg ccctgggtgg     2400
ctggatgtcc tacccttttat catccctcac cgacctacca acgtggagag ctgtcctgaa     2460
ggtaaaccag aagctctttg ggttgaagaa agatttacag ctcacattgc ccgggtccgt     2520
gatgtagaac ttctcactgg gcttgacttc tatcaggata aagtgcagcc tgtctctgaa     2580
attttgcaac taaagacata tttaccaaca tttgaaacca ctatt                     2625
```

[0552] SEQ.ID NO:77-ENPP1核苷酸序列：

[0553]

```
atggaacggg acggctgtgc cggcggagga tcaagaggcg gagaaggcgg cagagcccct      60
agagaaggac ctgccggcaa cggcagagac agaggcagat ctcatgccgc cgaagcccct     120
ggcgatcctc aggctgctgc ttctctgctg gcccccatgg atgtgggcga ggaacctctg     180
gaaaaggccg ccagagccag aaccgccaag gaccccaaca cctacaaggt gctgagcctg     240
gtgctgtccg tgtgcgtgct gaccaccatc ctgggctgca tcttcggcct gaagcccagc     300
tgcgccaaag aagtgaagtc ctgcaagggc cggtgcttcg agcggacctt cggcaactgc     360
agatgcgacg ccgcctgtgt ggaactgggc aactgctgcc tggactacca ggaaacctgc     420
atcgagcccg agcacatctg gacctgcaac aagttcagat gcggcgagaa gcggctgacc     480
agatccctgt gtgcctgcag cgacgactgc aaggacaagg gcgactgctg catcaactac     540
agcagcgtgt gccagggcga gaagtcctgg gtggaagaac cctgcgagag catcaacgag     600
ccccagtgcc ctgccggctt cgagacacct cctaccctgc tgttcagcct ggacggcttt     660
cgggccgagt acctgcacac atggggaggc ctgctgcccg tgatcagcaa gctgaagaag     720
tgcggcacct acaccaagaa catgcggccc gtgtacccca ccaagacctt ccccaaccac     780
tactccatcg tgaccggcct gtaccccgag agccacggca tcatcgacaa caagatgtac     840
gaccccaaga tgaacgccag cttcagcctg aagtccaaag agaagttcaa ccccgagtgg     900
tataagggcg agcccatctg ggtcaccgcc aagtaccagg gcctgaaaag cggcacattc     960
ttttggcccg gcagcgacgt ggaaatcaac ggcatcttcc ccgacatcta taagatgtac    1020
aacggcagcg tgcccttcga ggaacggatc ctggctgtgc tgcagtggct gcagctgccc    1080
aaggatgagc ggccccactt ctacaccctg tacctggaag aacctgacag cagcggccac    1140
agctacggcc ctgtgtccag cgaagtgatc aaggccctgc agcgggtgga cggcatggtg    1200
ggaatgctga tggacggcct gaaagagctg aacctgcaca gatgcctgaa cctgatcctg    1260
```

[0554]

```
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 gccccttcac cagaaacccc 1860
agagacaacc tgggctgtag ctgcaacccc agcatcctgc ccatcgagga cttccagacc 1920
cagttcaacc tgaccgtggc cgaggaaaag atcatcaagc acgagacact gccctacggc 1980
agaccccggg tgctgcagaa agagaacacc atctgcctgc tgagccagca ccagttcatg 2040
agcggctact cccaggacat cctgatgccc ctgtggacca gctacaccgt ggaccggaac 2100
gacagcttct ccaccgagga tttcagcaac tgcctgtacc aggatttccg gatccccctg 2160
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 ccccctgca ctgcgagaac ctggatacc 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
```

[0555] SEQ ID NO:78-天青杀素-ENPP1-FC核苷酸序列

[0556]

ggtaccgccacc**atg**acaagactgacagtgctggctctgctggccggactgttggcctcttctagagc
t**gct**ccttcctgcgccaaagaagtgaagtcctgcaagggcagatgcttcgagcggaccttcggcaact
gtagatgtgacgccgcttgcgtggaactgggcaactgctgcctggactaccaagagacatgcatcgag
cccgagcacatctggacctgcaacaagttcagatgcggcgagaagcggctgaccagatctctgtgcgc
ctgctctgacgactgcaaggacaagggcgactgctgcatcaactactcctctgtgtgccagggcgaga
agtcctgggttgaagaaccctgcgagtccatcaacgagcctcagtgtcctgccggcttcgagacacct
cctactctgctgttctccctggatggcttcagagccgagtacctgcatacttggggaggcctgctgcc
agtgatctccaagctgaagaagtgcggcacctacaccaagaacatgaggcctgtgtaccctaccaaga
cattccccaaccactactccatcgtgaccggcctgtatcctgagagccacggcatcatcgacaacaag
atgtacgaccccaagatgaacgcctccttcagcctgaagtccaaagagaagttcaaccccgagtggta
taagggcgagcctatctgggtcaccgctaagtaccagggactgaagtctggcaccttcttttggcctg
gctccgacgtggaaatcaacggcatcttccccgacatctataagatgtacaacggctccgtgcctttc
gaggaacgcattctggctgttctgcagtggctgcagctgcctaaggatgagaggcctcacttctacac
cctgtacctggaagaacctgactcctccggccactcttatggccctgtgtcctctgaagtgatcaagg
ccctgcagcgagtggacggaatggtcggaatgctgatggacggcctgaaagagctgaacctgcacaga
tgcctgaacctgatcctgatctccgaccacggcatggaacaggggagctgcaagaagtacatctacct
gaacaagtacctgggcgacgtgaagaacatcaaagtgatctacggcccagccgccagactgaggcctt
ctgatgtgcctgacaagtactactccttcaactacgagggaatcgcccggaacctgtcctgcagagag
cctaaccagcacttcaagccctacctgaagcactttctgcctaagcggctgcacttcgccaagtctga
cagaatcgagcccctgaccttctatctggaccctcagtggcagctggccctgaatcctagcgagagaa
agtactgtggctccggcttccacggctccgacaacgtgttctctaatatgcaggccctgttcgtcggc
tacggccctggctttaaacacggcatcgaggccgacaccttcgagaacatcgaggtgtacaatctgat
gtgtgacctgctgaatctgacccctgctcctaacaacggcacccacggatctctgaaccatctgctga
agaatcccgtgtacacccctaagcaccccaaagaggttcaccctctggtccagtgtcctttcaccaga
aatcctcgggacaacctgggctgctcttgcaacccttctatcctgcctatcgaggactttcagaccca
gttcaacctgaccgtggccgaggaaaagatcatcaagcacgagacactgccctacggcagacctagag
tgctgcagaaagagaacaccatctgcctgctgtcccagcaccagttcatgtccggctactcccaggac
atcctgatgcctctgtggacctcctacaccgtggaccggaacgatagcttctccaccgaggacttcag
caactgcctgtaccaggatttcagaatccctctgagccccgtgcacaagtgcagcttctacaagaaca
acaccaaggtgtcctacggcttcctgtctcctccacagctgaacaagaactccagcggcatctactct
gaggccctgctgaccaccaacatcgtgcccatgtaccagtccttccaagtgatctggcggtacttcca
cgacaccctgctgaggaagtacgccgaagaaagaaacggcgtgaacgtggtgtctggccccgtgttcg
acttcgactacgacggcagatgcgactctctggaaaacctgcggcagaaaagacgagtgatccggaat
caagagatcctgattcctacacacttctttatcgtgctgaccagctgcaaggatacctctcagacccc
tctgcactgcgagaatctggacaccctggccttcattctgcctcacagaaccgacaactccgagtcct
gtgtgcacggcaagcacgactcctcttgggtcgaagaactgctgatgctgcaccgggccagaatcacc

gatgtggaacacatcaccggcctgagcttctaccagcagcggaaagaacctgtgtccgatatcctgaa
gctgaaaacccatctgccaaccttcagccaagaggacctgatcaacgacaagacccacacctgtcctc
catgtcctgctccagaactgctcggaggcccctctgtgttcctgtttccacctaagccaaaggacaca
ctgatgatctctcggacccctgaagtgacctgcgtggtggtggatgtgtctcacgaagatcccgaagt
caagttcaattggtacgtggacggcgtggaagtgcacaacgccaagaccaagcctagagaggaacagt
acaactccacctacagagtggtgtccgtgctgactgtgctgcaccaggattggctgaacggcaaagag
tacaagtgcaaagtgtccaacaaggctctgcccgctcctatcgaaaagaccatctccaaggctaaggg
ccagcctcgggaacctcaggtttacaccctgcctccatctcgggaagagatgaccaagaaccaggtgt
ccctgacctgcctggtcaagggcttctaccttccgatatcgccgtggaatgggagtccaatggccag
cctgagaacaactacaagacaacccctcctgtgctggacagcgacggctcattcttcctgtactctaa
gctgacagtggacaagtcccggtggcagcaaggcaatgtgttttcctgctctgtgatgcacgaggccc
tccacaatcactacacccagaagtccctgtctctgtcccctggcaaa**tgatag**ctcgag

[0557] 图例-粗体＝起始/终止密码子;下划线＝信号肽的核苷酸序列。

[0558] SEQ ID NO:79-天青杀素-ENPP3-FC核苷酸序列

atgaccagactgaccgtgctggccctgctggccggcctgctggccagcagcagagccgccaa
gcagggcagctgcagaaagaagtgcttcgacgccagcttcagaggcctggagaactgcagatgcgacg
tggcctgcaaggacagaggcgactgctgctgggacttcgaggacacctgcgtggagagcaccagaatc
tggatgtgcaacaagttcagatgcggcgagaccagactggaggccagcctgtgcagctgcagcgacga
ctgcctgcagagaaaggactgctgcgccgactacaagagcgtgtgccagggcgagaccagctggctgg
aggagaactgcgacaccgcccagcagagccagtgccccgagggcttcgacctgccccccgtgatcctg
ttcagcatggacggcttcagagccgagtacctgtacacctgggacaccctgatgcccaacatcaacaa
gctgaagacctgcggcatccacagcaagtacatgagagccatgtaccccaccaagaccttccccaacc
actacaccatcgtgaccggcctgtaccccgagagccacggcatcatcgacaacaacatgtacgacgtg
aacctgaacaagaacttcagcctgagcagcaaggagcagaacaaccccgcctggtggcacggccagcc
catgaacctgaccgccatgtaccagggcctgaaggccgccacctacttctggcccggcagcgaggtgg
ccatcaacggcagcttccccagcatctacatgccctacaacggcagcgtgcccttcgaggagagaatc
agcaccctgctgaagtggctggacctgcccaaggccgagagacccagattctacaccatgtacttcga
ggagcccgacagcagcggccacgccggcggccccgtgagcgccagagtgatcaaggccctgcaggtgg
tggaccacgccttcggcatgctgatggagggcctgaagcagagaaacctgcacaactgcgtgaacatc
atcctgctggccgaccacggcatggaccagacctactgcaacaagatggagtacatgaccgactactt
ccccagaatcaacttcttctacatgtacgagggccccgcccccagaatcagagcccacaacatccccc
acgacttcttcagcttcaacagcgaggagatcgtgagaaacctgagctgcagaaagcccgaccagcac
ttcaagccctacctgacccccgacctgcccaagagactgcactacgccaagaacgtgagaatcgacaa
ggtgcacctgttcgtggaccagcagtggctggccgtgagaagcaagagcaacaccaactgcggcggcg
gcaaccacggctacaacaacgagttcagaagcatggaggccatcttcctggcccacggccccagcttc
aaggagaagaccgaggtggagcccttcgagaacatcgaggtgtacaacctgatgtgcgacctgctgag
aatccagcccgcccccaacaacggcacccacggcagcctgaaccacctgctgaaggtgcccttctacg
agcccagccacgccgaggaggtgagcaagttcagcgtgtgcggcttcgccaacccccctgcccaccgag
agcctggactgcttctgcccccacctgcagaacagcacccagctggagcaggtgaaccagatgctgaa
cctgacccaggaggagatcaccgccaccgtgaaggtgaacctgcccttcggcagacccagagtgctgc
agaagaacgtggaccactgcctgctgtaccacagagagtacgtgagcggcttcggcaaggccatgaga
atgcccatgtggagcagctacaccgtgccccagctgggcgacaccagccccctgcccccccaccgtgcc
cgactgcctgagagccgacgtgagagtgccccccagcgagagccagaagtgcagcttctacctggccg
acaagaacatcacccacggcttcctgtacccccccgccagcaacagaaccagcgacagccagtacgac
gccctgatcaccagcaacctggtgcccatgtacgaggagttcagaaagatgtgggactacttccacag
cgtgctgctgatcaagcacgccaccgagagaaacggcgtgaacgtggtgagcggccccatcttcgact
acaactacgacggccacttcgacgcccccgacgagatcaccaagcacctggccaacaccgacgtgccc
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cggctggctggacgtgctgcccttcatcatcccccacagacccaccaacgtggagagctgccccgagg
gcaagcccgaggccctgtgggtggaggagagattcaccgcccacatcgccagagtgagagacgtggag

ctgctgaccggcctggacttctaccaggacaaggtgcagcccgtgagcgagatcctgcagctgaagac
ctacctgcccaccttcgagaccaccatcgacaagacccacacctgccccccctgccccgccccgagc
