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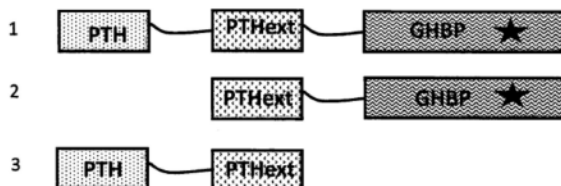
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(54) 发明名称

甲状旁腺激素融合多肽

(57) 摘要

本公开涉及了包含受体多肽的长效甲状旁腺激素或甲状旁腺激素样融合多肽,和其在治疗甲状旁腺功能减退和骨质疏松症中的用途。



1. 一种融合多肽,所述融合多肽包含包含甲状旁腺激素的氨基酸序列的多肽,包含生长激素受体的生长激素结合结构域的氨基酸序列的多肽,其中所述甲状旁腺激素作为翻译融合体直接或间接连接至所述生长激素受体的生长激素结合结构域。
2. 根据权利要求1所述的融合多肽,其中所述融合多肽包含由SEQ ID NO:10所示的氨基酸序列组成的甲状旁腺激素。
3. 根据权利要求1所述的融合多肽,其中所述融合多肽包含由氨基酸1-34或1-35组成的SEQ ID NO 10的片段。
4. 根据权利要求1所述的融合多肽,其中所述融合多肽包含由SEQ ID NO:9所示的序列组成的甲状旁腺激素。
5. 根据权利要求1所述的融合多肽,其中所述融合多肽包含由氨基酸1-34或1-35组成的SEQ ID NO:9的片段。
6. 根据权利要求1所述的融合多肽,其中所述融合多肽包含由SEQ ID NO:54所示的氨基酸序列组成的甲状旁腺激素。
7. 根据权利要求1所述的融合多肽,其中所述融合多肽包含由SEQ ID NO:37所示的氨基酸序列组成的甲状旁腺激素氨基酸序列。
8. 根据权利要求1所述的融合多肽,其中所述融合多肽包含由SEQ ID NO:40所示的氨基酸序列组成的甲状旁腺激素相关蛋白。
9. 根据权利要求1所述的融合多肽,其中所述融合多肽包含人生长激素受体的细胞外生长激素结合结构域多肽。
10. 根据权利要求9所述的融合多肽,其中所述融合多肽包含由SEQ ID NO 5所示的氨基酸序列组成的细胞外生长激素结合结构域多肽。
11. 根据权利要求10所述的融合多肽,其中所述融合多肽包含一个或多个选自由以下组成的组的氨基酸残基的修饰:如SEQ ID NO:5所示的W169、R43、E44、I103、W104、I105、P106、I164和D165,其中所述经修饰的多肽基本上缺乏生长激素结合活性或具有降低的生长激素结合活性。
12. 根据权利要求11所述的融合多肽,其中所述融合多肽包含如SEQ ID NO:5所示的氨基酸序列的氨基酸残基色氨酸104的缺失。
13. 根据权利要求12所述的融合多肽,其中所述融合多肽包含如SEQ ID NO:5所示的氨基酸序列的色氨酸104的取代。
14. 根据权利要求13所述的融合多肽,其中所述融合多肽包含如SEQ ID NO 7所示的丙氨酸取代为色氨酸104。
15. 根据权利要求1所述的融合多肽,其中所述融合多肽包含由SEQ ID NO:54所示的氨基酸序列组成的序列。
16. 根据权利要求1所述的融合多肽,其中所述融合多肽包含甲状旁腺受体结构域多肽,其中所述甲状旁腺受体结构域多肽位于所述融合多肽的羧基末端。
17. 根据权利要求1所述的融合多肽,其中所述融合多肽包含甲状旁腺受体结构域多肽,其中所述甲状旁腺受体结构域多肽位于所述融合多肽的氨基末端。
18. 根据权利要求1所述的融合多肽,其中所述融合多肽包含生长激素结合结构域多

肽,其中所述生长激素结合结构域多肽位于所述融合多肽的羧基末端。

19. 根据权利要求1所述的融合多肽,其中所述融合多肽包含生长激素结合结构域多肽,其中所述生长激素结合结构域多肽位于所述融合多肽的氨基末端。

20. 根据权利要求1所述的融合多肽,其中所述融合多肽由SEQ ID NO:15、20、27、28、33或34所示的氨基酸序列组成。

21. 根据权利要求20所述的融合多肽,其中所述融合多肽由SEQ ID NO:15或20所示的氨基酸序列组成。

22. 根据权利要求20所述的融合多肽,其中所述融合多肽由SEQ ID NO:20所示的氨基酸序列组成。

23. 根据权利要求20所述的融合多肽,其中所述融合多肽由SEQ ID NO:27所示的氨基酸序列组成。

24. 根据权利要求1所述的融合多肽,其中所述融合多肽由SEQ ID NO:44或49所示的氨基酸序列组成。

25. 根据权利要求1所述的融合多肽,其中所述融合多肽包含前肽。

26. 根据权利要求1所述的融合多肽,其中所述融合多肽还包含肽分泌信号。

27. 根据权利要求1所述的融合多肽,其包含:

i) 由SEQ ID NO:54所示的氨基酸序列组成的甲状旁腺激素多肽,

ii) 由肽组成的连接子,所述肽具有以四个拷贝的氨基酸序列Gly Gly Gly Gly Ser所示的氨基酸序列;和

iii) 由SEQ ID NO:7所示的氨基酸序列组成的生长激素受体多肽的生长激素结合结构域。

28. 一种编码根据权利要求1至27中任一项所述的融合多肽的核酸分子。

29. 一种包含根据权利要求28所述的核酸分子的载体。

30. 一种用根据权利要求28或29所述的核酸分子或载体转染或转化的经分离的细胞。

31. 一种用于产生融合多肽的方法,所述方法包括由以下组成的步骤:

i) 提供根据权利要求30所述的细胞和细胞培养基;

ii) 培养所述细胞;和

iii) 从所述细胞或培养基中分离根据本发明的融合多肽。

32. 一种包含根据权利要求1至27中任一项所述的融合多肽的药物组合物,所述药物组合物包含赋形剂或载体。

33. 权利要求1-27中任一项所述的融合多肽在制备用于治疗受试者的甲状旁腺功能减退的药物中的用途。

34. 权利要求1-27中任一项所述的融合多肽在制备用于治疗人受试者的骨质疏松症的药物中的用途。

35. 根据权利要求34所述的用途,其中所述融合多肽与碳酸钙和/或诸如钙化三醇或 α 钙化三醇的维生素D补充剂组合施用。

甲状旁腺激素融合多肽

发明领域

[0001] 本公开涉及了包含受体多肽的长效甲状旁腺激素融合多肽,其中所述受体多肽是甲状旁腺激素受体和/或生长激素受体;编码所述融合多肽的核酸分子;适于表达所述融合多肽的载体;用所述核酸或载体转化或转染的细胞;和所述多肽在治疗甲状旁腺功能减退中的用途。

[0002] 发明背景

[0003] 甲状旁腺功能减退以甲状旁腺激素(PTH)水平低为特征,它是一种罕见的疾患,并且它要么是先天性的,要么更常于颈部手术后获得。PTH由位于颈部甲状腺旁的四个甲状旁腺分泌,并且控制钙稳态、维生素D依赖性钙吸收、肾钙重吸收和肾磷酸盐清除。PTH刺激钙从骨中释放,并且增强钙在肠中的吸收。PTH水平降低会导致低钙血症,并且包括诸如神经肌肉过敏的症状,包括感觉异常、肌肉抽搐、喉部痉挛、手足搐搦和癫痫发作,并且如果不加治疗则可能导致死亡。

[0004] 目前的标准疗法是高剂量钙和活性维生素D;然而,许多患者显示,尽管治疗使得钙水平波动,但抑郁症的发病率增加,以及感染和肾并发症(诸如钙化和肾功能不全)的风险增加。PTH是一种84个氨基酸长的多肽,其包含一个34个氨基酸长的N末端生物活性结构域,被发现是一种有效的PTH受体激动剂。

[0005] 目前重组PTH以每日皮下注射的方式施用。已知PTH在体外不稳定,并且在体内半衰期较短,从而导致PTH水平发生波动,这与恶心和呕吐是相关的。US7550434、US7144861、US6770623、W02006/129995或W02013/108235公开了体外稳定PTH的组合物,并且W02011143406公开了具有增强的药物动力学和药效学的重组PTH类似物,所述重组PTH类似物包含至多36个氨基酸的经修饰的PTH片段。然而,本领域亟需增加对血清钙水平的控制且减少副作用的长效PTH生物制剂来最大限度地减少对每日皮下注射的需要。

[0006] 药物中使用的重组蛋白和肽通常遭受血清清除率增加。导致所施用的蛋白质从循环中去除的因素有两个组成部分:肾脏过滤和蛋白水解。典型地,分子量超过70kDa的蛋白质不能通过肾小球过滤来清除,因为它们太大而不能被过滤,然而,小分子量的蛋白质能通过肾小球过滤并在尿液中发现。一种增加蛋白质有效分子量和生产免疫原性降低的产品的方法是将蛋白质包覆在聚乙二醇(PEG)中。据信PEG是通过提供聚乙二醇化蛋白质中增加的流体动力学体积来减缓肾清除(Maxfield等, *Polymer*, 16:505-509(1975))。然而,蛋白质的聚乙二醇化会导致对它的受体的亲和力降低,从而降低生物学活性。W02009/013461中公开了一种改善蛋白质生物制剂的PK和PD的替代方法。与生长激素相比时,与人生长激素受体(GHR)细胞外结构域融合的人生长激素提高了PK和PD,使得PK提高了大约200倍。在目前未公布的PCT/GB2016/053218中,公开了GHR对非生长激素多肽的效应,其中瘦素和粒细胞集落刺激因子(GSCF)在与GHR融合时具有提高的PK和PD。

[0007] 本公开涉及了PTH融合多肽,其中融合至受体(例如其同源受体和/或GHR)的PTH具有提高的PK和PD。所述PTH融合多肽可用于治疗由PTH活性异常导致的疾患(包括甲状旁腺功能减退),以及治疗受益于PTH疗法的疾患(包括骨质疏松症)。

[0008] 发明概述

[0009] 根据本发明的一个方面,提供融合多肽,其包含

[0010] 包含甲状旁腺激素或其生物活性片段或类似物的氨基酸序列的多肽,

[0011] 包含受体多肽或其片段或类似物的氨基酸序列的多肽,其中所述甲状旁腺激素或其生物活性片段或类似物作为翻译融合体直接或间接连接至所述受体多肽。

[0012] “类似物”是指结合甲状旁腺激素受体或受体多肽氨基酸序列变体的甲状旁腺激素。甲状旁腺激素类似物包括但不限于编码甲状旁腺激素相关蛋白和其变体的氨基酸序列。

[0013] 在本发明的一个优选实施方案中,所述融合多肽包含含如SEQ ID NO:10所示的氨基酸序列或由所述氨基酸序列组成的甲状旁腺激素。

[0014] 在本发明的一个优选实施方案中,所述融合多肽包含含氨基酸1-28、1-29、1-30、1-31、1-32、1-33、1-34或1-35的SEQ ID NO 10的片段。

[0015] 在本发明的一个优选实施方案中,所述融合多肽包含含如SEQ ID NO:9所示的序列的甲状旁腺激素。

[0016] 在本发明的一个优选实施方案中,所述融合多肽包含含氨基酸1-28、1-29、1-30、1-31、1-32、1-33、1-34或1-35的SEQ ID NO 9的片段。