tgctgggcggccccagcgtgttcctgttcccccccaagcccaaggacaccctgatgatcagcagaacc
cccgaggtgacctgcgtggtggtggacgtgagccacgaggaccccgaggtgaagttcaactggtacgt
ggacggcgtggaggtgcacaacgccaagaccaagcccagagaggagcagtacaacagcacctacagag
tggtgagcgtgctgaccgtgctgcaccaggactggctgaacggcaaggagtacaagtgcaaggtgagc
aacaaggccctgcccgcccccatcgagaagaccatcagcaaggccaagggccagcccagagagccccca
ggtgtacaccctgcccccccagcagagaggagatgaccaagaaccaggtgagcctgacctgcctggtga
agggcttctaccccagcgacatcgccgtggagtgggagagcaacggccagcccgagaacaactacaag
accacccccccccgtgctggacagcgacggcagcttcttcctgtacagcaagctgaccgtggacaagag
cagatggcagcagggcaacgtgttcagctgcagcgtgatgcacgaggccctgcacaaccactacaccc
agaagagcctgagcctgagccccggcaag

[0559] ENPP1融合多肽和ENPP3融合多肽的克隆和表达

[0560] ENPP1或ENPP1多肽如US 2015/0359858A1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。

[0561] 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。

[0562] 将经修饰的ENPP1序列克隆到在C末端9-F 1IS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。

[0563] 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构建体是使用由ENPP1和ENPP2的信号序列(下文中的“ENPP1-2-1”或“ENPP121”)的组合构成的信号序列制备的。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。

[0564] 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。

[0565] 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。

[0566] 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。

[0567] 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。

[0568] ENPP1融合多肽和ENPP3融合多肽的产生和纯化

[0569] 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。

[0570] 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。

[0571] 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,《自然通讯》6:10006中确立的方案产生的，所述文献的内容特此通过全文引用的方式并入。

[0572] 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)。

[0573] 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。

[0574] 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。

[0575] 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)。

[0576] 剂量&施用模式

[0577] 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。

[0578] 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。

[0579] 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。

[0580] 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)。

[0581] 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。

[0582] 核酸施用和疗法

[0583] 用于ENPP1和ENPP3的体内表达的病毒载体

[0584] 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。

[0585] 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。

[0586] 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。几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。

[0587] 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。

[0588] 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.)。

[0589] 根据本公开的腺相关病毒载体

[0590] 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。

[0591] 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。

[0592] 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。

[0593] 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)。

[0594] 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。

[0595] 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。

[0596] 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。

[0597] 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。

[0598] 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。

[0599] 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外核苷酸焦磷酸酯酶/磷酸二酯酶(ENPP1)多肽序列。

[0600] 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。

[0601] 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。

[0602] 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。

[0603] 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)。

[0604] 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。

[0605] 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。

[0606] 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。

[0607] 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。

[0608] 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。

[0609] 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。

[0610] 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。

[0611] 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。

[0612] 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1x 108至约5x1016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}。

[0613] 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。

[0614] 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。

[0615] 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。

[0616] 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。

[0617] ENPP1多肽和ENPP3多肽的基于RNA的体内表达

[0618] 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。

[0619] 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。

[0620] 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。

[0621] dsRP的产生

[0622] 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。

[0623] 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。

[0624] 产生dsRNA病毒或dsRP的方法

[0625] 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。

[0626] 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。

[0627] 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。

[0628] 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。

[0629] 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。

[0630] ENPP1涂覆的支架和ENPP3涂覆的支架

[0631] 支架通常是用于保持存在于身体的各个部分中的开放内腔(例如,身体中的开口)使得含有那些内腔的身体的部分可以正常地起作用的细长结构。支架通常用于治疗动脉粥样硬化,即其中动脉变得部分并且有时完全被物质阻塞的血管系统的疾病,所述物质可以包含脂质、胆固醇、钙和各种类型的细胞,如平滑肌细胞和血小板。

[0632] 位于身体中的任何内腔内的支架不总是可以防止部分或完全再狭窄。具体地,支架并不总是防止动脉在经皮经腔血管成形术(PTA)之后再变窄。在一些情况下,在动脉或静脉中引入和存在支架本身可能产生创伤或组织损伤区,例如被称为内皮的动脉的内衬中的撕裂,从而在支架放置后需要另外的外科手术。

[0633] 据信此类创伤或组织损伤可以触发血管平滑肌细胞迁移,所述血管平滑肌细胞通常通过内皮与动脉内腔分离进入动脉内腔中,所述血管平滑肌细胞在所述动脉内腔中增殖以产生可能在大约几天或几周内阻塞动脉的细胞质。这种有时在PTA之后看到的再闭塞是再狭窄的实例。用如ENPP1药剂或ENPP3药剂等治疗剂涂覆支架预期预防和/或减少血管平滑肌细胞增殖,这进而减少再狭窄的发生或治疗再狭窄。

[0634] 在一些实施例中,患者需要外科手术和/或由于先前所植入非洗脱式支架的存在而具有组织损伤。

[0635] 在一些实施例中,患者需要外科手术和/或由于先前所植入洗脱式支架的存在而具有组织损伤,所述洗脱式支架洗脱除ENPP1药剂或ENPP3药剂之外的治疗剂。

[0636] 在一些实施例中,去除已导致组织损伤的先前支架,并且用ENPP1药剂涂覆的支架代替。

[0637] 在一些实施例中,去除已导致组织损伤的先前支架,并且用ENPP3药剂涂覆的支架代替。

[0638] 在一些实施例中,未去除导致组织损伤的先前支架,并且邻近先前支架植入ENPP1药剂涂覆的支架。

[0639] 在一些实施例中,未去除导致组织损伤的先前支架,并且邻近先前支架植入ENPP3药剂涂覆的支架。

[0640] ENPP1涂覆的支架或ENPP3涂覆的支架通常是由支架或互连长丝制成的中空圆柱形结构。支架通常通过将其以压缩状态与导管附连植入在身体中的其使用部位,所述导管被引导穿过身体到达支架使用部位。血管支架通常在血管中使用以使血管打开并提供改进的血流。支架可以在其被定位在期望部位处之后膨胀到使得其能够通过支撑内腔的壁来保持内腔打开的大小。血管支架可以塌缩以减小其直径,使得支架可以被引导穿过患者的动脉或静脉以到达展开部位。支架通常联接到球囊的外部以通过使球囊膨胀而膨胀,或者在去除约束,如保持支架处于其塌缩状态的线或套筒时自膨胀。

[0641] 血管支架通常由金属制成,以提供支撑阻塞的动脉壁所需的强度。两种优选金属是镍和钛的镍钛诺合金以及不锈钢。可以用于制造支架的其它材料为陶瓷、聚合物和塑料。聚合物可以是不具有官能团的聚合物。可替代地,聚合物可以是具有官能团,但任何官能团与ENPP1药剂或ENPP3药剂都无反应性的聚合物。聚合物可以包含可生物降解聚合物。例如,聚合物可以包含选自由以下组成的组的聚合物:聚羟基酸、聚酸酐、聚膦腈、草酸聚亚烷酯、可生物降解聚酰胺、聚原酸酯、聚磷酸酯、聚原碳酸酯及其共混物或共聚物。聚合物还可以包含单独的或与可生物降解聚合物组合的可生物稳定聚合物。例如,聚合物可以包含选自

由以下组成的组的聚合物:聚氨酯、硅酮、聚丙烯酸酯、聚酯、聚亚烷基氧化物、多元醇、聚烯烃、聚氯乙烯、纤维素以及其衍生物、氟化聚合物、可生物稳定聚酰胺以及其共混物或共聚物。

[0642] 不同支架设计对药物分布模式的影响已在实验研究中详细研究,并且还在临床试验中测试(Hwang CW、Wu D、Edelman ER.2001。生理转运力管理基于支架的递送的药物分配(Physiological transport forces govern drug distribution for stent-based delivery)《循环(Circulation)》,104:600-5;&Takebayashi H、Mintz GS、Carlier SG等人2004。非均匀支架分布与西罗莫司洗脱式支架植入后的更多新内膜增生相关(Nonuniform strut distribution correlates with more neointimal hyperplasia after Sirolimus-eluting stent implantation)《循环》,110:3430-4)。尽管迄今为止已经开发了大量支架设计,但仅多细胞设计是目前最常用的;其可以被分类为"封闭细胞"和"开放细胞"配置(Rogers CDK.2002。药物洗脱式支架:支架设计、递送媒剂和药物选择的作用(Drug-eluting stents:role of stent design,delivery vehicle,and drug selection)《心血管医学综述(Rev Cardiovasc Med)》,3(增刊5):S10-15)。封闭细胞支架在弯曲血管区段中展开时具有均匀的细胞膨胀和恒定细胞间隔,这提供了更均匀的药物分布(Rogers 2002)。开孔支架的表面覆盖率在弯曲区段中的内曲率与外曲率之间具有更大变化,但以较不均匀的药物分布为代价提供与弯曲表面的更好适形性(Rogers2002)。大多数当前支架使用封闭细胞设计。用于药物递送的最优支架设计在展开后将具有大支架表面积、小细胞间隙和最小撑杆变形,同时保持适形性、径向支撑和柔性以到达复杂的冠状病变。不同几何支架结构的几个实例描述于Paisal等人(Muhammad Sufyan Amir Paisal等人2017IOP会议系列:材料科学与工程化(IOP Conf.Ser.:Mater.Sci.Eng.165 012003)中。

[0643] 通过施涂分别包括有效量的ENPP1药剂或ENPP3药剂的涂层组合物来制备ENPP1涂覆的支架或ENPP3涂覆的支架。所述涂层组合物优选地包含足以对抑制斑块的再生长或抑制再狭窄或防止血管平滑细胞增殖在治疗上有效的量的ENPP1药剂或ENPP3药剂。

[0644] 在一个实施例中,基于涂层组合物的总重量,涂层组合物包括约1wt%至约50wt%ENPP1多肽。在另一实施例中,涂层组合物包括约5wt%至约30wt%ENPP1多肽。在又另一实施例中,涂层组合物包括约10wt%至约20wt%ENPP1多肽。

[0645] 在一个实施例中,基于涂层组合物的总重量,涂层组合物包括约1wt%至约50wt%ENPP3多肽。在另一实施例中,涂层组合物包括约5wt%至约30wt%ENPP3多肽。在又另一实施例中,涂层组合物包括约10wt%至约20wt%ENPP3多肽。

[0646] 在一个实施例中,涂层组合物包括约1μg/ml至约10mg/ml ENPP1多肽。在另一实施例中,涂层组合物包括约100μg/ml至5mg/ml ENPP1多肽。在又另一实施例中,涂层组合物包括约500μg/ml至约2mg/ml ENPP1多肽。

[0647] 在一相关实施例中,涂层组合物的ENPP1多肽为ENPP1-Fc。

[0648] 在一相关实施例中,涂层组合物的ENPP1多肽为ENPP1-白蛋白。

[0649] 在一个实施例中,涂层组合物包括约1μg/ml至约10mg/ml ENPP3多肽。在另一实施例中,涂层组合物包括约100μg/ml至5mg/ml ENPP3多肽。在又另一实施例中,涂层组合物包括约500μg/ml至约2mg/ml ENPP3多肽。

[0650] 在一相关实施例中,涂层组合物的ENPP3多肽为ENPP3-Fc。

[0651] 在一相关实施例中,涂层组合物的ENPP3多肽为ENPP3-白蛋白。

[0652] 在一个实施例中,涂层组合物包括约1ng/μl至约1000μg/μl ENPP1mRNA。在另一实施例中,涂层组合物包括约100ng/μl至10μg/μl ENPP1mRNA。在又另一实施例中,涂层组合物包括约50ng/μl至约5μg/μl ENPP1mRNA。

[0653] 在一个实施例中,涂层组合物包括约1ng/μl至约1000μg/μl ENPP1-Fc mRNA。在另一实施例中,涂层组合物包括约100ng/μl至10μg/μl ENPP1-Fc mRNA。在又另一实施例中,涂层组合物包括约50ng/μl至约5μg/μl ENPP1-Fc mRNA。

[0654] 在一个实施例中,涂层组合物包括约1ng/μl至约1000μg/μl ENPP1-白蛋白mRNA。在另一实施例中,涂层组合物包括约100ng/μl至10μg/μl ENPP1-白蛋白mRNA。在又另一实施例中,涂层组合物包括约50ng/μl至约5μg/μl ENPP1-白蛋白mRNA。

[0655] 在一个实施例中,涂层组合物包括约1ng/μl至约1000μg/μl ENPP3mRNA。在另一实施例中,涂层组合物包括约100ng/μl至5μg/μl ENPP3mRNA。在又另一实施例中,涂层组合物包括约500ng/μl至约2μg/μl ENPP3mRNA。

[0656] 在一个实施例中,涂层组合物包括约1ng/μl至约1000μg/μl ENPP3-Fc mRNA。在另一实施例中,涂层组合物包括约100ng/μl至5μg/μl ENPP3-Fc mRNA。在又另一实施例中,涂层组合物包括约500ng/μl至约2μg/μl ENPP3-Fc mRNA。

[0657] 在一个实施例中,涂层组合物包括约1ng/μl至约1000μg/μl ENPP3-白蛋白mRNA。在另一实施例中,涂层组合物包括约100ng/μl至5μg/μl ENPP3-白蛋白mRNA。在又另一实施例中,涂层组合物包括约500ng/μl至约2μg/μl ENPP3-白蛋白mRNA。

[0658] 支架可以涂覆有物质,如可生物降解或可生物稳定聚合物,以提高支架的生物相容性,从而使其不太可能引起患者的过敏或其它免疫应答。涂层物质还可以增加支架的强度。一些已知涂层物质包含有机酸、其衍生物和可生物降解或可生物稳定合成聚合物。可生物稳定涂层物质在体内不降解,可生物降解涂层物质在体内可以降解。

[0659] 涂层组合物包括有效量的载体,所述载体在涂层过程有助于确保如ENPP1药剂或ENPP3药剂等治疗分子粘附到支架表面,并且还有助于在支架放置部位处将治疗剂洗脱到体内。载体可以是液态载体或固态载体。涂层组合物可以可替代地在固态载体中包括多于一种固态化合物。涂层组合物可以进一步包括液态载体和固态载体两者。在仍另外的方面,涂层组合物还可以在载体中包括多于一种类型的非聚合物化合物或聚合物化合物,并且可以进一步在固态载体或液态载体中包括聚合物材料和非聚合物材料两者。

[0660] 在另一实施例中,可以将两种或更多种类型的可生物降解化合物(聚合物或非聚合物)一起共混,以获得供涂层组合物使用的液态载体。可生物降解化合物在其混合在一起,例如以形成均质溶液、混合物或悬浮液之前可以是液体。可替代地,可生物降解化合物中的一些可生物降解化合物在与其它液态可生物降解化合物混合之前可以是固体。固态可生物降解化合物优选地在其与液态可生物降解化合物混合时溶解,从而产生含有不同可生物降解化合物的液态载体组合物。

[0661] 在另一实施例中,涂层组合物的可生物降解载体组分是固体,所述固体在与生物活性组分和包含在涂层组合物中的任何其它组分混合时溶解。

[0662] 载体可以是聚合物载体。一些聚合物载体为合成聚合物。用作储器基质的合成聚合物的实例包含但不限于聚-正-甲丙烯酸丁酯、聚乙烯-乙酸乙烯酯、聚(丙交酯-共-Σ-己

内酯)共聚物、纤维蛋白、纤维素、磷酸胆碱。一些洗脱式支架包括含有装载有治疗分子的纳米腔的多孔300μm陶瓷层。药物洗脱式支架、支架结构和支架设计的实例可以在以下中找到:药物洗脱式支架:回顾与更新(Drug-Eluting Stent:A Review and Update),《血管健康与风险管理(Vasc Health Risk Manag.)》2005年12月;1(4):263-276以及现代支架:我们将去往何处(Modern Stents:Where Are We Going?),《Rambam Maimonides医学杂志(Rambam Maimonides Med J.)》2020年4月;11(2):e0017。

[0663] 涂层组合物中的载体可以是可生物降解或可生物稳定的。可生物降解聚合物通常用于合成可生物降解缝合线。这些聚合物包含聚羟基酸。适于本发明使用的聚羟基酸包含聚-L-乳酸、聚-DL-乳酸、聚乙醇酸、聚丙交酯,包含丙交酯(包含由如D-,L-乳酸和内消旋乳酸等乳酸的所有立体异构体制备的丙交酯)的均聚物和共聚物、聚内酯、聚己内酯、聚乙交酯、聚对二噁烷酮、聚1,4-二氧杂环庚烷-2-酮、聚1,5-二氧杂环庚烷-2-酮、聚6,6-二甲基-1,4-二噁烷-2-酮、聚羟戊酸酯、聚羟丁酸酯、聚三亚甲基碳酸酯聚合物和前述的共混物。

[0664] 适于本发明使用的聚内酯包含聚己内酯(如聚(e-己内酯))、聚戊内酯(如聚(d-戊内酯))和聚丁内酯(如聚(丁内酯))。可以使用的其它可生物降解聚合物为聚酸酐、聚磷腈、如合成多肽等可生物降解聚酰胺,所合成多肽如聚赖氨酸和聚天冬氨酸、草酸聚亚烷酯、聚原酸酯、聚磷酸酯和聚原碳酸酯。可以使用所列聚合物的中的任何聚合物的共聚物和共混物。除了存在或不存在括号之外相同的聚合物名称表示相同的聚合物。

[0665] 适于本发明使用的可生物稳定聚合物包含但不限于:聚氨酯;硅酮,如聚烷基硅氧烷,如聚二甲基硅氧烷和聚甲基丙烯酸丁酯;聚酯,如聚(对苯二甲酸乙烯酯);聚亚烷基氧化物,如聚氧化乙烯或聚乙二醇;多元醇,如聚乙烯醇和聚乙二醇;聚烯烃,如聚-5乙烯、聚丙烯、聚(乙烯-丙烯)橡胶和天然橡胶;聚氯乙烯;纤维素和改性纤维素衍生物,如人造丝、人造丝-三乙酸酯、纤维素乙酸酯、纤维素乙酸酯丁酸酯、赛璐酚(cellophane)、纤维素硝酸酯、纤维素丙酸酯;纤维素醚,如羧甲基纤维素和羟烷基纤维素;氟化聚合物,如聚四氟乙烯(特氟龙(Teflon));以及可生物稳定聚酰胺,如尼龙66和聚己内酰胺。也可以使用固定的动物组织,如戊二醛固定的牛心包。聚酯和聚酰胺可以是可生物降解或可生物稳定的。酯键和酰胺键易于水解,所述水解可以促成生物降解。

[0666] 在一些情况下,涂层组合物进一步包括有效量的非聚合物载体。非聚合物载体可以包含脂肪酸、生物相容性油或蜡中的一种或多种。非聚合物可生物降解载体的实例包含液态油酸、维生素E、花生油和棉籽油,这些为疏水且可生物相容的液体。在一些情况下,非聚合物载体或聚合物载体在室温和体温下可以是液体。在一些情况下,非聚合物载体或聚合物载体在室温和体温下可以是固体,或在室温下是固体并且在体温下是液体。

[0667] 在另一实施例中,聚合物溶液可以形成为膜,并且膜然后施涂于支架。可以使用形成膜的各种常规方法中的任何方法。例如,聚合物、ENPP1药剂或ENPP3药剂和溶剂优选地混合成溶液,并且然后倒入到平滑的平坦表面上,使得在对溶液进行干燥以去除溶剂之后形成涂层膜。然后可以对膜切割以装配其将要使用的支架。然后,膜可以如通过包裹安装在支架的外表面上。

[0668] 在另一实施例中,涂覆支架如下制备:通过向支架喷涂包括如ENPP1药剂或ENPP3药剂等治疗剂的液态载体,从而在支架的撑杆上产生均匀厚度的涂层。在另一实施例中,支架可以被浸没涂覆包括载体和治疗剂的涂层溶液或浸入在所述涂层溶液中,使得溶液完全

涂覆支架的撑杆。可替代地，可以向支架喷涂包括载体和治疗剂的涂层溶液，如用油漆刷。在这些涂层应用中的每种应用中，支架的外表面和内表面两者整体都优选地是涂覆的，但在一些实施例中，任一个表面或两个表面的仅一部分可是涂覆的。

[0669] 如以上所讨论的，涂层组合物包括生物活性组分和可生物降解载体组分。优选地，涂层组合物包括0.1重量％至100重量％的生物活性组分以及1重量％至99重量％的可生物降解载体组分。更优选地，涂层组合物包括0.1重量％至50重量％的生物活性组分以及50重量％至99.9重量％的可生物降解载体组分。涂层组合物可以多种方式制备，包含简单地将生物活性组分和载体组分混合在一起以形成混合物，例如溶液或悬浮液。可替代地，将生物活性组分和载体组分一起混合在合适的溶剂中，将涂层施涂到支架，并且去除溶剂。优选地，将涂层组合物施涂到处于其膨胀状态的支架。

[0670] 除支架之外，根据本文公开的发明的各方面的可以涂覆的其它医疗装置的实例包含导管、心瓣、起搏器引线、环状成形术环和其它医疗植入物。在其它具体实施例中，涂覆的血管成形术球囊和其它涂覆的医疗装置也可以包括本文公开的涂层组合物之一。然而，支架是优选的。涂层组合物可以通过任何多种方式施涂到支架(或其它医疗装置)，例如，通过将涂层组合物喷涂到支架上、通过将支架浸入在涂层组合物中或通过向支架喷涂涂层组合物。优选地，以其膨胀(即，直径放大)形式涂覆支架，使得将施涂足够量的涂层组合物以涂覆膨胀的支架的整个表面。当支架浸入在涂层组合物中时，可以如通过用油漆刷刷掉过量涂层组合物来去除支架的表面上的过量涂层组合物。在涂层应用中的每个涂层应用中，优选地支架的外表面和内表面两者是涂覆的。

[0671] 本文所述的涂层组合物优选地在已将支架引入到体内后部分或基本上部分保留在支架上，持续至少几天、持续数周并且更优选地持续数月，由此使如ENPP1药剂或ENPP3药剂等治疗剂缓慢释放到血流中。

[0672] 药物组合物和调配物

[0673] 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。

[0674] 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。

[0675] 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。

[0676] 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。

[0677] 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。

[0678] 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。

[0679] 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％。

[0680] 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。

[0681] 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。

[0682] 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。

[0683] 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。

[0684] 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。

[0685] 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。

[0686] 施用途径

[0687] 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。

[0688] 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。

[0689] “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。

[0690] 实例

[0691] 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。

[0692] 实例1:ENPP1-Fc融合蛋白在支架内再狭窄模型中的功效

[0693] 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。

[0694] 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。

[0695] 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。

[0696] 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。

[0697] 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。

[0698] 如图1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2)。

[0699] 表1和表2(如下)总结了治疗组所有深动脉的平均OCT值。

[0700] 表1.

[0701]

	第 14 天再损伤，深动脉				
	管腔面积（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

[0702] 表2.

[0703]

	第 42 天终止，深动脉				
	管腔面积（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

[0704] 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天具有更高的管腔面积。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3)。这些数据表明，ENPP1多肽尤其可用于抑制与外周动脉的损伤和/或外周动脉相关的内膜增厚。

[0705] 实例2：ENPP3-Fc融合蛋白在支架内再狭窄模型中的功效

[0706] 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。

[0707] 如实例1中所描述的,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。

[0708] ENPP3-Fc治疗从第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,记录了选定外周部位的最终术后血管造影术和OCT。

[0709] 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。

[0710] 不受任一理论的束缚,预期与媒剂对照组相比,用ENPP3-Fc治疗的动物将显示出较低的狭窄面积%。预期ENPP3多肽将尤其可用于抑制与外周动脉的损伤和/或外周动脉相关的内膜增厚。

[0711] 实例3-用于治疗动脉粥样硬化外周血管的ENPP1洗脱式涂覆支架。

[0712] 在此实例中,ENPP1多肽(ENPP1或ENPP1-Fc或ENPP1-白蛋白)涂覆支架抑制外周动脉中新生内膜形成和炎症从而减少血栓形成和/或血管闭塞的能力。

[0713] 不受任一理论束缚,预期诱导ENPP1多肽(ENPP1或ENPP1-Fc或ENPP1-白蛋白)在外周动脉中植入支架的部位处的过表达将导致以下中的一种或多种:(i)血小板激活降低,(ii)再狭窄和炎性应答减少,以及(iii)支架植入后VSMC增殖减少。这种疗法基于将ENPP1mRNA(或ENPP1-Fc mRNA或ENPP1-白蛋白mRNA)递送到内皮细胞,所述内皮细胞进而在mRNA翻译后在支架植入物的部位处表达ENPP1蛋白。

[0714] ENPP1mRNA的产生

[0715] 根据制造商的说明书,使用热启动高保真聚合酶试剂盒(HotStar HiFidelity Polymerase Kit)(德国希尔登的凯杰公司(Qiagen,Hilden,Germany))扩增含有ENPP1DNA模板的pcDNA 3.3质粒(德国埃伯斯贝格的Eurofins Genomics公司(Eurofins Genomics GmbH,Ebersberg,Germany))。用Qiaquick PCR纯化试剂盒(凯杰公司)对PCR产物(PCR循环仪:德国韦瑟灵的艾本德(Eppendorf,Wesseling,Germany))进行纯化。根据制造商的说明书,用MEGAscript1T7试剂盒(苏格兰格拉斯哥的Ambion公司(Ambion,Glasgow,Scotland))产生经体外转录的mRNA。

[0716] 为了对mRNA进行修饰,将3′-O-Mem7G(5')ppp(5')G RNA Cap结构类似物(德国法兰克福的新英格兰实验室(New England Biolabs,Frankfurt,Germany))以及被UTP和CTP取代的假尿苷-5'-三磷酸酯和5-甲基胞苷-5'-三磷酸酯(美国加利福尼亚州圣地亚哥的TriLink Biotech公司(TriLink Biotech,San Diego,CA,USA))分别添加到反应中。对于RNA酶抑制,每次反应添加1μl RNA酶抑制剂(沃尔瑟姆的赛默飞世尔科技公司(Thermo Scientific,Waltham))。然后用RNeasy试剂盒(凯杰公司)对经体外转录的mRNA进行纯化。使用南极磷酸酶试剂盒(Antarctic Phosphatase Kit)(新英格兰实验室)对经纯化的mRNA

去磷酸化，并且再次用RNeasy试剂盒(凯杰公司)进行纯化。重复相同的程序以使用eGFP DNA产生增强的绿色荧光蛋白(eGFP)mRNA。(Avci-Adali M,Behring A,Keller T,Krajewski S,Schlensak C,Wendel HP(2014)用体外合成且经修饰的mRNA成功转染人内皮细胞以诱导蛋白质表达的优化条件(Optimized conditions for successful transfection of human endothelial cells with in vitro synthesized and modified mRNA for induction of protein expression.)《生物工程学杂志(J Biol Eng)》8:8)。

[0717] 通过在通过经转染的HEK293细胞对ATP进行水解后测量游离磷酸盐来验证所产生的ENPP1mRNA的功能。将经ENPP1mRNA转染的HEK293细胞与20μM ATP(德国朗根费尔德的möLab公司(möLab,Langenfeld,Germany))或作为对照的PBS在摇动平台(Polymax 1040，德国施瓦巴赫的海道尔夫公司(Heidolph,Schwabach,Germany))上在37℃下一起温育10分钟。在酶促产物AMP累积的情况下，ATP底物在存在ENPP1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ENPP1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。

[0718] 支架涂层

[0719] 为了开发允许ENPP1mRNA局部递送和内皮细胞在体内转染的生物活性支架涂层，首先将产生的ENPP1mRNA涂覆在thermanox塑料载玻片上。因此，使用thermanox塑料载玻片(Nunc，美国赛默飞世尔科技公司(Thermo Scientific,USA))模拟支架涂层。首先，将每孔100.000个HEK293细胞接种在12孔板上。

[0720] 24小时后，将2μl Lipofectamin以及10μg ENPP1mRNA与50μl Opti-MEM混合，并且在室温下温育20分钟。同时，将来自聚乳酸-共-乙醇酸(PLGA)(达姆施塔特的赢创公司(Evoniks,Darmstadt))储备溶液(20mg/ml)的10μl稀释在990μl乙酸乙酯(最终浓度200μg/ml)中。然后将200μl PLGA溶液与转染复合物混合。