[0017] 在本发明的一个优选实施方案中,所述融合多肽包含含如SEQ ID NO:54所示的氨基酸序列或由所述氨基酸序列组成的甲状旁腺激素。

[0018] 在本发明的一个优选实施方案中,所述融合多肽包含含氨基酸1-28、1-29、1-30、1-31、1-32或1-33的SEQ ID NO 54的片段。

[0019] 在本发明的一个优选实施方案中,所述融合多肽包含甲状旁腺激素类似物或其片段,所述甲状旁腺激素类似物包含以下或由以下组成:式(I)的氨基酸序列

[0020] Xaa01-Val-Xaa03-Glu-Ile-Gln-Leu-Xaa08-His-Xaa10-Xaa11-Xaa12-Xaa13-Xaa14-Leu-Xaa16-Xaa17-Xaa18-Arg-Arg-Arg-Xaa22-Phe-Leu-Xaa25-Xaa26-Leu-Ile-Ala-Glu-Ile-His-Thr-Ala-Glu-Ile(SEQ ID NO:8)

[0021] (I) 其中Xaa01是Ser或Ala;Xaa03是Ser或Ala;Xaa08是Met或Leu;Xaa10是Asn、Ala、Val、Asp、Glu或Gln;Xaa11是Leu、Ala、Val、Met、Lys、Arg或Trp;Xaa12是Gly、Ala、His或Arg;Xaa13是Lys、Ala、Leu、Gln、Arg、His或Trp;Xaa14是His、Leu、Arg、Phe、Trp或Ser;Xaa16是Gln或Asn;Xaa17是Asp或Ser;Xaa18是Ala、Leu、Met、Glu、Ser或Phe;Xaa22是Ala、Phe、Glu、Ser、Leu、Asn、Trp或Lys;Xaa25是His、Arg、Leu、Trp或Lys;并且Xaa26是Lys、His、Ala、Ser、Asn或Arg,或其包含式(I)的氨基酸1-28、1-29、1-30、1-31、1-32、1-33、1-34或1-35的片段,只要Xaa18不为Leu或Met、Xaa22不为Phe及Xaa26不为His中的至少一者即可。

[0022] 在本发明的一个优选实施方案中,所述融合多肽包含含如SEQ ID NO:37所示的氨基酸序列或由所述氨基酸序列组成的甲状旁腺激素和甲状旁腺激素类似物氨基酸序列。

[0023] 在本发明的一个替代实施方案中,所述融合多肽包含含如SEQ ID NO:40所示的氨基酸序列的甲状旁腺激素相关蛋白或其生物活性片段或类似物。

[0024] 在本发明的一个优选实施方案中,所述融合多肽包含含氨基酸1-28、1-29、1-30、1-31、1-32、1-33、1-34或1-35的SEQ ID NO 40的片段。

[0025] 在本发明的一个优选实施方案中,所述融合多肽包含含甲状旁腺激素受体细胞外

结构域的受体多肽。

[0026] 在本发明的一个优选实施方案中,所述融合多肽包含含如SEQ ID NO:3所示的氨基酸序列或由所述氨基酸序列组成的甲状旁腺激素受体细胞外结构域。

[0027] 在本发明的另一优选实施方案中,所述融合多肽包含含与如SEQ ID NO:3所示的全长氨基酸序列10%至99%同一的氨基酸序列的甲状旁腺激素受体细胞外结构域或其片段,并且其中所述结构域或片段结合甲状旁腺激素、其片段或类似物。

[0028] 在本发明的另一优选实施方案中,所述融合多肽包含含与如SEQ ID NO 3所示的氨基酸序列10%、15%、20%、30%、40%、50%、60%、70%、80%、85%、90%、91%、92%、93%、94%、95%、96%、97%、98%或99%同一的氨基酸序列的甲状旁腺激素受体细胞外结构域或其片段,并且其中所述结构域结合甲状旁腺激素、其片段或类似物。

[0029] 在本发明的一个优选实施方案中,所述融合多肽包含编码甲状旁腺激素受体细胞外结构域的修饰的氨基酸序列,其中所述修饰是一个或多个选自由以下组成的组的氨基酸取代:如SEQ ID NO:3所示的I107 K、D109A、P104L或L159A。

[0030] 在本发明的另一优选实施方案中,所述融合多肽包含含如SEQ ID NO:3所示的I107K取代的甲状旁腺激素受体细胞外结构域。

[0031] 在本发明的一个优选实施方案中,所述融合多肽包含含如SEQ ID NO:10所示的序列的氨基酸残基1-14或由所述氨基酸残基组成的甲状旁腺激素。

[0032] 在本发明的一个替代实施方案中,所述融合多肽包含修饰的甲状旁腺激素受体细胞外结构域,其中所述修饰通过添加、缺失或取代至少一个氨基酸残基来进行,其中所述修饰的多肽基本上缺乏甲状旁腺激素结合活性或具有降低的甲状旁腺激素结合活性。

[0033] 在本发明的一个实施方案中,包含受体多肽的所述融合多肽替代地或另外地包含生长激素受体的生长激素结合结构域多肽。

[0034] 在本发明的一个优选实施方案中,所述融合多肽包含人生长激素受体的细胞外生长激素结合结构域多肽。

[0035] 在本发明的另一实施方案中,所述融合多肽包含含如SEQ ID NO 5所示的氨基酸序列的细胞外生长激素结合结构域多肽。

[0036] 在本发明的一个替代实施方案中,所述融合多肽包含修饰的细胞外生长激素结合结构域多肽,其中所述修饰通过添加、缺失或取代至少一个氨基酸残基来进行,其中所述修饰的多肽基本上缺乏生长激素结合活性或具有降低的生长激素结合活性。

[0037] 在本发明的一个优选实施方案中,所述融合多肽包含一个或多个选自由以下组成的组的氨基酸残基的修饰:如SEQ ID NO:5所示的W169、R43、E44、I103、W104、I105、P106、I164和D165。

[0038] 在本发明的一个优选实施方案中,所述融合多肽包含如SEQ ID NO:5所示的氨基酸序列的氨基酸残基色氨酸104的缺失。

[0039] 在本发明的一个替代实施方案中,所述融合多肽包含如SEQ ID NO:5所示的氨基酸序列的色氨酸104的取代。

[0040] 在本发明的一个优选实施方案中,所述融合多肽包含如SEQ ID NO 7所示的丙氨酸取代为色氨酸104。

[0041] 在本发明的另一优选实施方案中,所述融合多肽包含甲状旁腺激素片段或由所述

片段组成,所述片段包含SEQ ID NO:8的氨基酸残基1-28、1-29、1-30、1-31、1-32、1-33、1-34或1-35或由所述氨基酸残基组成。

[0042] 在另一优选实施方案中,所述融合多肽包含含如SEQ ID NO 8、9或10所示的氨基酸序列或由所述氨基酸序列组成的甲状旁腺激素或其类似物,其中所述甲状旁腺激素氨基酸序列通过添加、缺失或取代至少一个氨基酸残基来修饰,并且其中所述修饰的融合多肽保留甲状旁腺激素活性。

[0043] 在另一优选实施方案中,所述融合多肽包含含如SEQ ID NO 54所示的氨基酸序列或由所述氨基酸序列组成的甲状旁腺激素或其类似物,其中所述甲状旁腺激素氨基酸序列通过添加、缺失或取代至少一个氨基酸残基来修饰,并且其中所述修饰的融合多肽保留甲状旁腺激素活性。

[0044] 在另一优选实施方案中,所述融合多肽包含含如SEQ ID NO 37或40所示的氨基酸序列或由所述氨基酸序列组成的甲状旁腺激素类似物,其中所述甲状旁腺激素氨基酸序列通过添加、缺失或取代至少一个氨基酸残基来修饰,并且其中所述修饰的融合多肽保留甲状旁腺激素活性。

[0045] 在另一优选实施方案中,所述融合多肽包含修饰的氨基酸序列,所述修饰的氨基酸序列与如SEQ ID:NO 8、9或10所示的氨基酸序列的全长40%、45%、50%、55%、60%、65%、70%、75%、80%、85%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%同一。

[0046] 在另一优选实施方案中,所述融合多肽包含修饰的氨基酸序列,所述修饰的氨基酸序列与如SEQ ID:NO:40或37所示的氨基酸序列的全长40%、45%、50%、55%、60%、65%、70%、75%、80%、85%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%同一。

[0047] 在另一优选实施方案中,所述融合多肽包含修饰的氨基酸序列,所述修饰的氨基酸序列与如SEQ ID:NO:54所示的氨基酸序列的全长40%、45%、50%、55%、60%、65%、70%、75%、80%、85%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%同一。

[0048] 在本发明的一个优选实施方案中,所述融合多肽包含甲状旁腺受体结构域多肽,其中所述甲状旁腺受体结构域多肽位于所述融合多肽的羧基末端。

[0049] 在本发明的一个替代实施方案中,所述融合多肽包含甲状旁腺受体结构域多肽,其中所述甲状旁腺受体结构域多肽位于所述融合多肽的氨基末端。

[0050] 在本发明的一个替代实施方案中,所述融合多肽包含生长激素结合结构域多肽,其中所述生长激素结合结构域多肽位于所述融合多肽的羧基末端。

[0051] 在本发明的一个实施方案中,所述融合多肽包含生长激素结合结构域多肽,其中所述生长激素结合结构域多肽位于所述融合多肽的氨基末端。

[0052] 在本发明的一个优选实施方案中,所述融合多肽包含如SEQ ID NO:12、13、14、15、16、17、18、19、20、21、22、23、24、25、26、27、28、29、30、31、32、33、34、35或36所示的氨基酸序列或由所述氨基酸序列组成。

[0053] 在本发明的一个优选实施方案中,所述融合多肽包含如SEQ ID NO:15或20所示的氨基酸序列或由所述氨基酸序列组成。

[0054] 在本发明的一个优选实施方案中,所述融合多肽包含如SEQ ID NO:42、43、44、45、

46、47、48、49、50、51、52或53所示的氨基酸序列或由所述氨基酸序列组成。

[0055] 在本发明的一个优选实施方案中,所述融合多肽包含前肽。

[0056] 在本发明的另一优选实施方案中,所述前肽包含SEQ ID NO 11或由其组成。

[0057] 在本发明的一个替代的优选实施方案中,所述前肽包含SEQ ID NO 4或由其组成。

[0058] 在本发明的一个优选实施方案中,所述融合多肽还包含肽分泌信号。

[0059] 在本发明的一个优选实施方案中,所述融合多肽包含甲状旁腺激素肽分泌信号。

[0060] 在本发明的一个优选实施方案中,所述甲状旁腺激素肽分泌信号包含如SEQ ID NO 1所示的氨基酸序列。

[0061] 在本发明的一个优选实施方案中,所述融合多肽包含甲状旁腺激素相关蛋白肽分泌信号。

[0062] 在本发明的一个优选实施方案中,所述甲状旁腺激素相关蛋白肽分泌信号包含如SEQ ID NO 41所示的氨基酸序列。

[0063] 在本发明的一个替代的优选实施方案中,所述融合多肽包含生长激素肽分泌信号。

[0064] 在本发明的一个优选实施方案中,所述融合多肽包含含如SEQ ID NO:2所示的氨基酸序列的生长激素分泌信号。

[0065] 在本发明的一个优选实施方案中,所述融合多肽包含甲状旁腺激素、其片段或类似物并且直接或通过肽连接子间接连接至所述受体多肽。

[0066] 在本发明的一个替代实施方案中,所述甲状旁腺激素、片段或类似物作为框内翻译融合体直接连接至所述受体多肽。

[0067] 优选地,所述肽连接子包含氨基酸序列Gly Gly Gly Gly Ser。

[0068] 在另一优选实施方案中,所述肽连接子包含含氨基酸序列Gly Gly Gly Gly Ser的肽的1、2、3、4、5、6、7、8、9或10个重复单元。

[0069] 在另一优选实施方案中,所述肽连接子包含氨基酸序列Gly Gly Gly Gly Ser的4个重复单元。

[0070] 根据本发明的另一方面,提供编码根据本发明的融合多肽的核酸分子。

[0071] 根据本发明的另一方面,提供包含本发明的核酸分子的载体。

[0072] 在本发明的一个优选实施方案中,所述载体是适于表达本发明的核酸分子的表达载体。

[0073] 包含本发明的核酸的载体不需要包括启动子或其它调节序列,特别是在载体将用于将核酸引入细胞中以重组至基因组中用于稳定转染的情况下。优选地,载体中的核酸可操作地连接至合适的启动子或其它调节元件,用于在宿主细胞中转录。载体可以是在多种宿主中起作用的双功能表达载体。“启动子”是指转录起始位点上游的核苷酸序列,它包含转录所需的所有调节区。合适的启动子包括组成型、组织特异性、诱导型、发育型启动子或其它用于在真核或原核细胞中表达的启动子。“可操作地连接”是指作为同一核酸分子的一部分接合,适当地定位和定向以便从启动子开始转录。可操作地连接至启动子的DNA“处于启动子的转录起始调节之下”。

[0074] 在一个优选实施方案中,启动子是组成型、诱导型或可调节型启动子。

[0075] 根据本发明的另一方面,提供一种被本发明的核酸分子或载体转染或转化的细

胞。

[0076] 优选地,所述细胞是真核细胞。

[0077] 在本发明的一个优选实施方案中,所述细胞选自由以下组成的组:真菌细胞(例如毕赤酵母属某些种(*Pichia* spp)、酵母菌属某些种(*Saccharomyces* spp)、脉孢菌属某些种(*Neurospora* spp));昆虫细胞(例如,夜蛾属某些种(*Spodoptera* spp));哺乳动物细胞(例如COS细胞、CHO细胞);植物细胞。

[0078] 在本发明的一个替代实施方案中,所述细胞是原核细胞。

[0079] 根据本发明的一个方面,提供一种产生根据本发明的融合多肽的方法,所述方法包括由以下组成的步骤:

[0080] i) 提供本发明的细胞和细胞培养基;

[0081] ii) 培养所述细胞;和

[0082] iii) 从所述细胞或培养基中分离根据本发明的融合多肽。

[0083] 根据本发明的另一方面,提供一种包含根据本发明的融合多肽的药物组合物,所述药物组合物包含赋形剂或载体。

[0084] 在本发明的一个优选实施方案中,所述药物组合物与另一治疗剂组合。

[0085] 当施用,本发明的药物组合物以药学上可接受的制剂形式施用。此类制剂通常可以含有药学上可接受浓度的盐、缓冲剂、防腐剂、相容性载体和任选的其它治疗剂,例如化疗剂。

[0086] 本发明的药物组合物可以通过任何常规途径(包括注射)来施用。例如,施用和应用可以是皮下的。

[0087] 本发明的药物组合物以有效量施用。“有效量”是指单独或与其它剂量或协同药物一起产生所需响应的药物/组合物的量。这可能仅涉及暂时减缓疾病的进展,尽管更优选地,它涉及永久停止疾病的进展。这可以通过常规方法来监测,也可以根据诊断方法来监测。

[0088] 施用给受试者的药物组合物的剂量可以根据不同的参数来选择,特别是根据所使用的施用方式和受试者的状态(即年龄、性别)来选择。当施用,本发明的药物组合物以药学上可接受的量和药学上可接受的组合物应用。当用于药物时,盐应该是药学上可接受的,但是非药学上可接受的盐可以方便地用于制备其药学上可接受的盐,并且不排除在本发明的范围之外。此类药理学和药学上可接受的盐包括但不限于由以下酸制备的盐:氢氯酸、氢溴酸、硫酸、硝酸、磷酸、马来酸、乙酸、水杨酸、柠檬酸、甲酸、丙二酸、琥珀酸等。此外,药学上可接受的盐可以制备成碱金属盐或碱土金属盐,例如钠盐、钾盐或钙盐。

[0089] 如果需要,药物组合物可以与药学上可接受的载体组合。如本文所用术语“药学上可接受的载体”是指一种或多种适合施用至人中的相容性固体或液体填充剂、稀释剂或囊封物质。术语“载体”表示与活性成分组合以便于应用的天然或合成的有机或无机成分。药物组合物的各组分也能够与本发明的分子共混合并且相互混合,使得不存在会显著损害所需药物功效的相互作用。

[0090] 药物组合物可以含有合适的缓冲剂,包括:盐中的乙酸;盐中的柠檬酸;盐中的硼酸;和盐中的磷酸。药物组合物还可以任选地含有合适的防腐剂,诸如:苯扎氯铵;氯丁醇;对羟基苯甲酸酯和硫柳汞。

[0091] 药物组合物可以方便地以单位剂型存在,并且可以通过药学领域公知的任何方法来制备。所有方法都包括将活性剂与构成一种或多种辅助成分的载体结合在一起的步骤。通常,通过将活性化合物与液体载体、细碎的固体载体或二者结合在一起,然后,使产品成型(如果需要),来制备组合物。

[0092] 适于皮下施用的组合物方便地包含无菌水性或非水性制剂,该制剂优选与接受者的血液等渗。此制剂可以根据已知的方法使用合适的分散剂或湿润剂和悬浮剂来配制。无菌注射制剂也可以是非经肠可接受的无毒稀释剂或溶剂中的无菌注射溶液或悬浮液,例如1,3-丁二醇溶液。可以使用的可接受溶剂包括水、林格氏溶液(Ringer's solution)和等渗氯化钠溶液。此外,无菌不挥发油通常用作溶剂或悬浮介质。为此,可以使用任何稳定的不挥发油,包括合成的单甘油酯或二甘油酯。此外,诸如油酸的脂肪酸可用于制备注射剂。适用于皮下施用的载体配制剂可见于Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA中。

[0093] 根据本发明的一个方面,提供一种根据本发明的融合多肽,所述融合多肽用于治疗受试者的甲状旁腺功能减退。

[0094] 根据本发明的另一方面,提供一种治疗罹患甲状旁腺功能减退的人受试者的方法,所述方法包括施用有效量的根据本发明的融合多肽,从而治疗甲状旁腺功能减退。

[0095] 根据本发明的一个方面,提供一种根据本发明的融合多肽,所述融合多肽用于治疗人受试者的骨质疏松症。

[0096] 根据本发明的另一方面,提供一种治疗罹患骨质疏松症的人受试者的方法,所述方法包括施用有效量的根据本发明的融合多肽,从而治疗骨质疏松症。

[0097] 在本发明的一个优选实施方案或方法中,所述融合多肽包含如SEQ ID NO:40所示的氨基酸序列。

[0098] 在本发明的一个优选实施方案或方法中,所述融合多肽与碳酸钙和/或诸如钙化三醇或 α 钙化三醇的维生素D补充剂组合施用。

[0099] 在本发明的一个优选实施方案或方法中,所述甲状旁腺功能减退由甲状腺或颈部手术、自身免疫性疾病、放射疗法、癌症、艾迪森氏病(Addison's disease)或迪乔治综合征(Di-George syndrome)造成。

[0100] 在本发明的一个优选实施方案或方法中,所述融合多肽一天施用至少一次。

[0101] 在本发明的一个实施方案或方法中,所述融合多肽每周施用至少一次或两次。

[0102] 在本说明书的整个描述和权利要求中,词语“包含/包括(comprise)”和“含有(contain)”以及所述词语的变化形式(例如“包含/包括(comprising和comprises)”)意指“包括但不限于”,并且并非意图(并且不)排除其它部分、添加剂、组分、整体或步骤。

[0103] 在本说明书的整个描述和权利要求中,除非上下文另有要求,否则单数形式涵盖复数形式。特别是,在使用不定冠词的情况下,除非上下文另有要求,否则说明书应理解为考虑复数形式和单数形式。

[0104] 结合本发明的特定方面、实施方案或实施例描述的特性、整体、特征、化合物、化学部分或基团应理解为适用于本文描述的任何其它方面、实施方案或实施例,除非它们不相容。

[0105] 现在将仅通过实施例并参考以下各图来描述本发明的实施方案。

[0106] 附图简述

[0107] 图1:我们已经将PTH(残基1-34)与N末端PTH受体结构域(PTHrExt)和生长激素结合蛋白(GHBP)连接。GHBP是惰性部分,旨在增加分子量和延迟清除。PTH与PTHrExt的结合保护PTH免于降解,并产生“非活性”PTH池,所述“非活性”PTH池与活性PTH平衡,产生更具生理活性的PTH暴露。分子将在PTH分泌信号(包括或不包括前肽)或生长激素分泌信号的控制下表达,以允许在CHO细胞系中高效地加工;

[0108] 图2:纯化的蛋白质的SDS-PAGE分析。A)纯化的14A1,B)纯化的14A2b。蛋白质在CHO细胞系中表达,并使用Q-琼脂糖凝胶和抗生长激素受体亲和层析的组合从Hyclone SFM4CHO Utility培养基中纯化为分泌产物。蛋白质以约75-100kDa分离,并且是完整的,且没有降解迹象;

[0109] 图3:图14A1和14A2蛋白的体外生物活性。测试纯化的蛋白质刺激PTH响应细胞系UMR-106(大鼠成骨样细胞系)产生cAMP的能力。将细胞在测试分子的存在下刺激15分钟,并使用cAMP特异性Elisa测量细胞溶解物中的cAMP水平。阳性对照、PTH 1-34(100nM)、福司可林(Forskolin)(100 μ m)和阴性对照(仅细胞、仅缓冲液和对照蛋白,促红细胞生成素)都包括在该分析中。数据以pmol cAMP/ml \pm 标准偏差表示;

[0110] 图4甲状旁腺激素,基因座NM_000315 834bp mRNA线性PRI 2016年6月13日,定义智人甲状旁腺激素(PTH),转录变体1,mRNA,登录NM_000315,形式NM_000315.3,关键字RefSeq,来源智人(人)。a)信号肽加下划线,前肽以斜体/小写显示,成熟蛋白(1-34)以大写/粗体显示,b)起源,信号肽加下划线(116-190bp),前肽以小写/斜体显示,成熟蛋白以大写/粗体显示(209-460bp);

[0111] 图5用于融合蛋白的PTH 1-34;a)PTH 1-34的氨基酸序列,b)核苷酸序列(102bp),c)用于融合蛋白的PTH信号肽和前肽序列的氨基酸序列(前肽以小写/斜体显示),d)用于融合蛋白的PTH信号肽和前肽序列的核苷酸序列(前肽以小写/斜体显示);

[0112] 图6人甲状旁腺激素受体1,a)基因座NM_001184744 2007bp mRNA线性PRI 2016年10月6日,定义智人甲状旁腺激素1受体(PTH1R),转录变体2,mRNA,登录NM_001184744,形式NM_001184744.1,关键字RefSeq,来源智人(人),信号肽加下划线,成熟细胞外结构域以粗体显示(D29-I187);b)信号肽加下划线,成熟细胞外结构域以粗体显示;

[0113] 图7用于融合蛋白的PTH受体细胞外结构域

[0114] a)氨基酸序列(氨基酸D29-L187),b)核苷酸序列(477bp)

[0115] 图8人生长激素结合蛋白(GHBP),a)融合体的GHBP部分由氨基酸残基1-238(细胞外结构域)组成,并且包括W104A突变,GHBP核苷酸序列(714bp);b)氨基酸序列(氨基酸1-238);

[0116] 图9 GH分泌信号,a)氨基酸序列b)核苷酸序列;