[0721] 在室温下，以逐步方法向thermanox载玻片涂覆溶液。eGFP mRNA和无菌水用作对照。在将干燥的载玻片面朝下铺板到细胞上之前，向HEK293细胞提供新培养基。利用载玻片将细胞在37℃和5% CO_2下温育24小时、48小时和72小时，然后使用FACScan细胞仪进行分析。

[0722] 使用流式细胞术测量HEK293细胞的ENPP1的表达。利用抗ENPP1-荧光素异硫氰酸酯(FITC)抗体对ENPP1涂覆的thermonox载玻片暴露的细胞和对照细胞染色。对用ENPP1mRNA/PLGA覆盖的thermonox载玻片温育后的HEK293细胞进行的流式细胞分析预期显示出ENPP1mRNA从PLGA涂层释放，由此ENPP1表达的增加预期可在暴露于载玻片后24小时、48小时和72小时后检测到。

[0723] 与对照HEK293细胞相比，(其暴露于涂覆有单独的脂转染胺的thermonox载玻片)0.5-1μg的ENPP1mRNA预期即使在暴露24小时后也足以诱导暴露于ENPP1mRNA涂覆的thermonox载玻片的HEK细胞中ENPP1蛋白表达的增加。

[0724] 不受任一理论的束缚，本文提出，在支架植入物的部位处表达的ENPP1预期预防外周动脉中的内膜增殖并减少血小板闭塞。

[0725] 实例4-制备和植入用于治疗动脉粥样硬化外周血管的ENPP1涂覆支架

[0726] 在此实例中，使用幼年猪动物模型以植入ENPP1涂覆的支架以确定ENPP1涂覆的支

架抑制新内膜形成、再狭窄和炎症的功效。制备ENPP1药剂涂覆的支架，并且然后将所述支架植入在外周动脉中。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，如实例1中所描述的。

[0727] 制备ENPP1涂覆的支架

[0728] 任何支架都适于涂覆有ENPP1药剂。销售支架以供使用的商业来源的常见实例包含雅培公司、波士顿科学公司(Boston Scientific)、美敦力公司(Medtronic)、Alvimedica公司(Alvimedica)、乐普医疗技术公司(Lepu Medical Technology)、康蒂思公司(Cordis)、Balton公司(Balton)或百多力公司(Biotronik)。外周动脉支架的长度较短(12mm至18mm)，直径范围为5mm至8mm，通常用于放置在髂动脉和股动脉中。Henry等人详细描述了可用于外周动脉的不同类型的支架长度和直径(Henry等人，《德克萨斯心脏研究所杂志(Tex Heart Inst J.)》2000;27(2):119-126)。

[0729] 例如，裸金属支架等普通支架可以如下被转化为ENPP1涂覆的洗脱式支架：通过将包括ENPP1mRNA的聚合物膜放置在支架内部，或通过将包括ENPP1mRNA或ENPP1多肽的聚合物溶液或非聚合物溶液喷洒在支架表面上。

[0730] ENPP1聚合物膜的一些实例在以下示出，ENPP1聚合物膜可以放置在支架内部以产生ENPP1涂覆的洗脱式支架。任选地，可以将非聚合物载体，如维生素E、维生素E乙酸酯、维生素E琥珀酸酯、油酸、花生油和棉籽油添加到溶液中，改善ENPP1药剂在聚合物膜中的稳定性。

[0731] (a)ENPP1药剂涂层组合物(A)-10mg PCL(聚己内酯)聚合物和100μg ENPP1mRNA(或ENPP1-Fc mRNA或ENPP1-白蛋白mRNA)在室温下溶解于无菌双蒸馏水中。将溶液倒入到玻璃板上，并且使溶剂蒸发12-24小时。几乎完全去除溶剂后，从玻璃板上取出ENPP1装载的PCL膜，并且将所述膜切割成1.5cm乘1.5cm大小，然后将其进一步修整以适合支架的尺寸。然后将包括ENPP1mRNA(或ENPP1-Fc mRNA或ENPP1-白蛋白mRNA)的聚合物膜安装在不锈钢支架上。可以重复相同的方法以通过使用50μg载体DNA制备涂覆有表达ENPP1多肽(ENPP1或ENPP1-Fc或ENPP1-白蛋白)的载体的支架。

[0732] (b)ENPP1药剂涂层组合物(B)-10mg EVA(乙烯-乙酸乙烯酯)聚合物和100μg ENPP1mRNA(或ENPP1-Fc mRNA或ENPP1-白蛋白mRNA)在室温下溶解于无菌双蒸馏水中。将溶液倒入到玻璃板上，并且使溶剂蒸发12-24小时。在几乎完全去除溶剂后，从玻璃板上取出ENPP1-mRNA(或ENPP1-Fc mRNA或ENPP1-白蛋白mRNA)装载的EVA膜，并且将所述膜切割成1.5cm乘1.5cm大小。然后将包括ENPP1mRNA(或ENPP1-Fc mRNA或ENPP1-白蛋白mRNA)的聚合物膜安装在不锈钢支架上。可以重复相同的方法以通过使用50μg载体DNA制备涂覆有表达ENPP1多肽(ENPP1或ENPP1-Fc或ENPP1-白蛋白)的载体的支架。

[0733] 下文示出了包括ENPP1的喷雾溶液的一些实例，可以将喷雾溶液施涂到支架上以产生ENPP1涂覆的洗脱式支架。任选地，可以将非聚合物载体，如维生素E、维生素E乙酸酯、维生素E琥珀酸酯、油酸、花生油和棉籽油添加到喷雾溶液中，改善ENPP1药剂的稳定性。

[0734] (c)ENPP1药剂涂层组合物(C)-10mg PCL(聚己内酯)聚合物和100μg ENPP1mRNA在室温下溶解于无菌双蒸馏水中。使用半自动化喷雾器设备将包括ENPP1mRNA(或ENPP1-Fc mRNA或ENPP1-白蛋白mRNA)的100μl聚合物PCL溶液喷洒在支架(6mm x 20mm)上。雾化器喷雾系统提供以受控速率旋转并横越支架长度的装置。设备的横越组件含有以3ml/分钟的速

率向支架施涂雾化的聚己内酯溶液的玻璃喷雾器系统。施涂时，聚合物涂层通过施涂60℃加热的空气“回流”大约5秒。使聚合物回流的过程提供对支架表面的更好粘附。可以重复相同的方法以通过使用50μg载体DNA制备涂覆有表达ENPP1多肽(ENPP1或ENPP1-Fc或ENPP1-白蛋白)的载体的支架。

[0735] (d)ENPP1药剂涂层组合物(D)-A将未固化双部分硅酮橡胶的1％溶液溶解在三氯乙烯中，并且然后使用如上文(C)中所述的喷雾器喷雾系统将其喷洒到支架上。将涂覆支架在室温下干燥15分钟，以使三氯乙烯蒸发。在真空烘箱中将包括硅酮的涂覆支架加热持续四小时的时间段，以使硅酮涂层交联。从烘箱中取出涂覆支架并使其冷却持续1小时的时间段。将100μg ENPP1mRNA在室温下溶解于无菌双蒸馏水中。将100μl体积的包括ENPP1的喷雾溶液以逐滴方式施涂到每个支架的硅酮涂层。交联硅酮吸收溶液，在这种情况下溶剂随后在室温下蒸发，留下包埋在硅酮内的ENPP1mRNA(或ENPP1-Fc mRNA或ENPP1-白蛋白mRNA)。可以重复相同的方法以通过使用50μg载体DNA制备涂覆有表达ENPP1多肽(ENPP1或ENPP1-Fc或ENPP1-白蛋白)的载体的支架。溶剂随后在室温下蒸发，留下包埋在硅酮内的编码ENPP1的载体。

[0736] (e)ENPP1药剂涂层组合物(E)-10mg PCL(聚己内酯)聚合物和ENPP1多肽(ENPP1或ENPP1-Fc或ENPP1-白蛋白中的任一种)在室温下溶解在无菌双蒸馏水中，以达到10mg/ml的ENPP1多肽浓度。将包括ENPP1多肽(10mg/ml)的100μl聚合物PCL溶液喷洒在支架上，如(C)中所述。

[0737] (f)ENPP1药剂涂层组合物(F)-如(d)中所讨论的制备包括硅酮的涂覆支架。从烘箱中取出涂覆支架并使其冷却持续1小时的时间段。将ENPP1多肽(ENPP1或ENPP1-Fc或ENPP1-白蛋白)在室温下溶解在无菌双蒸馏水中，以达到10mg/ml的ENPP1多肽浓度。将100μl体积的包括ENPP1的喷雾溶液(10mg/ml)以逐滴方式施涂到每个支架的硅酮涂层。交联硅酮吸收溶液，在这种情况下溶剂随后在室温下蒸发，留下包埋在硅酮内的ENPP1mRNA。

[0738] 动物模型

[0739] 从商业来源采购重量为25-35kg的三十只4至5个月的幼年猪。三十个不锈钢通风口来自一个或多个商业来源，如雅培公司、波士顿科学公司、美敦力公司、Alvimedica公司、乐普医疗技术公司、康蒂思公司、Balton公司或百多力公司。遵循上文所示的用于涂覆的方案向由此获得的三十个不锈钢支架涂覆ENPP1mRNA。从雅培公司获得三十个裸金属支架(BMS)以用作对照设置。然后使用环氧乙烷对ENPP1涂覆的支架进行灭菌，压缩，并安装在球囊血管成形术导管上。然后使用标准球囊血管成形术技术使其在动脉中的部位处展开。使用裸金属支架的对照组也进行相同操作。

[0740] 在第0天损伤所有靶部位，以建立支架内再狭窄模型。如实例中所描述的，使用定量血管性血管造影术(QVA)绘制四个外周动脉部位。如实例1所描述的造成损伤。

[0741] 支架随机分配并放置在30头猪的外周(双侧深动脉和股浅动脉)动脉(每动脉一个支架)，每头猪一个涂覆支架。然后每天维持给猪服用100mg阿司匹林。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，记录了选定外周部位的最终术后血管造影术和OCT。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。

[0742] 计算使用ENPP1涂覆支架和裸金属支架的猪的管腔面积、支架面积、新生内膜厚度、新生内膜面积和狭窄％。预期与用裸金属支架治疗的媒剂对照组相比，使用ENPP1-Fc涂覆支架治疗的动物深动脉的管腔面积将更大。预期两组支架面积相似。与使用裸金属支架的媒剂对照动物相比，使用ENPP1-Fc涂覆支架治疗的动物的新生内膜厚度和新生内膜面积预期会减少。另外，与媒剂对照组相比，使用ENPP1-Fc治疗的动物的狭窄面积％预期显著降低。

[0743] 因此，通过使用ENPP1涂覆的支架来原位施用ENPP1药剂预期预防并有效治疗外周动脉中损伤部位处的肌内膜增殖和/或再狭窄。

[0744] 实例5-制备和植入用于治疗动脉粥样硬化外周血管的ENPP3涂覆支架

[0745] 在此实例中，使用幼年猪动物模型以植入ENPP3涂覆的支架以确定ENPP3涂覆的支架抑制新内膜形成、再狭窄和炎症的功效。制备ENPP3药剂涂覆的支架，并且然后将所述支架植入在外周动脉中。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，如实例1中所描述的。

[0746] 制备ENPP3涂覆的支架

[0747] 任何支架都适于涂覆有ENPP3药剂。销售支架以供使用的商业来源的常见实例包含雅培公司、波士顿科学公司、美敦力公司、Alvimedica公司、乐普医疗技术公司、康蒂思公司、Balton公司或百多力公司。外周动脉支架的长度较短(12mm至18mm)，直径范围为5mm至8mm，通常用于放置在髂动脉和股动脉中。Henry等人详细描述了可用于外周动脉的不同类型的支架长度和直径(Henry等人，《德克萨斯心脏研究所杂志》2000;27(2):119-126)。

[0748] 例如，裸金属支架等普通支架可以如下被转化为ENPP3涂覆的洗脱式支架：通过将包括ENPP3mRNA的聚合物膜放置在支架内部，或通过将包括ENPP3mRNA或ENPP3多肽的聚合物溶液或非聚合物溶液喷洒在支架表面上。

[0749] 下文示出了ENPP3聚合物膜的一些实例，可以将ENPP3聚合物膜放置在支架内部以产生ENPP3涂覆的洗脱式支架。任选地，可以将非聚合物载体，如维生素E、维生素E乙酸酯、维生素E琥珀酸酯、油酸、花生油和棉籽油添加到溶液中，改善ENPP1药剂在聚合物膜中的稳定性。

[0750] (g)ENPP3药剂涂层组合物(A)-10mg PCL(聚己内酯)聚合物和100μg ENPP1mRNA(或ENPP3-Fc mRNA或ENPP3-白蛋白mRNA)在室温下溶解于无菌双蒸馏水中。将溶液倒入到玻璃板上，并且使溶剂蒸发12-24小时。几乎完全去除溶剂后，从玻璃板上取出ENPP3装载的PCL膜，并且将所述膜切割成1.5cm乘1.5cm大小，然后将其进一步修整以适合支架的尺寸。然后将包括ENPP3mRNA(或ENPP3-Fc mRNA或ENPP3-白蛋白mRNA)的聚合物膜安装在不锈钢支架上。可以重复相同的方法以通过使用50μg载体DNA制备涂覆有表达ENPP1多肽(ENPP3或ENPP3-Fc或ENPP3-白蛋白)的载体的支架。

[0751] (h)ENPP3药剂涂层组合物(B)-10mg EVA(乙烯-乙酸乙烯酯)聚合物和100μg ENPP3mRNA(或ENPP3-Fc mRNA或ENPP3-白蛋白mRNA)在室温下溶解于无菌双蒸馏水中。将溶液倒入到玻璃板上，并且使溶剂蒸发12-24小时。几乎完全去除溶剂后，从玻璃板上取出ENPP3-mRNA(或ENPP3-Fc mRNA或ENPP3-白蛋白mRNA)装载的EVA膜，并且将所述膜切割成

1.5cm乘1.5cm大小。然后将包括ENPP3mRNA(或ENPP3-Fc mRNA或ENPP3-白蛋白mRNA)的聚合物膜安装在不锈钢支架上。可以重复相同的方法以通过使用50μg载体DNA制备涂覆有表达ENPP3多肽(ENPP3或ENPP3-Fc或ENPP3-白蛋白)的载体的支架。

[0752] 下文示出了包括ENPP3的喷雾溶液的一些实例,可以将喷雾溶液施涂到支架上以产生ENPP3涂覆的洗脱式支架。任选地,可以将非聚合物载体,如维生素E、维生素E乙酸酯、维生素E琥珀酸酯、油酸、花生油和棉籽油添加到喷雾溶液中,改善ENPP3药剂的稳定性。

[0753] (i)ENPP3药剂涂层组合物(C)-10mg PCL(聚己内酯)聚合物和100μg ENPP3mRNA在室温下溶解于无菌双蒸馏水中。使用半自动化喷雾器设备将包括ENPP3mRNA(或ENPP3-Fc mRNA或ENPP3-白蛋白mRNA)的100μl聚合物PCL溶液喷洒在支架(6mm x 20mm)上。雾化器喷雾系统提供以受控速率旋转并横越支架长度的装置。设备的横越组件含有以3ml/分钟的速率向支架施涂雾化的聚己内酯溶液的玻璃喷雾器系统。施涂时,聚合物涂层通过施涂60℃加热的空气"回流"大约5秒。使聚合物回流的过程提供对支架表面的更好粘附。可以重复相同的方法以通过使用50μg载体DNA制备涂覆有表达ENPP3多肽(ENPP3或ENPP3-Fc或ENPP3-白蛋白)的载体的支架。

[0754] (j)ENPP3药剂涂层组合物(D)-A将未固化双部分硅酮橡胶的1%溶液溶解在三氯乙烯中,并且然后使用如上文(C)中所述的喷雾器喷雾系统将其喷洒到支架上。将涂覆支架在室温下干燥15分钟,以使三氯乙烯蒸发。在真空烘箱中将包括硅酮的涂覆支架加热持续四小时的时间段,以使硅酮涂层交联。从烘箱中取出涂覆支架并使其冷却持续1小时的时间段。将100μg ENPP3mRNA在室温下溶解于无菌双蒸馏水中。将100μl体积的包括ENPP3的喷雾溶液以逐滴方式施涂到每个支架的硅酮涂层。交联硅酮吸收溶液,在这种情况下溶剂随后在室温下蒸发,留下包埋在硅酮内的ENPP3mRNA(或ENPP3-Fc mRNA或ENPP3-白蛋白mRNA)。可以重复相同的方法以通过使用50μg载体DNA制备涂覆有表达ENPP3多肽(ENPP3或ENPP3-Fc或ENPP3-白蛋白)的载体的支架。溶剂随后在室温下蒸发,留下包埋在硅酮内的编码ENPP3的载体。

[0755] (k)ENPP3药剂涂层组合物(E)-10mg PCL(聚己内酯)聚合物和ENPP3多肽(ENPP3或ENPP3-Fc或ENPP3-白蛋白中的任一种)在室温下溶解在无菌双蒸馏水中,以达到10mg/ml的ENPP3多肽浓度。将包括ENPP3多肽(10mg/ml)的100μl聚合物PCL溶液喷洒在支架上,如(C)中所述。

[0756] (l)ENPP3药剂涂层组合物(F)-如(d)中所讨论的制备包括硅酮的涂覆支架。从烘箱中取出涂覆支架并使其冷却持续1小时的时间段。将ENPP3多肽(ENPP3或ENPP3-Fc或ENPP3-白蛋白)在室温下溶解在无菌双蒸馏水中,以达到10mg/ml的ENPP3多肽浓度。将100μl体积的包括ENPP3的喷雾溶液(10mg/ml)以逐滴方式施涂到每个支架的硅酮涂层。交联硅酮吸收溶液,在这种情况下溶剂随后在室温下蒸发,留下包埋在硅酮内的ENPP3mRNA。

[0757] 动物模型

[0758] 从商业来源采购重量为25-35kg的三十只4至5个月的幼年猪。三十个不锈钢通风口来自一个或多个商业来源,如雅培公司、波士顿科学公司、美敦力公司、Alvimedica公司、乐普医疗技术公司、康蒂思公司、Balton公司或百多力公司。遵循上文所示的用于涂覆的方案向由此获得的三十个不锈钢支架涂覆ENPP1mRNA。从雅培公司获得三十个裸金属支架(BMS)以用作对照设置。然后使用环氧乙烷对ENPP3涂覆的支架进行灭菌,压缩,并安装在球

囊血管成形术导管上。然后使用标准球囊血管成形术技术使其在动脉中的部位处展开。使用裸金属支架的对照组也进行相同操作。

[0759] 在第0天损伤所有靶部位，以建立支架内再狭窄模型。如实例中所描述的，使用定量血管性血管造影术(QVA)绘制四个外周动脉部位。如实例1所描述的造成损伤。

[0760] 支架随机分配并放置在30头猪的外周(双侧深动脉和股浅动脉)动脉(每动脉一个支架)，每头猪一个涂覆支架。然后每天维持给猪服用100mg阿司匹林。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，记录了选定外周部位的最终术后血管造影术和OCT。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。

[0761] 计算使用ENPP3涂覆支架和裸金属支架的猪的管腔面积、支架面积、新生内膜厚度、新生内膜面积和狭窄％。预期与用裸金属支架治疗的媒剂对照组相比，使用ENPP3-Fc涂覆支架治疗的动物深动脉的管腔面积将更大。预期两组支架面积相似。与使用裸金属支架的媒剂对照动物相比，使用ENPP3-Fc涂覆支架治疗的动物的新生内膜厚度和新生内膜面积预期会减少。另外，与媒剂对照组相比，使用ENPP3-Fc治疗的动物的狭窄面积％预期显著降低。

[0762] 因此，通过使用ENPP3涂覆的支架来原位施用ENPP3药剂预期预防并有效治疗外周动脉中损伤部位处的肌内膜增殖和/或再狭窄。

[0763] 通过引用并入

[0764] 本文提及的每个美国和外国专利以及待决专利申请和公开的公开内容通过引用以其整体具体并入本文，序列表和附图的内容也是如此。

[0765] 等效形式

[0766] 本领域的技术人员仅使用常规实验将认识到或者能够确定本文描述的具体实施例的许多等效形式。这些等效形式旨在被以下附权利要求书涵盖。设想了任何多个从属权利要求或实例中公开的实施例的任何组合在本公开的范围内。

[0767] 其它实施例

[0768] 根据前述描述，将显而易见的是可以对本文描述的公开进行各种变化和修改以使其适于各种使用和条件，包含使用不同的信号序列来表达ENPP1或ENPP3的功能变体或其在具有不同启动子或不同细胞类型的增强子的本领域已知用于治疗特征在于存在病理性钙化或骨化的任何疾病的不同病毒载体中的组合在根据本公开的范围内。根据本公开的其它实施例处于下述权利要求内。

[0769] 在本文中的变量的任何定义中对要素的列表的详述包含作为任何单个要素或所列要素的组合(或子组合)的变量的定义。针对本文的实施例的详述包含作为任何单个实施例或与任何其它实施例或其部分的组合的实施例。

[0770] 本说明书中所提及的所有公开和专利申请都指示本公开所属领域的技术人员的水平。所有公开和专利申请在此都通过引用并入本文中，其引用程度就如同特定并且单独地指示每一篇单独公开或专利申请要通过引用并入一样。

[0771] 其它实施例在以下权利要求内。

序列表

<110> Inozyme制药公司(Inozyme Pharma, Inc.)

Westfaelische Wilhelms-Universitaet Muenster

Thompson, David

Rutsch, Frank

Nitschke, Yvonne

<120> 用于治疗外周动脉疾病的组合物和方法

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<160> 72

<170> PatentIn 3.5版

<210> 1

<211> 925

<212> PRT

<213> 人工序列

<220>

<223> ENPP1氨基酸序列-野生型

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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 Val Leu Ser Leu
65 70 75 80
Val Leu Ser Val Cys Val Leu Thr Thr Ile Leu Gly Cys Ile Phe Gly
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Leu Lys Pro Ser Cys Ala Lys Glu Val Lys Ser Cys Lys Gly Arg Cys
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Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Leu Ala
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Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His Phe Tyr
355 360 365
Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr Gly Pro
370 375 380
Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly Met Val
385 390 395 400
Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg Cys Leu
405 410 415
Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser Cys Lys
420 425 430
Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn Ile Lys
435 440 445

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

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

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

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Ser His Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala

195 200 205

Ser Phe Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys

210 215 220

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

225 230 235 240

Thr Phe Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro

245 250 255

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

260 265 270

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

275 280 285

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

290 295 300

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

305 310 315 320

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

325 330 335

Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser
340 345 350
Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn
355 360 365
Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val
370 375 380
Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu
385 390 395 400
Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe
405 410 415
Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu
420 425 430
Thr Phe Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu
435 440 445
Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser
450 455 460
Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys His Gly
465 470 475 480
Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys
485 490 495
Asp Leu Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser
500 505 510
Leu Asn His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His Pro Lys
515 520 525
Glu Val His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp
530 535 540
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545 550 555 560
Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His
565 570 575
Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr
580 585 590
Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp
595 600 605
Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser
610 615 620
Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile
625 630 635 640
Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys

645 650 655
Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser
660 665 670
Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr
675 680 685
Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg
690 695 700
Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val
705 710 715 720
Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg
725 730 735
Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His
740 745 750
Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu
755 760 765
His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr
770 775 780
Asp Asn Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val
785 790 795 800
Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His
805 810 815
Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp
820 825 830
Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp Leu
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Ile Asn Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
850 855 860
Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
865 870 875 880
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
885 890 895
Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
900 905 910
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
915 920 925
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
930 935 940
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
945 950 955 960

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
965 970 975
Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
980 985 990
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
995 1000 1005
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
1010 1015 1020
Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
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Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
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Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg Cys Asp Ala Ala Cys
35 40 45
Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln Glu Thr Cys Ile Glu
50 55 60

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

370 375 380
Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu
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Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe
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Leu Pro Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu
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Arg Lys Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser
450 455 460
Asn Met Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys His Gly
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Ile Glu Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys
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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
530 535 540
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Gln Thr Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His
565 570 575
Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr
580 585 590
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595 600 605
Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser
610 615 620
Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile
625 630 635 640
Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys
645 650 655
Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser
660 665 670
Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr
675 680 685

Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg
690 695 700
Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val
705 710 715 720
Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg
725 730 735
Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His
740 745 750
Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu
755 760 765
His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr
770 775 780
Asp Asn Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val
785 790 795 800
Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His
805 810 815
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820 825 830
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835 840 845
Ile Asn Met Lys Trp Val Thr Phe Leu Leu Leu Leu Phe Val Ser Gly
850 855 860
Ser Ala Phe Ser Arg Gly Val Phe Arg Arg Glu Ala His Lys Ser Glu
865 870 875 880
Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu
885 890 895
Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu
900 905 910
His Ala Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val
915 920 925
Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe
930 935 940
Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu
945 950 955 960
Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe
965 970 975
Leu Gln His Lys Asp Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro
980 985 990
Glu Ala Glu Ala Met Cys Thr Ser Phe Lys Glu Asn Pro Thr Thr Phe

995 1000 1005

Met Gly His Tyr Leu His Glu Val Ala Arg Arg His Pro Tyr Phe
1010 1015 1020

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

Pro Lys Leu Asp Gly Val Lys Glu Lys Ala Leu Val Ser Ser Val
1055 1060 1065

Arg Gln Arg Met Lys Cys Ser Ser Met Gln Lys Phe Gly Glu Arg
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Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Thr Phe Pro
1085 1090 1095

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

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

Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met Cys Glu Asn Gln Ala
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Thr Ile Ser Ser Lys Leu Gln Thr Cys Cys Asp Lys Pro Leu Leu
1145 1150 1155

Lys Lys Ala His Cys Leu Ser Glu Val Glu His Asp Thr Met Pro
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Ala Asp Leu Pro Ala Ile Ala Ala Asp Phe Val Glu Asp Gln Glu
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Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Thr
1190 1195 1200

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

Leu Leu Leu Arg Leu Ala Lys Lys Tyr Glu Ala Thr Leu Glu Lys
1220 1225 1230

Cys Cys Ala Glu Ala Asn Pro Pro Ala Cys Tyr Gly Thr Val Leu
1235 1240 1245

Ala Glu Phe Gln Pro Leu Val Glu Glu Pro Lys Asn Leu Val Lys
1250 1255 1260

Thr Asn Cys Asp Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln
1265 1270 1275

Asn Ala Ile Leu Val Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser
1280 1285 1290

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

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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
305 310 315 320
Met Val Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg
325 330 335
Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser

340 345 350

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

355 360 365

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

370 375 380

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

385 390 395 400

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

405 410 415

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

420 425 430

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

435 440 445

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

450 455 460

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

465 470 475 480

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

485 490 495

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

500 505 510

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

515 520 525

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

530 535 540

Asn Leu Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe

545 550 555 560

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

565 570 575

Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr

580 585 590

Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp

595 600 605

Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser

610 615 620

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

625 630 635 640

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

645 650 655

Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser
660 665 670
Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr
675 680 685
Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg
690 695 700
Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val
705 710 715 720
Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg
725 730 735
Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His
740 745 750
Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Ala Pro
755 760 765
Ser Cys Ala Lys Glu Val Lys Ser Cys Lys Gly Arg Cys Phe Glu Arg
770 775 780
Thr Phe Gly Asn Cys Arg Cys Asp Ala Ala Cys Val Glu Leu Gly Asn
785 790 795 800
Cys Cys Leu Asp Tyr Gln Glu Thr Cys Ile Glu Pro Glu His Ile Trp
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Thr Cys Asn Lys Phe Arg Cys Gly Glu Lys Arg Leu Thr Arg Ser Leu
820 825 830
Cys Ala Cys Ser Asp Asp Cys Lys Asp Lys Gly Asp Cys Cys Ile Asn
835 840 845
Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp Val Glu Glu Pro Cys
850 855 860
Glu Ser Ile Asn Glu Pro Gln Cys Pro Ala Gly Phe Glu Thr Pro Pro
865 870 875 880
Thr Leu Leu Phe Ser Leu Asp Gly Phe Arg Ala Glu Tyr Leu His Thr
885 890 895
Trp Gly Gly Leu Leu Pro Val Ile Ser Lys Leu Lys Lys Cys Gly Thr
900 905 910
Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr Lys Thr Phe Pro Asn
915 920 925
His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly Ile Ile
930 935 940
Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala Ser Phe Ser Leu Lys
945 950 955 960
Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys Gly Glu Pro Ile Trp

965 970 975
Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly Thr Phe Phe Trp Pro
980 985 990
Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro Asp Ile Tyr Lys Met
995 1000 1005
Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Leu Ala Val Leu
1010 1015 1020
Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His Phe Tyr Thr
1025 1030 1035
Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr Gly Pro
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Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly Met
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Cys Leu Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly
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Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val
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Lys Asn Ile Lys Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro
1115 1120 1125
Ser Asp Val Pro Asp Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile
1130 1135 1140
Ala Arg Asn Leu Ser Cys Arg Glu Pro Asn Gln His Phe Lys Pro
1145 1150 1155
Tyr Leu Lys His Phe Leu Pro Lys Arg Leu His Phe Ala Lys Ser
1160 1165 1170
Asp Arg Ile Glu Pro Leu Thr Phe Tyr Leu Asp Pro Gln Trp Gln
1175 1180 1185
Leu Ala Leu Asn Pro Ser Glu Arg Lys Tyr Cys Gly Ser Gly Phe
1190 1195 1200
His Gly Ser Asp Asn Val Phe Ser Asn Met Gln Ala Leu Phe Val
1205 1210 1215
Gly Tyr Gly Pro Gly Phe Lys His Gly Ile Glu Ala Asp Thr Phe
1220 1225 1230
Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Asn Leu
1235 1240 1245
Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His Leu
1250 1255 1260

Leu Lys Asn Pro Val Tyr Thr Pro Lys His Pro Lys Glu Val His
1265 1270 1275
Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp Asn Leu
1280 1285 1290
Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe Gln
1295 1300 1305
Thr Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His
1310 1315 1320
Glu Thr Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn
1325 1330 1335
Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser
1340 1345 1350
Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg
1355 1360 1365
Asn Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln
1370 1375 1380
Asp Phe Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr
1385 1390 1395
Lys Asn Asn Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln
1400 1405 1410
Leu Asn Lys Asn Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr
1415 1420 1425
Thr Asn Ile Val Pro Met Tyr Gln Ser Phe Gln Val Ile Trp Arg
1430 1435 1440
Tyr Phe His Asp Thr Leu Leu Arg Lys Tyr Ala Glu Glu Arg Asn
1445 1450 1455
Gly Val Asn Val Val Ser Gly Pro Val Phe Asp Phe Asp Tyr Asp
1460 1465 1470
Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln Lys Arg Arg Val
1475 1480 1485
Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe Phe Ile Val
1490 1495 1500
Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His Cys Glu