[0117] 图10 PTH-(g4s)4-PTHrEx-(g4s)4-GHBP(代码编号14A1);PTH信号肽:小写,PTH(氨基酸1-34):大写/下划线,PTHrExt(氨基酸1-159):粗体/小写,GHBP(氨基酸1-238):大写;连接子区域(g4s)4:大写/粗体;a)核苷酸序列,b)蛋白质序列;

[0118] 图11 PTH-(g4s)4-PTHrExt-(g4s)4-GHBP(代码编号14A2),PTH信号肽和前肽:小写,PTH(氨基酸1-34):大写/下划线,PTHrExt(氨基酸1-159):小写/粗体,GHBP(氨基酸1-238):大写,连接子区域(g4s)4:大写/粗体;a)核苷酸序列,b)蛋白质序列;

[0119] 图12 PTH- (g4s) 4-PTHrExt- (g4s) 4-GHBP(代码编号14A3),GH信号肽:小写,PTH(氨基酸1-34):大写/下划线,PTHrExt(氨基酸1-159):小写/粗体,GHBP(氨基酸1-238):大写,连接子区域(g4s)4:大写/粗体;a)核苷酸序列,b)蛋白质序列;

[0120] 图13 PTH- (g4s) 4-GHBP(代码编号14A4),GH信号肽:小写,PTH(氨基酸1-34):大写/下划线,GHBP(氨基酸1-238):大写,连接子区域(g4s)4:大写/粗体;a)核苷酸序列,b)蛋白质序列;

[0121] 图14 PTH- (g4s) 4-PTHrExt_Hist(代码编号14A5_Hist),GH信号肽:小写,PTH(氨基酸1-34):大写/下划线,PTHrExt(氨基酸1-159):小写/粗体,连接子区域(g4s)4:大写/粗体,C末端6x Hist标签:大写/下划线,a)核苷酸序列,b)蛋白质序列;

[0122] 图15 PTH- (g4s) 4-PTHrExt(代码编号14A5),GH信号肽:小写,PTH(氨基酸1-34):大写/下划线,PTHrExt(氨基酸1-159):小写/粗体,连接子区域(g4s)4:大写/粗体;a)核苷酸序列,b)蛋白质序列;

[0123] 图16 PTH- (g4s) 4-PTHrExt_Hist(代码编号14A6_Hist),PTH信号肽和前肽:小写,PTH(氨基酸1-34):大写/下划线,PTHrExt(氨基酸1-159):小写/粗体,连接子区域(g4s)4:大写/粗体,C末端6x Hist标签:大写/下划线;a)核苷酸序列,b)蛋白质序列;

[0124] 图17 PTH- (g4s) 4-PTHrExt_Hist(代码编号14A6),PTH信号肽和前肽:小写,PTH(氨基酸1-34):大写/下划线,PTHrExt(氨基酸1-159):小写/粗体,连接子区域(g4s)4:大写/粗体;a)核苷酸序列,b)蛋白质序列;

[0125] 图18 PTH- (g4s) 4-GHBP(代码编号14A7),PTH信号肽和前肽:小写,PTH(氨基酸1-34):大写/下划线,GHBP(氨基酸1-238):大写,连接子区域(g4s)4:大写/粗体;a)核苷酸序列,b)蛋白质序列;

[0126] 图19 PTH- (g4s) 4-PTHrExt(I135K) - (g4s) 4-GHBP(代码编号14A8),PTH信号肽和前肽:小写,PTH(氨基酸1-34):大写/下划线,PTHrExt(I135K)(氨基酸1-159):小写/粗体(I135K变化加下划线)。GHBP(氨基酸1-238):大写,连接子区域(g4s)4:大写/粗体;a)核苷酸序列,b)蛋白质序列;

[0127] 图20 PTH- (g4s) 4-GHBP(代码编号14A9),GH信号肽:小写,PTH(氨基酸1-34):大写/下划线,PTHrExt(I135K)(氨基酸1-159):小写/粗体(I135K变化加下划线),GHBP(氨基酸1-238):大写,连接子区域(g4s)4:大写/粗体;a)核苷酸序列,b)蛋白质序列;

[0128] 图21 PTH- (g4s) 4-PTHrExt(I135K) -Hist(代码编号14A10),PTH信号肽:小写,PTH(氨基酸1-34):大写/下划线,PTHrExt(I135K)(氨基酸1-159):小写/粗体(I135K变化加下划线),连接子区域(g4s)4:大写/粗体,C末端6x Hist标签:大写/下划线;a)核苷酸序列,b)蛋白质序列;

[0129] 图22 PTH- (g4s) 4-PTHrExt(I135K) -Hist(代码编号14A11-Hist),GH信号肽:小写,PTH(氨基酸1-34):大写/下划线,PTHrExt(I135K)(氨基酸1-159):小写/粗体(I135K变化加下划线),连接子区域(g4s)4:大写/粗体,C末端6x Hist标签:大写/下划线;a)核苷酸序列,b)蛋白质序列;

[0130] 图23 PTH序列(氨基酸1-84);

[0131] 图24(SEQ ID NO 40):PTHrP(1-36);

[0132] 图25(SEQ ID NO 41):PTHrP信号序列;

[0133] 图26(SEQ ID NO 4):PTHrP前肽;

[0134] 图27:显示PTH融合分子的结构示意模型。1A:PTH(紫色)与PTHrExt(绿色)连接,PTHrExt又与GHBP(橙色)连接。连接子以灰色线显示。W104A变化以蓝色显示在GHBP上。假设结合至PTHrExt的PTH(非活性状态:A)与被释放并且能够结合PTHr1的PTH(活性状态,B)之间存在平衡状态。1B:PTH(紫色)与GHBP(橙色)连接。连接子以灰色线显示。W104A变化以蓝色显示在GHBP上;

[0135] 图28A和B:通过非还原条件下的10%SDS-PAGE(考马斯染色)对纯化的PTH融合分子进行的分析。图2A:泳道1:5 μ g 14A2c泳道2:5 μ g 14A3b。14A2c(含有PTH前肽)从60-100kDa作为两个扩散条带分离。14A3b(GHss)以约75-100kDa的单个扩散条带来分辨。图2B:泳道3:6 μ g 14A7泳道4:3 μ g 14A4。蛋白质纯度经过判断>90%。从1升滚瓶培养物中获得约10mg 14A2c、约4mg 14A3b、1.42mg 14A7和0.29mg 14A4纯化的蛋白。C:蛋白印迹(Western blot)抗PTH 14A2c和14A3b。通过非还原条件下的10%SDS-PAGE对纯化的PTH融合分子进行的分析。将样品转移到PVDF膜上,并用抗人PTH(1-34)特异性抗体进行探测。泳道1-3:14A2c,荷载为125ng、250ng和500ng。泳道4-6:14A3b,荷载为125ng、250ng和500ng。14A2c对抗PTH抗体的检测更敏感。代表3个独立蛋白质印迹实验;

[0136] 图29A:cAMP的体外诱导。在37 $^{\circ}$ C/5%CO₂下,用500nM PTH融合体或100nM人PTH 1-34将UMR-106细胞攻击15分钟。将细胞溶解,并使用R&D systems参数cAMP Elisa测量cAMP水平。数据显示为log pmol cAMP/ml \pm SD。发现14A2c的cAMP水平是14A3b的11倍:平均值 \pm SD 264 \pm 12对25 \pm 0.95pmol cAMP/ml。与PTH 1-34相比,两种融合体均显示出降低的生物学活性:平均值 \pm SD 2551 \pm 186pmol cAMP/ml。一式两份进行的n=1实验的平均值。B:针对cAMP活性进行的双荧光素酶报告测定。用报告质粒pGL4.29/CRE/Luc2/Hygro和转染对照质粒phRL(Renilla)转染UMR-106细胞,并在37 $^{\circ}$ C/5%CO₂下用PTH融合体或人PTH 1-34攻击5小时。使用Promega双荧光素酶测定试剂盒溶解细胞并测量荧光素酶活性。数据显示为对照的诱导倍数 \pm SD。14A2c比14A3b更具生物活性,分别相当于100nM和500nM时的约1.3至1.6增加倍数:平均诱导倍数 \pm SD,16.5 \pm 1.7,63 \pm 5.9对12.4 \pm 1.0,40.3 \pm 3.1。三次值的平均值。与同等浓度100nM的PTH 1-34相比,两种融合体均显示出降低的生物学活性:平均值 \pm SD,67.3 \pm 1.6。代表三个单独的实验。C:用于比较所有4种PTH融合分子的cAMP活性的双荧光素酶报告测定。用报告质粒pGL4.29/CRE/Luc2/Hygro和转染对照质粒phRL(Renilla)转染UMR-106细胞,并在37 $^{\circ}$ C/5%CO₂下用PTH融合体或人PTH 1-34攻击5小时。使用Promega双荧光素酶测定试剂盒溶解细胞并测量荧光素酶活性。数据显示为对照的诱导倍数 \pm SD。活性模式类似于先前对于14A2c和14A3b对PTH进行的测定。两种PTH-GHBP融合分子(14A4,49 \pm 4.17和14A7,44 \pm 0.42)在100nM时均比PTH-PTHrExt-GHBP融合分子(14A2c,15 \pm 0.09和14A3b,7.7 \pm 3.13)更具活跃。在100nM时,14A4和14A7的活性均与PTH活性(54 \pm 2.7)相当。D:使用双荧光素酶报告测定确定PTH和PTH融合体的EC₅₀值。PTH的EC₅₀为32 \pm 10.67nM(n=4个实验),效能为14A2c(EC₅₀=579 \pm 138nM,n=3个实验)的约18倍,效能为14A3b(EC₅₀=896nM,n=1)的28倍,效能为14A7(EC₅₀=153nM,n=1个实验)的4.7倍。

[0137] 发明详述

[0138]

代码(SEQ ID)	分子描述
14A1 (12)	PTHss-PTH-(g4s)4-PTHrExt-(g4s)4-GHBP

14A2 (13)	PTHss-pp-PTH- (g4s) 4-PTHrExt- (g4s) 4-GHBP
14A3 (14)	GHss-PTH- (g4s) 4-PTHrExt- (g4s) 4-GHBP
14A4 (15)	GHss-PTH- (g4s) 4-GHBP
14A5 (16)	GHss-PTH- (g4s) 4-PTHrExt
14A5_Hist (17)	GHss-PTH- (g4s) 4-PTHrExt-Hist
14A6_Hist (18)	PTHss-pp-PTH- (g4s) 4-PTHrExt-Hist
14A6 (19)	PTHss-pp-PTH- (g4s) 4-PTHrExt
14A7 (20)	PTHss-pp-PTH- (g4s) 4-GHBP
14A8 (21)	PTHss-pp-PTH- (g4s) 4-PTHrExt (I135K) - (g4s) 4-GHBP
14A9 (22)	GHss-PTH- (g4s) 4-PTHrExt (I135K) - (g4s) 4-GHBP
14A10_Hist (23)	PTHss-pp-PTH- (g4s) 4-PTHrExt (I135K) -Hist
14A11_Hist (24)	GHss-pp-PTH- (g4s) 4-PTHrExt (I135K) -Hist
14A12 (25)	PTHss-pp-LA:PTH- (g4s) 4-PTHrExt- (g4s) 4-GHBP
14A13 (26)	GHss-LA:PTH- (g4s) 4-PTHrExt- (g4s) 4-GHBP
14A15 (27)	PTHss-pp-LA:PTH- (g4s) 4-GHBP
14A16 (28)	GHss-LA:PTH- (g4s) 4-GHBP
14A17 (29)	PTHss-pp-LA:PTH- (g4s) 4-PTHrExt-Hist
14A18 (30)	GHss-LA:PTH- (g4s) 4-PTHrExt-Hist
14A19 (31)	PTHss-pp-PTH(1-84) - (g4s) 4-PTHrExt- (g4s) 4-GHBP
14A20 (32)	GHss-PTH(1-84) - (g4s) 4-PTHrExt- (g4s) 4-GHBP
14A21 (33)	PTHss-pp-PTH(1-84) - (g4s) 4-GHBP
14A22 (34)	GHss-PTH(1-84) - (g4s) 4-GHBP
14A23 (35)	PTHss-pp-PTH(1-84) - (g4s) 4-PTHrExt-Hist
14A24 (36)	GHss-PTH(1-84) - (g4s) 4-PTHrExt-Hist