1505 1510 1515
Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp Asn
1520 1525 1530
Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu
1535 1540 1545
Glu Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His

1550 1555 1560
Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser
1565 1570 1575
Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu
1580 1585 1590
Asp

<210> 5
<211> 888
<212> PRT
<213> 人工序列
<220>
<223> ENPP2氨基酸序列-野生型
<400> 5

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

Lys Thr Phe Pro Asn Leu Tyr Thr Leu Ala Thr Gly Leu Tyr Pro Glu
210 215 220
Ser His Gly Ile Val Gly Asn Ser Met Tyr Asp Pro Val Phe Asp Ala
225 230 235 240
Thr Phe His Leu Arg Gly Arg Glu Lys Phe Asn His Arg Trp Trp Gly
245 250 255
Gly Gln Pro Leu Trp Ile Thr Ala Thr Lys Gln Gly Val Lys Ala Gly
260 265 270
Thr Phe Phe Trp Ser Val Val Ile Pro His Glu Arg Arg Ile Leu Thr
275 280 285
Ile Leu Gln Trp Leu Thr Leu Pro Asp His Glu Arg Pro Ser Val Tyr
290 295 300
Ala Phe Tyr Ser Glu Gln Pro Asp Phe Ser Gly His Lys Tyr Gly Pro
305 310 315 320
Phe Gly Pro Glu Met Thr Asn Pro Leu Arg Glu Ile Asp Lys Ile Val
325 330 335
Gly Gln Leu Met Asp Gly Leu Lys Gln Leu Lys Leu His Arg Cys Val
340 345 350
Asn Val Ile Phe Val Gly Asp His Gly Met Glu Asp Val Thr Cys Asp
355 360 365
Arg Thr Glu Phe Leu Ser Asn Tyr Leu Thr Asn Val Asp Asp Ile Thr
370 375 380
Leu Val Pro Gly Thr Leu Gly Arg Ile Arg Ser Lys Phe Ser Asn Asn
385 390 395 400
Ala Lys Tyr Asp Pro Lys Ala Ile Ile Ala Asn Leu Thr Cys Lys Lys
405 410 415
Pro Asp Gln His Phe Lys Pro Tyr Leu Lys Gln His Leu Pro Lys Arg
420 425 430
Leu His Tyr Ala Asn Asn Arg Arg Ile Glu Asp Ile His Leu Leu Val
435 440 445
Glu Arg Arg Trp His Val Ala Arg Lys Pro Leu Asp Val Tyr Lys Lys
450 455 460
Pro Ser Gly Lys Cys Phe Phe Gln Gly Asp His Gly Phe Asp Asn Lys
465 470 475 480
Val Asn Ser Met Gln Thr Val Phe Val Gly Tyr Gly Ser Thr Phe Lys
485 490 495
Tyr Lys Thr Lys Val Pro Pro Phe Glu Asn Ile Glu Leu Tyr Asn Val
500 505 510
Met Cys Asp Leu Leu Gly Leu Lys Pro Ala Pro Asn Asn Gly Thr His

515 520 525

Gly Ser Leu Asn His Leu Leu Arg Thr Asn Thr Phe Arg Pro Thr Met

530 535 540

Pro Glu Glu Val Thr Arg Pro Asn Tyr Pro Gly Ile Met Tyr Leu Gln

545 550 555 560

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

565 570 575

Asn Lys Leu Asp Glu Leu Asn Lys Arg Leu His Thr Lys Gly Ser Thr

580 585 590

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

595 600 605

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

610 615 620

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

625 630 635 640

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

645 650 655

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

660 665 670

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

675 680 685

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

690 695 700

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

705 710 715 720

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

725 730 735

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

740 745 750

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

755 760 765

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

770 775 780

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

785 790 795 800

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

805 810 815

Ser Ser Phe Ile Leu Pro His Arg Pro Asp Asn Glu Glu Ser Cys Asn

820 825 830

Ser Ser Glu Asp Glu Ser Lys Trp Val Glu Glu Leu Met Lys Met His
835 840 845
Thr Ala Arg Val Arg Asp Ile Glu His Leu Thr Ser Leu Asp Phe Phe
850 855 860
Arg Lys Thr Ser Arg Ser Tyr Pro Glu Ile Leu Thr Leu Lys Thr Tyr
865 870 875 880
Leu His Thr Tyr Glu Ser Glu Ile
885

<210> 6
<211> 827
<212> PRT
<213> 人工序列
<220>
<223> ENPP3的胞外结构域
<400> 6
Glu Lys Gln Gly Ser Cys Arg Lys Lys Cys Phe Asp Ala Ser Phe Arg
1 5 10 15
Gly Leu Glu Asn Cys Arg Cys Asp Val Ala Cys Lys Asp Arg Gly Asp
20 25 30
Cys Cys Trp Asp Phe Glu Asp Thr Cys Val Glu Ser Thr Arg Ile Trp
35 40 45
Met Cys Asn Lys Phe Arg Cys Gly Glu Thr Arg Leu Glu Ala Ser Leu
50 55 60
Cys Ser Cys Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys Cys Ala Asp
65 70 75 80
Tyr Lys Ser Val Cys Gln Gly Glu Thr Ser Trp Leu Glu Glu Asn Cys
85 90 95
Asp Thr Ala Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp Leu Pro Pro
100 105 110
Val Ile Leu Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr Leu Tyr Thr
115 120 125
Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys Thr Cys Gly Ile
130 135 140
His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr Phe Pro Asn
145 150 155 160
His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly Ile Ile
165 170 175
Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser Leu Ser
180 185 190

Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro Met Trp
195 200 205
Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe Trp Pro
210 215 220
Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr Met Pro
225 230 235 240
Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu Leu Lys
245 250 255
Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr Met Tyr
260 265 270
Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val Ser Ala
275 280 285
Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala Phe Gly Met Leu
290 295 300
Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn Ile Ile
305 310 315 320
Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys Met Glu
325 330 335
Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr Met Tyr Glu
340 345 350
Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro His Asp Phe Phe
355 360 365
Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg Lys Pro
370 375 380
Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys Arg Leu
385 390 395 400
His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His Leu Phe Val Asp
405 410 415
Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys Gly Gly
420 425 430
Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala Ile Phe
435 440 445
Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu Pro Phe
450 455 460
Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg Ile Gln
465 470 475 480
Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His Leu Leu Lys
485 490 495
Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys Phe Ser

500 505 510

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

515 520 525

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

530 535 540

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

545 550 555 560

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

565 570 575

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

580 585 590

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

595 600 605

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

610 615 620

Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys Asn Ile

625 630 635 640

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

645 650 655

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

660 665 670

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

675 680 685

Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile Phe Asp

690 695 700

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

705 710 715 720

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

725 730 735

Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro Gly Trp

740 745 750

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

755 760 765

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

770 775 780

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

785 790 795 800

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

805 810 815

Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile
820 825

<210> 7

<211> 875

<212> PRT

<213> 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)..(1074)
<223> 表示Fc序列
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<222> (848)..(1074)
<223> 表示Fc序列
<400> 8

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

Leu Tyr Thr Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys Thr
145 150 155 160
Cys Gly Ile His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr
165 170 175
Phe Pro Asn His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser His
180 185 190
Gly Ile Ile Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn Phe
195 200 205
Ser Leu Ser Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly Gln
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> (848)..(1465)

<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
<220>
<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> 信号序列的切割点
<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
<220>
<223> ENPP51-ALB氨基酸序列
<220>
<221> SIGNAL
<222> (24)..(25)
<223> 信号序列的切割点
<220>
<221> SIGNAL
<222> (24)..(25)
<223> 信号肽序列的切割点
<220>
<221> MISC_FEATURE
<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
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Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Tyr Tyr Ala
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Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys Ala Glu Ala Asp
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Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val Lys Glu Lys
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1160 1165 1170
Glu His Asp Thr Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp
1175 1180 1185
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Pro Asp Tyr Ser Val Ser Leu Leu Leu Arg Leu Ala Lys Lys Tyr
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Glu Ala Thr Leu Glu Lys Cys Cys Ala Glu Ala Asn Pro Pro Ala
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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
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Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile Leu Asn
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Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His Val
1340 1345 1350
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1355 1360 1365

Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys
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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
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Lys His Lys Pro Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met
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Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp
1430 1435 1440
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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
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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
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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
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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
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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
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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
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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
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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
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Leu His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
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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

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

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

1115 1120 1125

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

1130 1135 1140

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

1145 1150 1155

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

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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

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

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

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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

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

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

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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
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Lys Ser Cys Lys Gly Arg Cys Phe Glu Arg Thr Phe Gly Asn Cys Arg
        35                  40                  45
Cys Asp Ala Ala Cys Val Glu Leu Gly Asn Cys Cys Leu Asp Tyr Gln
    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
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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
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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
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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
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785 790 795 800
Asp Ser Ser Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile
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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
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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
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Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
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Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
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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
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Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
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Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
900 905 910
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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
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Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
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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
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
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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
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
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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
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Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
1070 1075

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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

Asn Thr Ile Cys Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser
595 600 605

Gln Asp Ile Leu Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn
610 615 620

Asp Ser Phe Ser Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe
625 630 635 640

Arg Ile Pro Leu Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn
645 650 655

Thr Lys Val Ser Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn
660 665 670
Ser Ser Gly Ile Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro
675 680 685
Met Tyr Gln Ser Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu
690 695 700
Leu Arg Lys Tyr Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly
705 710 715 720
Pro Val Phe Asp Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn
725 730 735
Leu Arg Gln Lys Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro
740 745 750
Thr His Phe Phe Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr
755 760 765
Pro Leu His Cys Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His
770 775 780
Arg Thr Asp Asn Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser
785 790 795 800
Trp Val Glu Glu Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val
805 810 815
Glu His Ile Thr Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val
820 825 830
Ser Asp Ile Leu Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu
835 840 845
Asp Arg Ser Gly Ser Gly Gly Ser Met Lys Trp Val Thr Phe Leu Leu
850 855 860
Leu Leu Phe Val Ser Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg
865 870 875 880
Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu
885 890 895
Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln
900 905 910
Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu Val Thr Asp
915 920 925
Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys
930 935 940
Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu
945 950 955 960
Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro

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

Pro Lys Asn Leu Val Lys Thr Asn Cys Asp Leu Tyr Glu Lys Leu
1265 1270 1275
Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val Arg Tyr Thr Gln
1280 1285 1290
Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu Ala Ala Arg
1295 1300 1305
Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu Pro Glu Asp
1310 1315 1320
Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile Leu Asn
1325 1330 1335
Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His Val
1340 1345 1350
Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe
1355 1360 1365
Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys
1370 1375 1380
Ala Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu
1385 1390 1395
Lys Glu Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val
1400 1405 1410
Lys His Lys Pro Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met
1415 1420 1425
Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp
1430 1435 1440
Lys Asp Thr Cys Phe Ser Thr Glu Gly Pro Asn Leu Val Thr Arg
1445 1450 1455
Cys Lys Asp Ala Leu Ala Arg Ser Trp Ser His Pro Gln Phe Glu
1460 1465 1470
Lys

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<211> 1072
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<223> ENPP7-NPP3-Fc序列
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Ala Pro Gly Ala Lys Gln Gly Ser Cys Arg Lys Lys Cys Phe Asp Ala
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Ser Phe Arg Gly Leu Glu Asn Cys Arg Cys Asp Val Ala Cys Lys Asp
35 40 45
Arg Gly Asp Cys Cys Trp Asp Phe Glu Asp Thr Cys Val Glu Ser Thr
50 55 60
Arg Ile Trp Met Cys Asn Lys Phe Arg Cys Gly Glu Arg Leu Glu Ala
65 70 75 80
Ser Leu Cys Ser Cys Ser Asp Asp Cys Leu Gln Arg Lys Asp Cys Cys
85 90 95
Ala Asp Tyr Lys Ser Val Cys Gln Gly Glu Thr Ser Trp Leu Glu Glu
100 105 110
Asn Cys Asp Thr Ala Gln Gln Ser Gln Cys Pro Glu Gly Phe Asp Leu
115 120 125
Pro Pro Val Ile Leu Phe Ser Met Asp Gly Phe Arg Ala Glu Tyr Leu
130 135 140
Tyr Thr Trp Asp Thr Leu Met Pro Asn Ile Asn Lys Leu Lys Thr Cys
145 150 155 160
Gly Ile His Ser Lys Tyr Met Arg Ala Met Tyr Pro Thr Lys Thr Phe
165 170 175
Pro Asn His Tyr Thr Ile Val Thr Gly Leu Tyr Pro Glu Ser His Gly
180 185 190
Ile Ile Asp Asn Asn Met Tyr Asp Val Asn Leu Asn Lys Asn Phe Ser
195 200 205
Leu Ser Ser Lys Glu Gln Asn Asn Pro Ala Trp Trp His Gly Gln Pro
210 215 220
Met Trp Leu Thr Ala Met Tyr Gln Gly Leu Lys Ala Ala Thr Tyr Phe
225 230 235 240
Trp Pro Gly Ser Glu Val Ala Ile Asn Gly Ser Phe Pro Ser Ile Tyr
245 250 255
Met Pro Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Ser Thr Leu
260 265 270

Leu Lys Trp Leu Asp Leu Pro Lys Ala Glu Arg Pro Arg Phe Tyr Thr
275 280 285
Met Tyr Phe Glu Glu Pro Asp Ser Ser Gly His Ala Gly Gly Pro Val
290 295 300
Ser Ala Arg Val Ile Lys Ala Leu Gln Val Val Asp His Ala Phe Gly
305 310 315 320
Met Leu Met Glu Gly Leu Lys Gln Arg Asn Leu His Asn Cys Val Asn
325 330 335
Ile Ile Leu Leu Ala Asp His Gly Met Asp Gln Thr Tyr Cys Asn Lys
340 345 350
Met Glu Tyr Met Thr Asp Tyr Phe Pro Arg Ile Asn Phe Phe Tyr Met
355 360 365
Tyr Glu Gly Pro Ala Pro Arg Ile Arg Ala His Asn Ile Pro His Asp
370 375 380
Phe Phe Ser Phe Asn Ser Glu Glu Ile Val Arg Asn Leu Ser Cys Arg
385 390 395 400
Lys Pro Asp Gln His Phe Lys Pro Tyr Leu Thr Pro Asp Leu Pro Lys
405 410 415
Arg Leu His Tyr Ala Lys Asn Val Arg Ile Asp Lys Val His Leu Phe
420 425 430
Val Asp Gln Gln Trp Leu Ala Val Arg Ser Lys Ser Asn Thr Asn Cys
435 440 445
Gly Gly Gly Asn His Gly Tyr Asn Asn Glu Phe Arg Ser Met Glu Ala
450 455 460
Ile Phe Leu Ala His Gly Pro Ser Phe Lys Glu Lys Thr Glu Val Glu
465 470 475 480
Pro Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu Leu Arg
485 490 495
Ile Gln Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn His Leu
500 505 510
Leu Lys Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys
515 520 525
Phe Ser Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu Asp
530 535 540
Cys Phe Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn
545 550 555 560
Gln Met Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val
565 570 575
Asn Leu Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val Asp His

580 585 590

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

595 600 605

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

610 615 620

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

625 630 635 640

Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys

645 650 655

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

660 665 670

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

675 680 685

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

690 695 700

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

705 710 715 720

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

725 730 735

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

740 745 750

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

755 760 765

Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn

770 775 780

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

785 790 795 800

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

805 810 815

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

820 825 830

Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile Asp Lys Thr

835 840 845

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser

850 855 860

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

865 870 875 880

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

885 890 895

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

930 935 940

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

Arg Glu Asn Tyr Gly Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro
965 970 975

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

Pro Pro Phe Glu Arg Pro Glu Ala Glu Ala Met Cys Thr Ser Phe Lys
995 1000 1005

Glu Asn Pro Thr Thr Phe Met Gly His Tyr Leu His Glu Val Ala
1010 1015 1020

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

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

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

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

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

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

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

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr
1130 1135 1140

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

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

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

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

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

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

Glu Ala Thr Leu Glu Lys Cys Cys Ala Glu Ala Asn Pro Pro Ala
1235 1240 1245
Cys Tyr Gly Thr Val Leu Ala Glu Phe Gln Pro Leu Val Glu Glu
1250 1255 1260
Pro Lys Asn Leu Val Lys Thr Asn Cys Asp Leu Tyr Glu Lys Leu
1265 1270 1275
Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val Arg Tyr Thr Gln
1280 1285 1290
Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu Ala Ala Arg
1295 1300 1305
Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu Pro Glu Asp
1310 1315 1320
Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile Leu Asn
1325 1330 1335
Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His Val
1340 1345 1350
Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe
1355 1360 1365
Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys
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Ala Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu
1385 1390 1395

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

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

Val Pro Pro Ser Glu Ser Gln Lys Cys Ser Phe Tyr Leu Ala Asp Lys
645 650 655
Asn Ile Thr His Gly Phe Leu Tyr Pro Pro Ala Ser Asn Arg Thr Ser
660 665 670
Asp Ser Gln Tyr Asp Ala Leu Ile Thr Ser Asn Leu Val Pro Met Tyr
675 680 685
Glu Glu Phe Arg Lys Met Trp Asp Tyr Phe His Ser Val Leu Leu Ile
690 695 700
Lys His Ala Thr Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Ile
705 710 715 720
Phe Asp Tyr Asn Tyr Asp Gly His Phe Asp Ala Pro Asp Glu Ile Thr
725 730 735
Lys His Leu Ala Asn Thr Asp Val Pro Ile Pro Thr His Tyr Phe Val
740 745 750
Val Leu Thr Ser Cys Lys Asn Lys Ser His Thr Pro Glu Asn Cys Pro
755 760 765
Gly Trp Leu Asp Val Leu Pro Phe Ile Ile Pro His Arg Pro Thr Asn
770 775 780
Val Glu Ser Cys Pro Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu
785 790 795 800
Arg Phe Thr Ala His Ile Ala Arg Val Arg Asp Val Glu Leu Leu Thr
805 810 815
Gly Leu Asp Phe Tyr Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu
820 825 830
Gln Leu Lys Thr Tyr Leu Pro Thr Phe Glu Thr Thr Ile Gly Gly Gly
835 840 845
Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Met Lys Trp Val Thr
850 855 860
Phe Leu Leu Leu Leu Phe Val Ser Gly Ser Ala Phe Ser Arg Gly Val
865 870 875 880
Phe Arg Arg Glu Ala His Lys Ser Glu Ile Ala His Arg Tyr Asn Asp
885 890 895
Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu Ile Ala Phe Ser Gln
900 905 910
Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala Lys Leu Val Gln Glu
915 920 925
Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Ala Asn
930 935 940
Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile

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

Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu Phe Gln Pro Leu
1250 1255 1260
Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys Asp Leu Tyr
1265 1270 1275
Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu Val Arg
1280 1285 1290
Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu
1295 1300 1305
Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu
1310 1315 1320
Pro Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala
1325 1330 1335
Ile Leu Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser
1340 1345 1350
Glu His Val Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg
1355 1360 1365
Pro Cys Phe Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys
1370 1375 1380
Glu Phe Lys Ala Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr
1385 1390 1395
Leu Pro Glu Lys Glu Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala
1400 1405 1410
Glu Leu Val Lys His Lys Pro Lys Ala Thr Ala Glu Gln Leu Lys
1415 1420 1425
Thr Val Met Asp Asp Phe Ala Gln Phe Leu Asp Thr Cys Cys Lys
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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
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500 505 510
Leu Lys Val Pro Phe Tyr Glu Pro Ser His Ala Glu Glu Val Ser Lys
515 520 525
Phe Ser Val Cys Gly Phe Ala Asn Pro Leu Pro Thr Glu Ser Leu Asp
530 535 540
Cys Phe Cys Pro His Leu Gln Asn Ser Thr Gln Leu Glu Gln Val Asn
545 550 555 560
Gln Met Leu Asn Leu Thr Gln Glu Glu Ile Thr Ala Thr Val Lys Val
565 570 575
Asn Leu Pro Phe Gly Arg Pro Arg Val Leu Gln Lys Asn Val Asp His

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

Gly Gly Ser Met Lys Trp Val Thr Phe Leu Leu Leu Leu Phe Val Ser
900 905 910
Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg Glu Ala His Lys Ser
915 920 925
Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly
930 935 940
Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp
945 950 955 960
Glu His Ala Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys
965 970 975
Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu
980 985 990
Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly
995 1000 1005
Glu Leu Ala Asp Cys Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu
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Cys Phe Leu Gln His Lys Asp Asp Asn Pro Ser Leu Pro Pro Phe
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1040 1045 1050
Pro Thr Thr Phe Met Gly His Tyr Leu His Glu Val Ala Arg Arg
1055 1060 1065
His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Tyr Tyr Ala Glu Gln
1070 1075 1080
Tyr Asn Glu Ile Leu Thr Gln Cys Cys Ala Glu Ala Asp Lys Glu
1085 1090 1095
Ser Cys Leu Thr Pro Lys Leu Asp Gly Val Lys Glu Lys Ala Leu
1100 1105 1110
Val Ser Ser Val Arg Gln Arg Met Lys Cys Ser Ser Met Gln Lys
1115 1120 1125
Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser
1130 1135 1140
Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr Lys Leu Ala
1145 1150 1155
Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly Asp Leu
1160 1165 1170
Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met Cys
1175 1180 1185
Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys Cys Asp

1190 1195 1200

Lys Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val Glu His

1205 1210 1215

Asp Thr Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp Phe Val

1220 1225 1230

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

1235 1240 1245

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

1250 1255 1260

Tyr Ser Val Ser Leu Leu Leu Arg Leu Ala Lys Lys Tyr Glu Ala

1265 1270 1275

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

1280 1285 1290

Gly Thr Val Leu Ala Glu Phe Gln Pro Leu Val Glu Glu Pro Lys

1295 1300 1305

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

1310 1315 1320

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

1325 1330 1335

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

1340 1345 1350

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

1355 1360 1365

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

1370 1375 1380

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

1385 1390 1395

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

1400 1405 1410

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

1415 1420 1425

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

1430 1435 1440

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

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

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

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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
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Met Glu Gln Gly Ser Cys Lys Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu
355 360 365
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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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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
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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
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
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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
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Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val Ser
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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
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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Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe Phe
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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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Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala
50 55 60