[0139] 表1

[0140] PTHss=甲状旁腺激素分泌信号;pp=前肽;GHss=生长激素分泌信号;PTH=(所述氨基酸1-34或1-84或其片段);PTHrExt=PTH受体细胞外结构域;GHBP=生长激素结合蛋白(氨基酸1-238);(g4s)4=氨基酸GGGS的4个重复;Hist标记=HHHHHH;I135K=PTHrExt中异亮氨酸-135突变为赖氨酸;LA:PTH=长效PTH[如正文中所述的PTH 1-14与PTHrP的融合体]。

[0141] 上述融合体中的连接子区域由多个GGGS组成。在表1给出的实例中,连接子区域由4 x GGGGS组成,但是可以使用变量多倍体形式。

[0142] 在选定的构建体中PTHrExt中存在的I135K变化已显示降低了PTH对受体的结合。其它氨基酸变化也可以以组合使用或作为单点突变(诸如D137A、P132L和L187A)使用。(SEQ ID NO:56)。

[0143] 以下序列中PTHrExt的编号是指在丙氨酸28处加工的成熟蛋白质,因此D29-I187在以下序列中称为氨基酸1-159(SEQ ID NO:3)。

[0144] 如果需要,所有上述PTH序列均可以用PTH 1-84及其变量置换。

[0145] 表2:所有提出的PTHrP融合构建体(SEQ ID 42-53)的列表

[0146]	分子描述
14A25 (42)	PTHrPss-pp-PTHrP- (g4s) 4-PTHrExt- (g4s) 4-GHBP
14A26 (43)	GHss-PTHrP- (g4s) 4-PTHrExt- (g4s) 4-GHBP
14A27 (44)	GHss-PTHrP- (g4s) 4-GHBP
14A28 (45)	GHss-PTHrP- (g4s) 4-PTHrExt
14A29_Hist (46)	GHss-PTHrP- (g4s) 4-PTHrExt-Hist
14A30_Hist (47)	PTHrPss-pp-PTHrP- (g4s) 4-PTHrExt-Hist
14A31 (48)	PTHrPss-pp-PTHrP- (g4s) 4-PTHrExt
14A32 (49)	PTHrPss-pp-PTHrP- (g4s) 4-GHBP
14A33 (50)	PTHrPss-pp-PTHrP- (g4s) 4-PTHrExt (I135K) - (g4s) 4-GHBP
14A34 (51)	GHss-PTHrP- (g4s) 4-PTHrExt (I135K) - (g4s) 4-GHBP
14A35_Hist (52)	PTHrPss-pp-PTHrP- (g4s) 4-PTHrExt (I135K) -Hist
14A36_Hist (53)	GHss-pp-PTHrP- (g4s) 4-PTHrExt (I135K) -Hist

[0147] PTHrPss=甲状旁腺激素相关蛋白分泌信号;pp=前肽;GHss=生长激素分泌信号;PTHrP=(氨基酸1-36或其片段);PTHrExt=PTH受体细胞外结构域;GHBP=生长激素结合蛋白(氨基酸1-238);(g4s)4=氨基酸GGGS的4个重复;Hist标记=HHHHHH;I135K=PTHrExt中异亮氨酸-135突变为赖氨酸

[0148] 表3 SEQ ID号汇总

[0149]	SEQ ID NO	名称
	1	PTH 信号肽: MIPAKDMAKVMIVMLAICFLTKSDG
	2	GH 分泌信号: MATGSRTSLLLAFGLLCLPWLQEGSA

[0150]

3	PTH 受体 ECO (1-159): DDVMTKEEQIFLLHRAQAQCEKRLKEVLQRPASIMESDKGWTSAST SGKPRKDKASGKLYPESEEDKEAPTGSRYRGRPCLPEWDHILCWP LGAPGEVVAVPCPDYIYDFNHKGHAYRRCDRNGSWELVPGHNR TWANYSECVKFLTNETREREVFDRL
4	PTHrP 前肽: rsveglsrll
5	GH 受体 ECO (1-238): FSGSEATAAiLSRAPWSLQSVN PGLKTNSSKEPKFTKCRSPERETF SCHWTDEVVHHGTKNLGPQLF YTRRNTQEW TQEWKECPDYVSAGENSCYFNSSFTSIWIPYCIKLT SNGGTVDEKCFVDEIVQDPPIALNW TLLNVSLTGIHADIQVRW EAPRNADIQKGMVLEYELQYKEVNETKWKMM DPILTTSPVYSLKVDKEYEVRVRSKQRN SGNYGEFSEVLYVTLPQMSQ
7	GH ECO 取代: w104a 取代 FSGSEATAAiLSRAPWSLQSVNPGLKTNSSKEPKFTKCRSPERETF SCHWTDEVVHHGTKNLGPQLFYTRRNTQEW TQEWKECPDYVSAGE NSCYFNSSFTSIAIPYCIKLT SNGGTVDEKCFVDEIVQDPPIALNW TLLNVSLTGIHADIQVRWEAPRNADIQKGMVLEYELQYKEVN ETKWKMM DPILTTSPVYSLKVDKEYEVRVRSKQRNSGNYGEFSEVLYVTLP QMSQ
8	PTH 式(I): 一般氨基酸式(1-36)
9	PTH 1-84: SVSEIQLM HNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPRK KEDNVLVESHEKSLGEADKADVNVLTAKKSQ
10	PTH 定义的式(I): Ala-Val-Ala-Glu-Ile-Gln-Leu-Met-His-Gln-Arg-Ala-Lys-Trp-Ile-Gln-Asp-Ala-Arg-Arg-Arg-Ala-Phe-Leu-His-Lys-Leu-Ile-Ala-Glu-Ile-His-Thr-Ala-Glu-Ile, 或其包含所述序列(1-36)的氨基酸 1-28、1-29、1-30、1-31、1-32、1-33、1-34 或 1-35 的片段。
11	PTH 前肽: ksvkkrr
12-36	表 1 的构建体
37	PTH 短(LA PTH): LA-PTH ([Ala1,3,12,Gln10,Arg11,Trp14]PTH(1-14)/[Ala18,22,Lys26]PTHrP(15-36)COOH)
40	PTHrP (1-36): AVSEHQLLHDKGKSIQDLRRRFFLHHLIAEIHTAEI
41	PTHrP 信号序列: MQRRLVQQWSVAVFLLSYAVPSCG
42-53	表 2 的构建体
54	PTH 1-34: SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNF
55	PTH ECO 信号肽: MGTARIAPGLALLCCPVLSSAYALVDA

56	全长 PTH 受体: MGTARIAPGLALLCCPVLSSAYALVDADDVMTKEEQIFLLHRA QAQCEKRLKEVLQRPASIMESDKGWTSASTSGKPRKDKASGKL YPESEEDKEAPTGSRYRGRPCLEWDHILCWPLGAPGEWAVPCP DYIYDFNHKGHAYRRCRNGSWELVPGHNRTWANYSECVKFLT NETREREVFDRLGMIYTVGYSVSLASLTVAVLILAYFRRLHCTR NYIHMHLFLSFMLRAVSIFVKDAVLYSGATLDEAERLTEEELRAIA QAPPPATAAAGYAGCRVAVTFFLYFLATNYYWILVEGLYLHSL IFMAFFSEKKYLWGFTVFGWGLPAVFVAVWVSVRATLANTGC WDLSSGNKKWIIQVPILASIVLNFILFINIVRVLATKLRNAGRCD TRQQYRKLKSTLVLMPLEFGVHYIVFMATPYTEVSGTLWQVQMH YEMLFNSFQGFFVAIIYCFNGEVQAEIKKSWRWTALDFKRKARS GSSSYSYGPMVSHTSVTNVGPRVGLGLPLSPRLLPTATTNGHPQL PGHAKPGTPALETLETPPAMAAPKDDGFLNGSCSGLDEEASGP ERPPALLQEEWETVM	
57	SEQ ID NO 1、11 和 9 的融合体	
58	编码 SEQ ID NO 57 的 DNA 序列	
59	编码 SEQ ID NO 59 的 DNA 序列	
60	SEQ ID NO 1 和 11 的融合体	
[0151]	61	编码 SEQ ID NO 60 的 DNA 序列
62	编码 SEQ ID NO 56 的 DNA 序列	
63	编码 SEQ ID NO 3 的 DNA 序列	
64	编码 SEQ ID NO 7 的 DNA 序列	
65	编码 SEQ ID NO 2 的 DNA 序列	
66	编码 SEQ D NO 12 的 DNA 序列	
67	编码 SEQ D NO 13 的 DNA 序列	
68	编码 SEQ D NO 14 的 DNA 序列	
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74	编码 SEQ D NO 20 的 DNA 序列	
75	编码 SEQ D NO 21 的 DNA 序列	
76	编码 SEQ D NO 22 的 DNA 序列	
77	编码 SEQ D NO 23 的 DNA 序列	
6	编码 SEQ D NO 24 的 DNA 序列	

[0152] 材料和方法

[0153] PTH融合体的构建:分子是通过基因合成(Eurofin MWG)和标准的DNA操纵技术的组合来构建的。将编码全长PTH融合体的重组基因克隆至修饰的哺乳动物表达质粒 PSecTag/FRT/V5/Hist-TOPO(Invitrogen)中。根据制造商的说明书,在CHO Flp-In细胞系(Invitrogen)中产生稳定的细胞系,并将其适应Hyclone SFM4CHO Utility(Thermo Scientific)中的无血清培养基。PTH融合体处于PTH或GH信号肽的分泌表达之下。

[0154] 表达和纯化:将细胞在Hyclone SFM4CHO Utility培养基中在滚瓶培养中保持,每2-3天传代一次,使细胞密度保持在 0.25×10^6 个活细胞/ml (VCPM) 与 1.5×10^6 VCPM之间。为了进行表达研究,以 0.5×10^6 VCPM对滚瓶进行接种,使其在37°C、5%CO₂下生长,并且使其达到 1×10^6 VCPM。加入丙戊酸至最终浓度为2mM,温度降至31°C。使细胞生长长达8-10天,其中存活率仍为约70%,此时在4°C下通过使用Beckman JLA 16-25转子以 $22,000 \times g$ 离心20分钟对收获物进行净化。加入EDTA和盐酸苯脒,分别至最终浓度为5mM和10mM,使用Vivaflow 200切向流浓缩器将培养基浓缩并冷冻存储在-20°C。通过阴离子交换(Q-琼脂糖凝胶FF,GE Healthcare)和亲和层析(抗GHBP抗体柱)从该浓缩物中纯化目标蛋白。通过Bradford蛋白质测定法测量蛋白质浓度,并通过非还原条件下的SDS-PAGE对样品进行分析,并且要么用考马斯蓝进行染色,要么使用市售的抗PTH 1-34抗体(Abeam 14493)或内部开发的抗GHBP抗体进行蛋白质印渍。将纯化的样品等分并存储在-80°C。

[0155] 体外生物活性:测试纯化的蛋白质刺激PTH响应细胞系UMR-106(大鼠成骨样细胞系)产生cAMP的能力。在存在测试分子的情况下将细胞刺激15分钟,并且使用cAMP特异性Elisa(R&D systems)测量细胞溶解物中的cAMP水平。