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

370 375 380
Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly Met Val
385 390 395 400
Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg Cys Leu
405 410 415
Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser Cys Lys
420 425 430
Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn Ile Lys
435 440 445
Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val Pro Asp
450 455 460
Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu Ser Cys
465 470 475 480
Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe Leu Pro
485 490 495
Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu Thr Phe
500 505 510
Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu Arg Lys
515 520 525
Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser Asn Met
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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
Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr Ile Cys
660 665 670
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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
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770 775 780
Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val Phe Asp
785 790 795 800
Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln Lys
805 810 815
Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe Phe
820 825 830
Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His Cys
835 840 845
Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp Asn
850 855 860
Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu Glu
865 870 875 880
Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile Thr
885 890 895
Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile Leu
900 905 910
Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp 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
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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

His Ile Trp Thr Cys Asn Lys Phe Arg Cys Gly Glu Lys Arg Leu Thr
145 150 155 160

Arg Ser Leu Cys Ala Cys Ser Asp Asp Cys Lys Asp Lys Gly Asp Cys
165 170 175

Cys Ile Asn Tyr Ser Ser Val Cys Gln Gly Glu Lys Ser Trp Val Glu
180 185 190

Glu Pro Cys Glu Ser Ile Asn Glu Pro Gln Cys Pro Ala Gly Phe Glu
195 200 205

Thr Pro Pro Thr Leu Leu Phe Ser Leu Asp Gly Phe Arg Ala Glu Tyr
210 215 220

Leu His Thr Trp Gly Gly Leu Leu Pro Val Ile Ser Lys Leu Lys Lys
225 230 235 240

Cys Gly Thr Tyr Thr Lys Asn Met Arg Pro Val Tyr Pro Thr Lys Thr
245 250 255

Phe Pro Asn His Tyr Ser Ile Val Thr Gly Leu Tyr Pro Glu Ser His
260 265 270

Gly Ile Ile Asp Asn Lys Met Tyr Asp Pro Lys Met Asn Ala Ser Phe
275 280 285

Ser Leu Lys Ser Lys Glu Lys Phe Asn Pro Glu Trp Tyr Lys Gly Glu
290 295 300

Pro Ile Trp Val Thr Ala Lys Tyr Gln Gly Leu Lys Ser Gly Thr Phe
305 310 315 320

Phe Trp Pro Gly Ser Asp Val Glu Ile Asn Gly Ile Phe Pro Asp Ile
325 330 335

Tyr Lys Met Tyr Asn Gly Ser Val Pro Phe Glu Glu Arg Ile Leu Ala
340 345 350
Val Leu Gln Trp Leu Gln Leu Pro Lys Asp Glu Arg Pro His Phe Tyr
355 360 365
Thr Leu Tyr Leu Glu Glu Pro Asp Ser Ser Gly His Ser Tyr Gly Pro
370 375 380
Val Ser Ser Glu Val Ile Lys Ala Leu Gln Arg Val Asp Gly Met Val
385 390 395 400
Gly Met Leu Met Asp Gly Leu Lys Glu Leu Asn Leu His Arg Cys Leu
405 410 415
Asn Leu Ile Leu Ile Ser Asp His Gly Met Glu Gln Gly Ser Cys Lys
420 425 430
Lys Tyr Ile Tyr Leu Asn Lys Tyr Leu Gly Asp Val Lys Asn Ile Lys
435 440 445
Val Ile Tyr Gly Pro Ala Ala Arg Leu Arg Pro Ser Asp Val Pro Asp
450 455 460
Lys Tyr Tyr Ser Phe Asn Tyr Glu Gly Ile Ala Arg Asn Leu Ser Cys
465 470 475 480
Arg Glu Pro Asn Gln His Phe Lys Pro Tyr Leu Lys His Phe Leu Pro
485 490 495
Lys Arg Leu His Phe Ala Lys Ser Asp Arg Ile Glu Pro Leu Thr Phe
500 505 510
Tyr Leu Asp Pro Gln Trp Gln Leu Ala Leu Asn Pro Ser Glu Arg Lys
515 520 525
Tyr Cys Gly Ser Gly Phe His Gly Ser Asp Asn Val Phe Ser Asn Met
530 535 540
Gln Ala Leu Phe Val Gly Tyr Gly Pro Gly Phe Lys His Gly Ile Glu
545 550 555 560
Ala Asp Thr Phe Glu Asn Ile Glu Val Tyr Asn Leu Met Cys Asp Leu
565 570 575
Leu Asn Leu Thr Pro Ala Pro Asn Asn Gly Thr His Gly Ser Leu Asn
580 585 590
His Leu Leu Lys Asn Pro Val Tyr Thr Pro Lys His Pro Lys Glu Val
595 600 605
His Pro Leu Val Gln Cys Pro Phe Thr Arg Asn Pro Arg Asp Asn Leu
610 615 620
Gly Cys Ser Cys Asn Pro Ser Ile Leu Pro Ile Glu Asp Phe Gln Thr
625 630 635 640
Gln Phe Asn Leu Thr Val Ala Glu Glu Lys Ile Ile Lys His Glu Thr

645 650 655

Leu Pro Tyr Gly Arg Pro Arg Val Leu Gln Lys Glu Asn Thr Ile Cys
660 665 670

Leu Leu Ser Gln His Gln Phe Met Ser Gly Tyr Ser Gln Asp Ile Leu
675 680 685

Met Pro Leu Trp Thr Ser Tyr Thr Val Asp Arg Asn Asp Ser Phe Ser
690 695 700

Thr Glu Asp Phe Ser Asn Cys Leu Tyr Gln Asp Phe Arg Ile Pro Leu
705 710 715 720

Ser Pro Val His Lys Cys Ser Phe Tyr Lys Asn Asn Thr Lys Val Ser
725 730 735

Tyr Gly Phe Leu Ser Pro Pro Gln Leu Asn Lys Asn Ser Ser Gly Ile
740 745 750

Tyr Ser Glu Ala Leu Leu Thr Thr Asn Ile Val Pro Met Tyr Gln Ser
755 760 765

Phe Gln Val Ile Trp Arg Tyr Phe His Asp Thr Leu Leu Arg Lys Tyr
770 775 780

Ala Glu Glu Arg Asn Gly Val Asn Val Val Ser Gly Pro Val Phe Asp
785 790 795 800

Phe Asp Tyr Asp Gly Arg Cys Asp Ser Leu Glu Asn Leu Arg Gln Lys
805 810 815

Arg Arg Val Ile Arg Asn Gln Glu Ile Leu Ile Pro Thr His Phe Phe
820 825 830

Ile Val Leu Thr Ser Cys Lys Asp Thr Ser Gln Thr Pro Leu His Cys
835 840 845

Glu Asn Leu Asp Thr Leu Ala Phe Ile Leu Pro His Arg Thr Asp Asn
850 855 860

Ser Glu Ser Cys Val His Gly Lys His Asp Ser Ser Trp Val Glu Glu
865 870 875 880

Leu Leu Met Leu His Arg Ala Arg Ile Thr Asp Val Glu His Ile Thr
885 890 895

Gly Leu Ser Phe Tyr Gln Gln Arg Lys Glu Pro Val Ser Asp Ile Leu
900 905 910

Lys Leu Lys Thr His Leu Pro Thr Phe Ser Gln Glu Asp Arg Ser Gly
915 920 925

Ser Gly Gly Ser Met Lys Trp Val Thr Phe Leu Leu Leu Leu Phe Val
930 935 940

Ser Gly Ser Ala Phe Ser Arg Gly Val Phe Arg Arg Glu Ala His Lys
945 950 955 960

Ser Glu Ile Ala His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys
965 970 975
Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr
980 985 990
Asp Glu His Ala Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr
995 1000 1005
Cys Val Ala Asp Glu Ser Ala Ala Asn Cys Asp Lys Ser Leu His
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Thr Leu Phe Gly Asp Lys Leu Cys Ala Ile Pro Asn Leu Arg Glu
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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
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Glu 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

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

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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

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820 825 830
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Glu Gly Lys Pro Glu Ala Leu Trp Val Glu Glu Arg Phe Thr Ala His
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885 890 895
Gln Asp Lys Val Gln Pro Val Ser Glu Ile Leu Gln Leu Lys Thr Tyr
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Leu Pro Thr Phe Glu Thr Thr Ile Asp Lys Thr His Thr Cys Pro Pro
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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
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Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
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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
1100 1105 1110

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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
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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

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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
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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
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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
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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
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Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys Cys Ala
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Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly Val
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Ser Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala
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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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Ala Ala Asp Lys Asp Thr Cys Phe Ser Thr Glu Gly Pro Asn Leu
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Val Thr Arg Cys Lys Asp Ala Leu Ala
1535 1540

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Gly Arg Ala Pro Arg Glu Gly Pro Ala Gly Asn Gly Arg Asp Arg Gly
20 25 30
Arg Ser His Ala Ala Glu Ala Pro Gly Asp Pro Gln Ala Ala Ala Ser
35 40 45
Leu Leu Ala Pro Met Asp Val Gly Glu Glu Pro Leu Glu Lys Ala Ala
50 55 60

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

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<400> 33

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

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

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

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

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

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<211> 618
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<400> 35

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

Glu Leu Leu Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys
180 185 190
Cys Ala Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly
195 200 205
Val Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys
210 215 220
Ser Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225 230 235 240
Ala Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr
245 250 255
Lys Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly
260 265 270
Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met
275 280 285
Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys Cys Asp
290 295 300
Lys Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val Glu His Asp
305 310 315 320
Thr Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp Phe Val Glu Asp
325 330 335
Gln Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
340 345 350
Thr Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Asp Tyr Ser Val Ser
355 360 365
Leu Leu Leu Arg Leu Ala Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys
370 375 380
Cys Ala Glu Ala Asn Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu
385 390 395 400
Phe Gln Pro Leu Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys
405 410 415
Asp Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu
420 425 430
Val Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445
Glu Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu
450 455 460
Pro Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile
465 470 475 480
Leu Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His

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

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<211> 16
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Leu Phe Thr Phe Ala Val Gly Val Asn Ile Cys Leu Gly Phe Thr Ala
1 5 10 15

<210> 37
<211> 20
<212> PRT
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<223> 信号序列ENPP7
<400> 37
Met Arg Gly Pro Ala Val Leu Leu Thr Val Ala Leu Ala Thr Leu Leu
1 5 10 15
Ala Pro Gly Ala
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<210> 38
<211> 22

<212> PRT
<213> 人工序列
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<400> 38

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Ala Pro Gly Ala Gly Ala
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<400> 39

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Met Glu Arg Asp Gly Cys Ala Gly Gly Gly Ser Arg Gly Gly Glu Gly
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Gly Arg Ala Pro Arg Glu Gly Pro Ala Gly Asn Gly Arg Asp Arg Gly
            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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Lys
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Met Thr Ser Lys Phe Leu Leu Val Ser Phe Ile Leu Ala Ala Leu Ser
1 5 10 15
Leu Ser Thr Thr Phe Ser
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<210> 42
<211> 19
<212> PRT
<213> 人工序列
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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
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<400> 43
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
1 5 10 15

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<400> 45
Glu Glu Glu Glu Glu Glu Glu Pro Arg Gly Asp Thr
1 5 10

<210> 46
<211> 12
<212> PRT
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<400> 46
Ala Pro Trp His Leu Ser Ser Gln Tyr Ser Arg Thr
1 5 10

<210> 47
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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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Val Thr Lys His Leu Asn Gln Ile Ser Gln Ser Tyr
1 5 10

<210> 49

<211> 15
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1 5 10 15
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Gly Gly Ser Gly Gly Ser
1 5
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<211> 7
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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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Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp
1 5 10 15
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Leu Val Ile Met Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5 10 15
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Val Ile Met Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5 10 15
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Ile Met Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5 10
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Met Ser Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5 10
<210> 57

<211> 12
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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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Leu Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5 10
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Gly Leu Gly Leu Gly Leu Gly Leu Arg Lys
1 5 10
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<400> 60
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1 5
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Leu Gly Leu Gly Leu Arg Lys
1 5
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Gly Leu Gly Leu Arg Lys
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Leu Gly Leu Arg Lys
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Gly Leu Arg Lys
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Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys
1 5 10 15
<210> 67
<211> 15
<212> PRT
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<400> 67
Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp Asp
1 5 10 15
<210> 68
<211> 50
<212> PRT
<213> 人工序列
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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
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15
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20 25 30

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly

35 40 45

Gly Ser

50

<210> 69

<211> 2625

<212> DNA

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<400> 69

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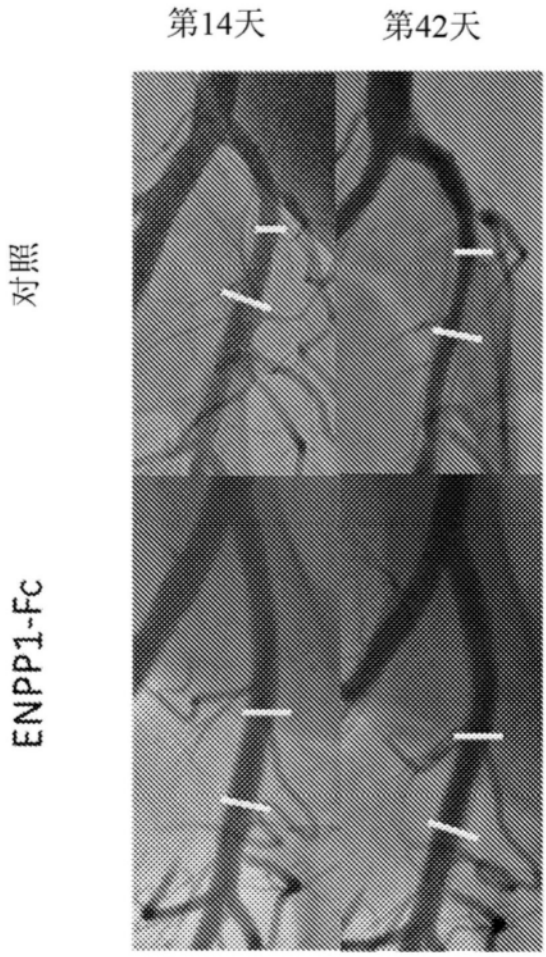


图1

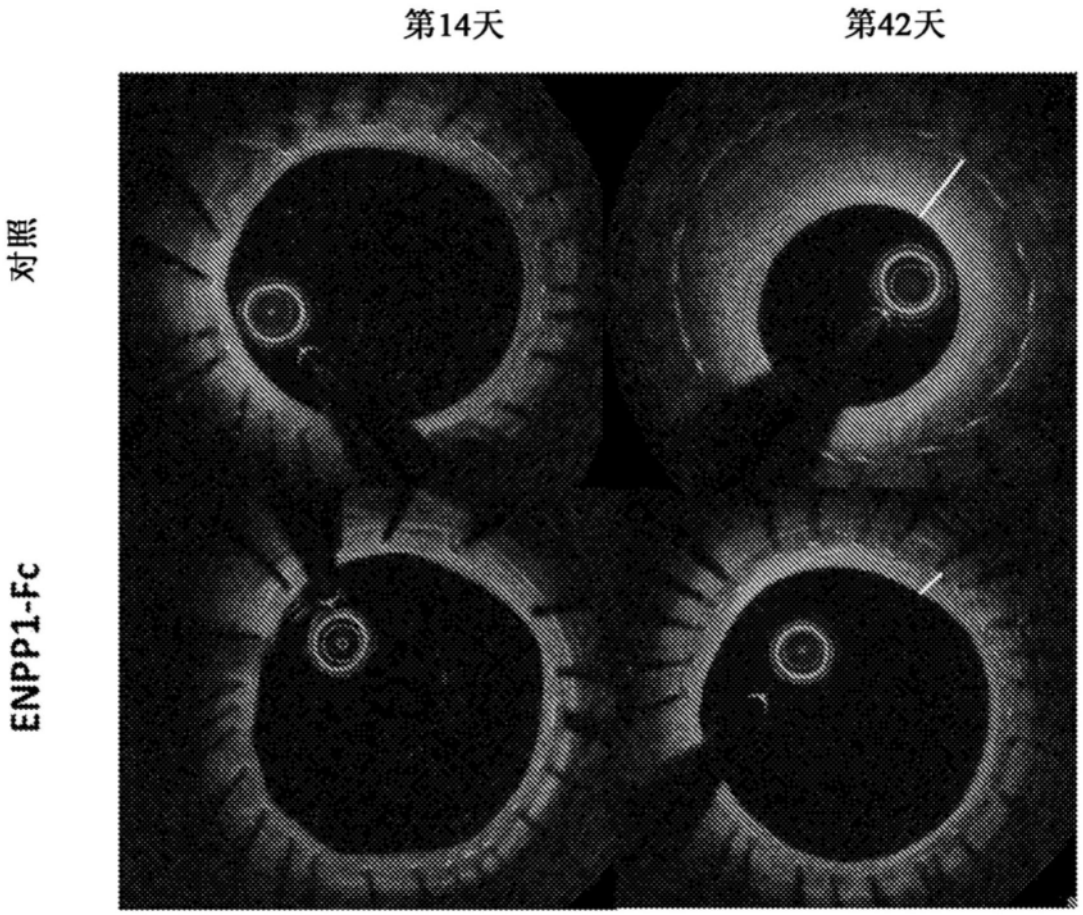


图2

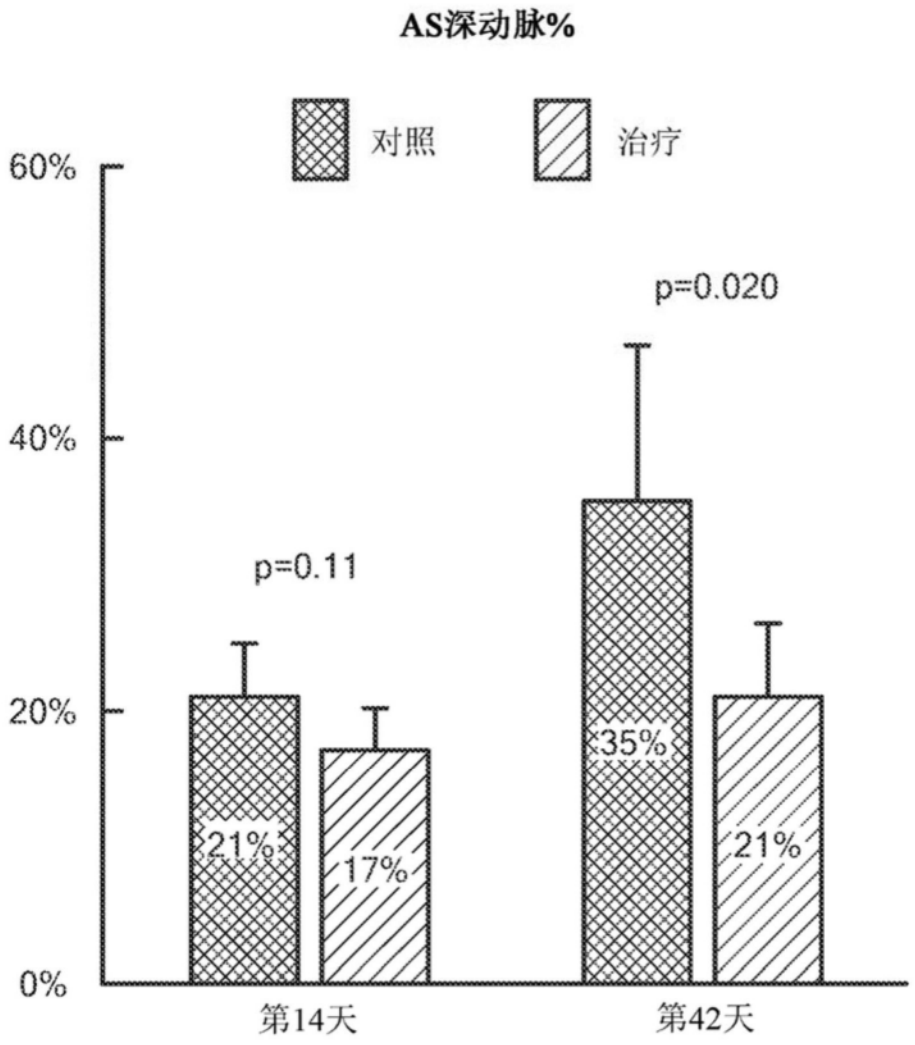


图3

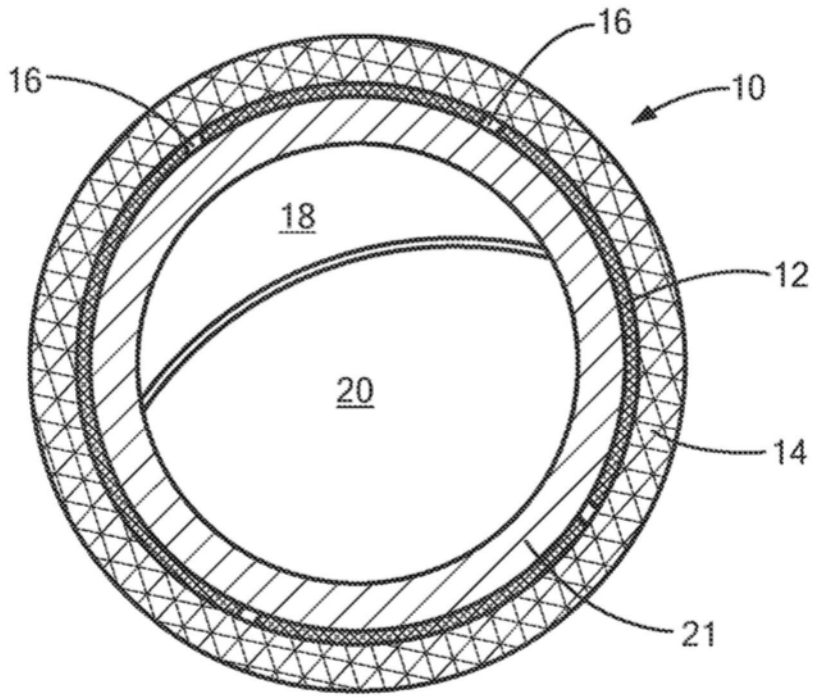


图4A

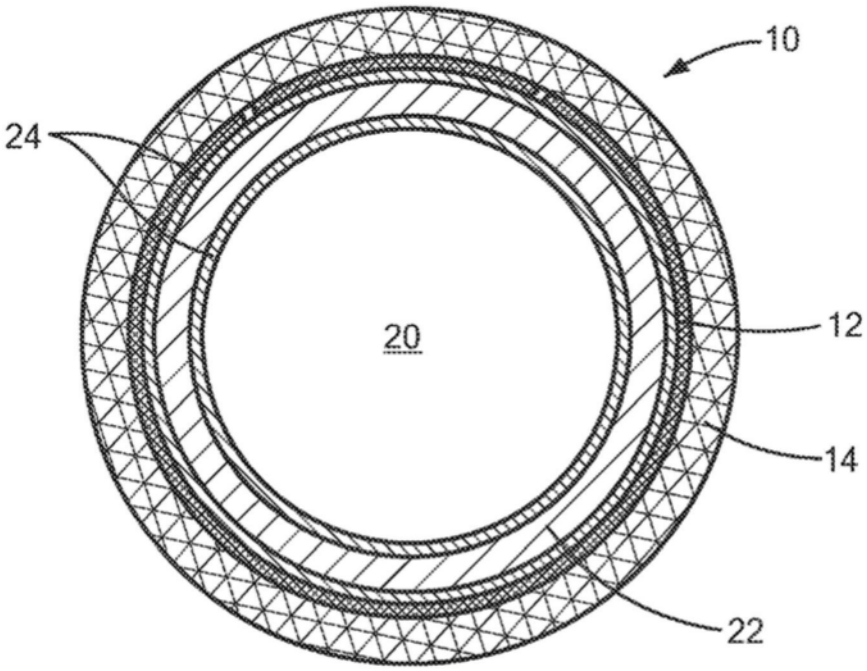


图4B