[0156] 甲状旁腺功能减退的动物模型

[0157] Shimizu等在对LA-PT的研究中使用了甲状旁腺功能减退的动物模型。在这个模型中,在治疗前对大鼠进行甲状腺甲状旁腺切除术(TPTX)。简言之:对从Charles River Laboratories Japan, Inc获得的6周龄大鼠进行了手术TPTX。手术后,在每个笼子内供应含有1.10%钙和1.09%用自来水润湿的磷酸盐的颗粒饲料(pellet food)(CE-2;CLEA Japan, Inc., Tokyo, Japan),以便假手术和TPTX大鼠容易获取和消化。从第二天起,选择在TPTX手术后5天展现低于8.0mg/dL的sCa的手术后大鼠进行后续肽注射研究。

[0158] 实施例1

[0159] 根据用N-结构域PTH受体进行的PTH的晶体结构分析[1],PTH显示为位于由N-末端受体部分形成的凹槽中。正是这种相互作用的模式被假设为保护PTH免于降解并产生PTH的“非活性池”,从而延长所述PTH的生物活性以产生长效PTH。有人提出新的分子(见图1)将是PTH(残基1-34),N-末端PTH受体结构域(PTHrExt,最常见的残基D29-L187,但不限于其它组合)与生长激素结合蛋白(GHBP,残基1-238)之间的融合体。GHBP是惰性部分,经设计以增加M_w并因此延迟清除。它将含有W104A突变,以防止在循环中与GH发生相互作用。

[0160] 实施例2

[0161] 最初的表达研究证明,我们能够在CHO细胞系中以足够的水平(约10mg/L)表达和纯化PTH融合分子,从而有充分理由进行进一步的进展。如通过SDS-PAGE所判断,所有的分子均显现为完整的,并且纯度>95%。

[0162] 迄今为止测试的两种PTH融合分子均具有生物活性,并且在体外cAMP测定中产生剂量响应。

[0163] 实施例3

[0164] PTH1-34已经在存在或不存在PTH受体的细胞外结构域(PTHextR)的情况下与生长激素结合蛋白(GHbp)融合。然后表达具有GH(GHss)或PTH(PTHss)信号序列和前肽(pp)的分子。因此,产生了以下4种分子:

[0165] • 14A2c = PTHss-pp-PTH(1-34) - (g4s)4-PTHrExt - (g4s)4-GHbp (SEQ ID NO 13)

[0166] • 14A3b=GHss-PTH(1-34) - (g4s)4-PTHrExt - (g4s)4-GHbp (SEQ ID NO 14)

[0167] • 14A4=GHss-PTH(1-34) - (g4s)4-GHbp (SEQ ID NO 15)

[0168] • 14A7=PTHss-pp-PTH(1-34) - (g4s)4-GHbp (SEQ ID NO 20)

[0169] 已经产生了所有4种分子的稳定克隆,所有稳定的克隆均表达蛋白质,并且所有4种蛋白质均已在GHbp亲和柱上得到纯化。使用GHss的那些蛋白质的表达水平较低,并且SDS-PAGE分析和生物测定表明,在N末端有额外的氨基酸的翻译产物的加工可能不完全,并且具有GHss的那些蛋白质与具有PTHss的那些蛋白质的糖基化可能不同。(图28)这将在具有PTHss的分子的设计中PTH需要它自己的信号序列来进行前原PTH序列的完全加工相符合。在所用的两种生物测定中,所有分子均显示出生物活性,并且有证据表明,包括PTHextR的分子生物活性较低(图29和30)。

[0170] PTH融合分子:设计和假设

[0171] 甲状旁腺激素(PTH)是一种84个氨基酸的肽,其生物学活性存在于残基1-34中。甲状旁腺响应于低血清钙水平而产生PTH。PTH作用于骨和肾上的甲状旁腺受体(PTHr1),从而促进钙从骨中释放,减缓钙从肾中排泄,增加从肠中吸收并促进磷酸盐从肾中排泄。在甲状旁腺功能减退(HypoPT)中,甲状旁腺缺失或受损,因此不能产生任何或足够量的甲状旁腺激素。最初的治疗是使用口服钙和活性VD3补充剂。最近,用Natpara (PTH 1-84)替代HypoPT中的PTH已获得许可,但需要每日sc注射,并且因钙水平波动而变得复杂。持续泵送疗法是有效的,但对大多数患者来说不切实际。因此,亟需提供恒定的生理PTH活性水平的长效PTH分子。以前我们已经证明生长激素与其结合蛋白(GHBP)的融合可以产生长效生长激素(1)。使用这种技术,我们已经产生了大量的PTH融合分子(见图1A和B)。预测PTH融合体通过增加蛋白质大小而具有延长的循环半衰期,同时保持生物学活性。作为对图1A所示PTH融合体的进一步改进,假设PTH将与PTHrExt形成分子内相互作用,防止降解,并提供血管内活性PTH池。为了防止GH结合,将GHBP部分中的色氨酸-104单个氨基酸变化为丙氨酸(W104A)引入所有PTH融合分子中。所有的PTH融合体均将使用天然存在的PTH前肽序列或GH分泌信号来表达。

[0172] 参考文献

[0173] Shimizu, M., et al., Pharmacodynamic Actions of a Long-Acting PTH Analog (LA-PTH) in Thyroparathyroidectomized (TPTX) Rats and Normal Monkeys. *J Bone Miner Res*, 2016. 31(7): p. 1405-12

- [0001] 序列表
- [0002] <110> 谢菲尔德大学(University of Sheffield)
- [0003] <120> 甲状旁腺激素融合多肽
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[0315]	Asp Lys Glu Ala Pro Thr Gly Ser Arg Tyr Arg Gly Arg Pro Cys Leu	
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[0323]	Pro Gly His Asn Arg Thr Trp Ala Asn Tyr Ser Glu Cys Val Lys Phe	
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[0325]	Leu Thr Asn Glu Thr Arg Glu Arg Glu Val Phe Asp Arg Leu Gly Gly	
[0326]		225 230 235 240
[0327]	Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly	
[0328]		245 250 255
[0329]	Gly Ser Phe Ser Gly Ser Glu Ala Thr Ala Ala Ile Leu Ser Arg Ala	
[0330]		260 265 270
[0331]	Pro Trp Ser Leu Gln Ser Val Asn Pro Gly Leu Lys Thr Asn Ser Ser	
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[0333]	Lys Glu Pro Lys Phe Thr Lys Cys Arg Ser Pro Glu Arg Glu Thr Phe	
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[0335]	Ser Cys His Trp Thr Asp Glu Val His His Gly Thr Lys Asn Leu Gly
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[0337]	Pro Ile Gln Leu Phe Tyr Thr Arg Arg Asn Thr Gln Glu Trp Thr Gln
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[0343]	Leu Thr Ser Asn Gly Gly Thr Val Asp Glu Lys Cys Phe Ser Val Asp
[0344]	370 375 380
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[0346]	385 390 395 400
[0347]	Asn Val Ser Leu Thr Gly Ile His Ala Asp Ile Gln Val Arg Trp Glu
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[0349]	Ala Pro Arg Asn Ala Asp Ile Gln Lys Gly Trp Met Val Leu Glu Tyr
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[0351]	Glu Leu Gln Tyr Lys Glu Val Asn Glu Thr Lys Trp Lys Met Met Asp
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[0353]	Pro Ile Leu Thr Thr Ser Val Pro Val Tyr Ser Leu Lys Val Asp Lys
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[0355]	Glu Tyr Glu Val Arg Val Arg Ser Lys Gln Arg Asn Ser Gly Asn Tyr
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[0372]	Val Ser Glu Ile Gln Leu Met His Asn Leu Gly Lys His Leu Asn Ser
[0373]	35 40 45
[0374]	Met Glu Arg Val Glu Trp Leu Arg Lys Lys Leu Gln Asp Val His Asn
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[0387]		145	150	155
[0388]	Arg Gly Arg Pro Cys Leu Pro Glu Trp Asp His Ile Leu Cys Trp Pro			
[0389]		165	170	175
[0390]	Leu Gly Ala Pro Gly Glu Val Val Ala Val Pro Cys Pro Asp Tyr Ile			
[0391]		180	185	190
[0392]	Tyr Asp Phe Asn His Lys Gly His Ala Tyr Arg Arg Cys Asp Arg Asn			
[0393]		195	200	205
[0394]	Gly Ser Trp Glu Leu Val Pro Gly His Asn Arg Thr Trp Ala Asn Tyr			
[0395]		210	215	220
[0396]	Ser Glu Cys Val Lys Phe Leu Thr Asn Glu Thr Arg Glu Arg Glu Val			
[0397]		225	230	235
[0398]	Phe Asp Arg Leu Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly			
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[0406]	Pro Glu Arg Glu Thr Phe Ser Cys His Trp Thr Asp Glu Val His His			
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[0408]	Gly Thr Lys Asn Leu Gly Pro Ile Gln Leu Phe Tyr Thr Arg Arg Asn			
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[0412]	Ala Gly Glu Asn Ser Cys Tyr Phe Asn Ser Ser Phe Thr Ser Ile Ala			
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[0414]	Ile Pro Tyr Cys Ile Lys Leu Thr Ser Asn Gly Gly Thr Val Asp Glu			
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[0422]	Trp Met Val Leu Glu Tyr Glu Leu Gln Tyr Lys Glu Val Asn Glu Thr					
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[0424]	Lys Trp Lys Met Met Asp Pro Ile Leu Thr Thr Ser Val Pro Val Tyr					
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[0426]	Ser Leu Lys Val Asp Lys Glu Tyr Glu Val Arg Val Arg Ser Lys Gln					
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[0428]	Arg Asn Ser Gly Asn Tyr Gly Glu Phe Ser Glu Val Leu Tyr Val Thr					
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[0447]	Trp Leu Arg Lys Lys Leu Gln Asp Val His Asn Phe Gly Gly Gly Gly					
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[0453]	Gln Ala Gln Cys Glu Lys Arg Leu Lys Glu Val Leu Gln Arg Pro Ala					
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[0455]	Ser Ile Met Glu Ser Asp Lys Gly Trp Thr Ser Ala Ser Thr Ser Gly					
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[0479]	Phe Ser Cys His Trp Thr Asp Glu Val His His Gly Thr Lys Asn Leu
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[0492]	405 410 415
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[0499]	Lys Glu Tyr Glu Val Arg Val Arg Ser Lys Gln Arg Asn Ser Gly Asn
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 [0516] 20 25 30
 [0517] Leu Met His Asn Leu Gly Lys His Leu Asn Ser Met Glu Arg Val Glu
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[0566]	Leu Met His Asn Leu Gly Lys His Leu Asn Ser Met Glu Arg Val Glu
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[0568]	Trp Leu Arg Lys Lys Leu Gln Asp Val His Asn Phe Gly Gly Gly Gly
[0569]	50 55 60
[0570]	Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
[0571]	65 70 75 80
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[0573]	85 90 95
[0574]	Gln Ala Gln Cys Glu Lys Arg Leu Lys Glu Val Leu Gln Arg Pro Ala
[0575]	100 105 110
[0576]	Ser Ile Met Glu Ser Asp Lys Gly Trp Thr Ser Ala Ser Thr Ser Gly
[0577]	115 120 125
[0578]	Lys Pro Arg Lys Asp Lys Ala Ser Gly Lys Leu Tyr Pro Glu Ser Glu
[0579]	130 135 140
[0580]	Glu Asp Lys Glu Ala Pro Thr Gly Ser Arg Tyr Arg Gly Arg Pro Cys
[0581]	145 150 155 160
[0582]	Leu Pro Glu Trp Asp His Ile Leu Cys Trp Pro Leu Gly Ala Pro Gly
[0583]	165 170 175
[0584]	Glu Val Val Ala Val Pro Cys Pro Asp Tyr Ile Tyr Asp Phe Asn His
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[0607]	Trp Leu Arg Lys Lys Leu Gln Asp Val His Asn Phe Gly Gly Gly Gly		
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[0611]	Asp Asp Val Met Thr Lys Glu Glu Gln Ile Phe Leu Leu His Arg Ala		
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[0613]	Gln Ala Gln Cys Glu Lys Arg Leu Lys Glu Val Leu Gln Arg Pro Ala		
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[0615]	Ser Ile Met Glu Ser Asp Lys Gly Trp Thr Ser Ala Ser Thr Ser Gly		
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[0617]	Lys Pro Arg Lys Asp Lys Ala Ser Gly Lys Leu Tyr Pro Glu Ser Glu		
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[0619]	Glu Asp Lys Glu Ala Pro Thr Gly Ser Arg Tyr Arg Gly Arg Pro Cys		
[0620]	145	150	155
[0621]	Leu Pro Glu Trp Asp His Ile Leu Cys Trp Pro Leu Gly Ala Pro Gly		
[0622]	165	170	175
[0623]	Glu Val Val Ala Val Pro Cys Pro Asp Tyr Ile Tyr Asp Phe Asn His		
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[0625]	Lys Gly His Ala Tyr Arg Arg Cys Asp Arg Asn Gly Ser Trp Glu Leu		
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[0693]	Gly Gly Gly Gly Ser Asp Asp Val Met Thr Lys Glu Glu Gln Ile Phe			
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[0697]	Leu Gln Arg Pro Ala Ser Ile Met Glu Ser Asp Lys Gly Trp Thr Ser			
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[0703]	Arg Gly Arg Pro Cys Leu Pro Glu Trp Asp His Ile Leu Cys Trp Pro			
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[0707]	Tyr Asp Phe Asn His Lys Gly His Ala Tyr Arg Arg Cys Asp Arg Asn			
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[0711]	Ser Glu Cys Val Lys Phe Leu Thr Asn Glu Thr Arg Glu Arg Glu Val			
[0712]	225	230	235	240

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[0756]	260 265 270
[0757]	Met Met Asp Pro Ile Leu Thr Thr Ser Val Pro Val Tyr Ser Leu Lys
[0758]	275 280 285
[0759]	Val Asp Lys Glu Tyr Glu Val Arg Val Arg Ser Lys Gln Arg Asn Ser
[0760]	290 295 300
[0761]	Gly Asn Tyr Gly Glu Phe Ser Glu Val Leu Tyr Val Thr Leu Pro Gln
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[0782]	65 70 75 80
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[0794]	165 170 175
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[0796]	180 185 190

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[0799]	Gly Ser Trp Glu Leu Val Pro Gly His Asn Arg Thr Trp Ala Asn Tyr
[0800]	210 215 220
[0801]	Ser Glu Cys Val Lys Phe Leu Thr Asn Glu Thr Arg Glu Arg Glu Val
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[0803]	Phe Asp Arg Leu Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
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[1812]	Ile Leu Cys Trp Pro Leu Gly Ala Pro Gly Glu Val Val Ala Val Pro		175
[1813]		180	185
[1814]	Cys Pro Asp Tyr Ile Tyr Asp Phe Asn His Lys Gly His Ala Tyr Arg		
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[1816]	Arg Cys Asp Arg Asn Gly Ser Trp Glu Leu Val Pro Gly His Asn Arg		
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[1818]	Thr Trp Ala Asn Tyr Ser Glu Cys Val Lys Phe Leu Thr Asn Glu Thr		
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[1820]	Arg Glu Arg Glu Val Phe Asp Arg Leu Gly Gly Gly Gly Ser Gly Gly		
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[1822]	Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Phe Ser Gly		255
[1823]		260	265
[1824]	Ser Glu Ala Thr Ala Ala Ile Leu Ser Arg Ala Pro Trp Ser Leu Gln		
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[1826]	Ser Val Asn Pro Gly Leu Lys Thr Asn Ser Ser Lys Glu Pro Lys Phe		
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[1828]	Thr Lys Cys Arg Ser Pro Glu Arg Glu Thr Phe Ser Cys His Trp Thr		
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[1830]	Asp Glu Val His His Gly Thr Lys Asn Leu Gly Pro Ile Gln Leu Phe		
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[1842]	Gly Ile His Ala Asp Ile Gln Val Arg Trp Glu Ala Pro Arg Asn Ala		
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[1844]	Asp Ile Gln Lys Gly Trp Met Val Leu Glu Tyr Glu Leu Gln Tyr Lys		
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[1852]	Val Leu Tyr Val Thr Leu Pro Gln Met Ser Gln		
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[1867]	Leu Leu His Asp Lys Gly Lys Ser Ile Gln Asp Leu Arg Arg Arg Phe		
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[1869]	Phe Leu His His Leu Ile Ala Glu Ile His Thr Ala Glu Ile Gly Gly		
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[1873]	Gly Ser Asp Asp Val Met Thr Lys Glu Glu Gln Ile Phe Leu Leu His		
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[1875]	Arg Ala Gln Ala Gln Cys Glu Lys Arg Leu Lys Glu Val Leu Gln Arg		
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[1877]	Pro Ala Ser Ile Met Glu Ser Asp Lys Gly Trp Thr Ser Ala Ser Thr		
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[1881]	Ser Glu Glu Asp Lys Glu Ala Pro Thr Gly Ser Arg Tyr Arg Gly Arg		
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[1883]	Pro Cys Leu Pro Glu Trp Asp His Ile Leu Cys Trp Pro Leu Gly Ala		
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[1885]	Pro Gly Glu Val Val Ala Val Pro Cys Pro Asp Tyr Ile Tyr Asp Phe		
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[1887]	Asn His Lys Gly His Ala Tyr Arg Arg Cys Asp Arg Asn Gly Ser Trp		
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[1891]	Val Lys Phe Leu Thr Asn Glu Thr Arg Glu Arg Glu Val Phe Asp Arg
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[1894]	245 250 255
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[1896]	260 265 270
[1897]	Ser Arg Ala Pro Trp Ser Leu Gln Ser Val Asn Pro Gly Leu Lys Thr
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[1901]	Glu Thr Phe Ser Cys His Trp Thr Asp Glu Val His His Gly Thr Lys
[1902]	305 310 315 320
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[1906]	340 345 350
[1907]	Asn Ser Cys Tyr Phe Asn Ser Ser Phe Thr Ser Ile Ala Ile Pro Tyr
[1908]	355 360 365
[1909]	Cys Ile Lys Leu Thr Ser Asn Gly Gly Thr Val Asp Glu Lys Cys Phe
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[1911]	Ser Val Asp Glu Ile Val Gln Pro Asp Pro Pro Ile Ala Leu Asn Trp
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[1921]	Val Asp Lys Glu Tyr Glu Val Arg Val Arg Ser Lys Gln Arg Asn Ser
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[1947]	Ser Gly Gly Gly Gly Ser Phe Ser Gly Ser Glu Ala Thr Ala Ala Ile	
[1948]		100 105 110
[1949]	Leu Ser Arg Ala Pro Trp Ser Leu Gln Ser Val Asn Pro Gly Leu Lys	
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[1967]	Val Arg Trp Glu Ala Pro Arg Asn Ala Asp Ile Gln Lys Gly Trp Met	
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[1969]	Val Leu Glu Tyr Glu Leu Gln Tyr Lys Glu Val Asn Glu Thr Lys Trp	
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[1971]	Lys Met Met Asp Pro Ile Leu Thr Thr Ser Val Pro Val Tyr Ser Leu	
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[2031]	20 25 30		
[2032]	Leu Leu His Asp Lys Gly Lys Ser Ile Gln Asp Leu Arg Arg Arg Phe		
[2033]	35 40 45		
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[2042]	Pro Ala Ser Ile Met Glu Ser Asp Lys Gly Trp Thr Ser Ala Ser Thr		
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[2087]	Ala Ser Gly Lys Leu Tyr Pro Glu Ser Glu Glu Asp Lys Glu Ala Pro			
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[2089]	Thr Gly Ser Arg Tyr Arg Gly Arg Pro Cys Leu Pro Glu Trp Asp His			
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[2095]	Arg Cys Asp Arg Asn Gly Ser Trp Glu Leu Val Pro Gly His Asn Arg			
[2096]	210 215 220			
[2097]	Thr Trp Ala Asn Tyr Ser Glu Cys Val Lys Phe Leu Thr Asn Glu Thr			
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[2115]	Arg Leu Ala Val Ser Glu His Gln Leu Leu His Asp Lys Gly Lys Ser
[2116]	35 40 45
[2117]	Ile Gln Asp Leu Arg Arg Arg Phe Phe Leu His His Leu Ile Ala Glu
[2118]	50 55 60
[2119]	Ile His Thr Ala Glu Ile Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
[2120]	65 70 75 80
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[2127]	Lys Gly Trp Thr Ser Ala Ser Thr Ser Gly Lys Pro Arg Lys Asp Lys
[2128]	130 135 140
[2129]	Ala Ser Gly Lys Leu Tyr Pro Glu Ser Glu Glu Asp Lys Glu Ala Pro
[2130]	145 150 155 160
[2131]	Thr Gly Ser Arg Tyr Arg Gly Arg Pro Cys Leu Pro Glu Trp Asp His
[2132]	165 170 175
[2133]	Ile Leu Cys Trp Pro Leu Gly Ala Pro Gly Glu Val Val Ala Val Pro
[2134]	180 185 190
[2135]	Cys Pro Asp Tyr Ile Tyr Asp Phe Asn His Lys Gly His Ala Tyr Arg
[2136]	195 200 205
[2137]	Arg Cys Asp Arg Asn Gly Ser Trp Glu Leu Val Pro Gly His Asn Arg
[2138]	210 215 220
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[2161]	65 70 75 80
[2162]	Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Phe Ser Gly Ser Glu Ala
[2163]	85 90 95
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[2172]	Arg Asn Thr Gln Glu Trp Thr Gln Glu Trp Lys Glu Cys Pro Asp Tyr
[2173]	165 170 175
[2174]	Val Ser Ala Gly Glu Asn Ser Cys Tyr Phe Asn Ser Ser Phe Thr Ser
[2175]	180 185 190
[2176]	Ile Ala Ile Pro Tyr Cys Ile Lys Leu Thr Ser Asn Gly Gly Thr Val
[2177]	195 200 205
[2178]	Asp Glu Lys Cys Phe Ser Val Asp Glu Ile Val Gln Pro Asp Pro Pro
[2179]	210 215 220
[2180]	Ile Ala Leu Asn Trp Thr Leu Leu Asn Val Ser Leu Thr Gly Ile His
[2181]	225 230 235 240
[2182]	Ala Asp Ile Gln Val Arg Trp Glu Ala Pro Arg Asn Ala Asp Ile Gln

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[2186]	Glu Thr Lys Trp Lys Met Met Asp Pro Ile Leu Thr Thr Ser Val Pro					
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[2188]	Val Tyr Ser Leu Lys Val Asp Lys Glu Tyr Glu Val Arg Val Arg Ser					
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- [2923] tttgaccgcc tg 732
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[2984] agccaa 1506

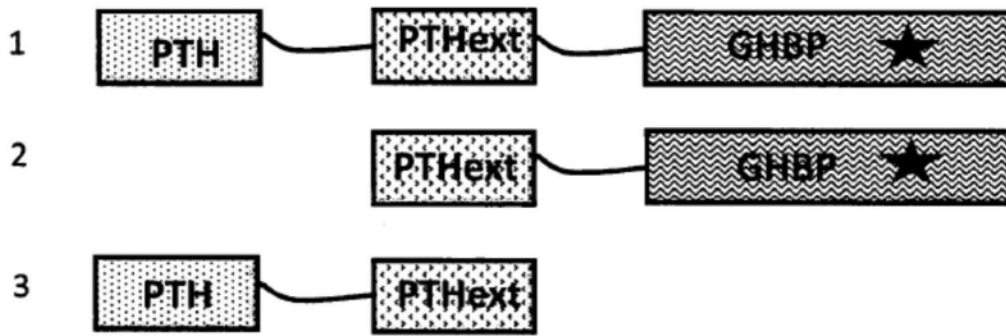


图1

A: 纯化的 14A1

KDa

100
75
50
37
25
20



SDS-PAGE分析:
考马斯染色的凝胶

1. 标准品
2. 1 μg 蛋白质
3. 2 μg 蛋白质
4. 4 μg 蛋白质
5. 8 μg 蛋白质

B: 纯化的 14A2b

KDa

100
75
50
37
25
20



SDS-PAGE分析:
考马斯染色的凝胶

1. 10 μg 蛋白质
2. 标准品

图2

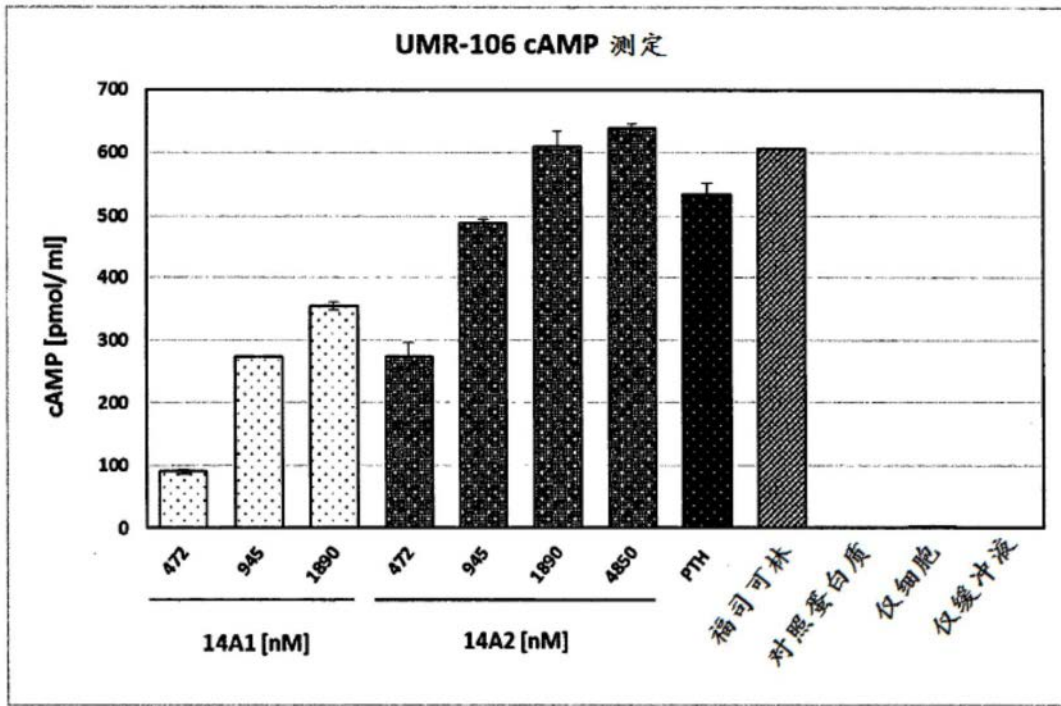


图3

a) (SEQ ID NO 1, 11 和 9)SEQ ID NO 57
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b) SEQ ID NO 58

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1 AAAAGTCACC ATTTAAGGGG TCTGCAGTCC AATTCATCAG TTGTCTTTAG TTTACTCAGC
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121 ACCTGCAAAA GACATGGCTA AAGTTATGAT TGTCAATGTT GCAATTTGTT TTCTTACAAA
181 ATCGGATGGG aaatctgtta agaagagaTC TGTGAGTGAA ATACAGCTTA TGCATAACCT
241 GGGAAAACAT CTGAACTCGA TGGAGAGAGT AGAATGGCTG CGTAAGAAGC TGCAGGATGT
301 GCACAATTTT GTTGCCCTFG GAGCTCCTCT AGCTCCCAGA GATGCTGGTT CCCAGAGGCC
361 CCGAAAAAAG GAAGACAATG TCTTGGTTGA GAGCCATGAA AAAAGTCTTG GAGAGGCAGA
421 CAAAGCTGAT GTGAATGTAT TAACTAAAGC TAAATCCCAG TGAAAATGAA AACAGATATT
481 GTCAGAGTTC TGCTTAGAC AGTGTAGGGC AACAATACAT GCTGCTAAT CAAAGCTCTA
541 TTAAGATTTT CAAGTGCCAA TATTTCTGAT ATAACAACT ACATGTAATC CATCACTAGC
601 CATGATAACT GCAATTTTAA TTGATTATTC TGATTCCAAT TTTATTCATT TGAGTTATTT
661 TAATTATCTT TTCTATTGTT TATTCTTTTT AAAGTATGTT ATTGCATAAT TTATAAAGA
721 ATAAAATGTC ACTTTTAAAC CTCTCTTCTA CCTTAAATG TAAAACAAA ATGTAATGAT
781 CATAAGTCTA AATAAATGAA GTATTTCTCA CTCATTGCAA GTAAAAAAA AAAA
    
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图4

a) (SEQ ID No 54)SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNF

b) SEQ ID NO 59

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 GCAGGATGTGCACAATTTT

c) (SEQ ID NO 1 和 SEQ ID NO 11) SEQ ID NO 60 MIPAKDMAKVMIVMLAICFLTKSDGksvkkr

d) SEQ ID NO 61
 ATGATACTGCAAAAGACATGGCTAAAGTTATGATTGTCATGTTGGCAATTTGTTTTCTTACAAAATCGGATGGGaatc
 tgtaagaagagatc

图5

a) (SEQ ID NO 56)
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 SGKLYPESEEDKEAPTGSRYRGRPCLPEWDHILCWPLGAPGEVVAVPCPDYIYDFNHKGHAYRRCDRNGSWELVPGHNRTWAN
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b) SEQ ID NO 62

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121	CTCAGCTCCG	CGTACCGCGCT	GGTGGATGCA	GATGACGTCA	TGACTAAAGA	GGAACAGATC
181	TTCTGCTGC	ACCGTGCTCA	GGCCCACTGC	GAAAAACGGC	TCAAGGAGGT	CCTGCAGAGG
241	CCAGCCAGCA	TAATGGAATC	AGACAAGGGA	TGGACATCTG	CGTCCACATC	AGGGAAGCCC
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361	ACTGGCAGCA	GGTACCGAGG	GCGCCCTGT	CTGCCGGAAT	GGGACCACAT	CCTGTGCTGG
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481	AATCACAAG	GCCATGCCTA	CCGACGCTGT	GACCGCAATG	GCAGCTGGGA	GCTGGTGCCT
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601	CGTGAACGGG	AGGTGTTTGA	CCGCCTGGGC	ATGATTTACA	CCGTGGGCTA	CTCCGTGTCC
661	CTGGCGTCCC	TCACCGTAGC	TGTGCTCATC	CTGCCTACT	TTAGGCGGCT	GCACTGCACG
721	CGCAACTACA	TCCACATGCA	CCTGTTCCTG	TCCTTCATGC	TGCGCGCCGT	GAGCATCTTC
781	GTC AAGGACG	CTGTGCTCTA	CTCTGGCGCC	ACGCTTGATG	AGGCTGAGCG	CCTCACCGAG
841	GAGGAGCTGC	GCGCCATCGC	CCAGGCGCCC	CCGCCGCTG	CCACCGCCG	TGCCGGCTAC
901	GCGGGTGC	GGGTGGCTGT	GACCTTCTTC	CTTACTTCC	TGGCCACCAA	CTACTACTGG
961	ATTCTGGTGG	AGGGGCTGTA	CCTGCACAGC	CTCATCTTCA	TGGCCTTCTT	CTCAGAGAAG
1021	AAGTACCTGT	GGGGCTTCAC	AGTCTTCGGC	TGGGGTCTGC	CCGCTGTCTT	CGTGGCTGTG
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1141	AAAAAGTGGA	TCATCCAGGT	GCCCATCCTG	GCCTCCATTG	TGCTCAACTT	CATCCTCTTC
1201	ATCAATATCG	TCCGGGTGCT	CGCCACCAAG	CTGCGGGAGA	CCAACGCCG	CCGCTGTGAC
1261	ACACGGCAGC	AGTACCGGAA	GCTGCTCAA	TCCACGCTGG	TGCTCATGCC	CCTCTTTGGC
1321	GTCCACTACA	TTGTCTTCAT	GGCCACACCA	TACACCGAGG	TCTCAGGGAC	GCTCTGGCAA
1381	GTCCAGATGC	ACTATGAGAT	GCTCTTCAAC	TCCTTCCAGG	GATTTTTTGT	CGCAATCATA
1441	TACTGTTTCT	GCAATGGCGA	GGTACAAGCT	GAGATCAAGA	AATCTTGGAG	CCGCTGGACA
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1561	ATGGTGTCCC	ACACAAGTGT	GACCAATGTC	GGCCCCGTG	TGGGACTCGG	CCTGCCCTC
1621	AGCCCCCGCC	TACTGCCAC	TGCCACCACC	AACGGCCACC	CTCAGCTGCC	TGGCCATGCC
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1861	GGCTGGACCT	GCTGACATAG	TGGATGGACA	GATGGACCAA	AAGATGGGTG	GTTGAATGAT
1921	TTCCCACTCA	GGGCTGGGGC	CAAGAGGAAA	AACAGGGAAA	AAAAGAAAAA	AAAAAGAAAA
1981	AGGAAAAGGA	AAAAAATAAA	AAAAAATA			

图6

a) (SEQ ID NO 3)
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 RVFDR

b) SEQ ID NO 63

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 CACCAGGTGA GGTGGTGGCT GTGCCCTGTC CGGACTACAT TTATGACTTC AATCACAAG GCCATGCCTA
 CCGACGCTGT GACCGCAATG GCAGCTGGGA GCTGGTGCCT GGGCACAACA GGACGTGGGC CAACTACAGC
 GAGTGTGTCA AATTTCTCAC CAATGAGACT CGTGAACGGG AGGTGTTTGA CCGCCTG

图7

a) SEQ ID NO 64

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 AACATCAGTTCAGTGTACTCATTGAAAGTGGATAAGGAATATGAAGTGCCTGTGAGATCCAAACAACGAAACTCTGGAAT
 ATGGCGAGTTCAGTGAGGTGCTCTATGTAACACTTCCTCAGATGAGCCAA

b) (SEQ ID NO 7)

FSGSEATAAILLSRAPWSLQSVNPLKTNSSKEPKFKRSPERETF SCHWTDEVHHTKNLGPIQLFYTRRNTQEWQEWKEC
 PDYVSAGENSCYFNSSFTSIAIPYCIKLTNSGGTVDEKCFVDEIVQDPPIALNWTLLNVSLTGIHADIQVRWEAPRNADIQ
 KGWMVLEYELQYKEVNETKWKMMDPILTTSVPVYSLKVDKEYEVRVRSKQRNSGNYGEFSEVLYVTLPQMSQ

图8

a) (SEQ ID NO 2)

MATGSRTSLLLAFGLLCLPWLQEGSA

b) SEQ ID NO 65

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图9

a) SEQ ID NO 66
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b) (SEQ ID NO 12)

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 lcwplgagpgevavpcpdyiydfnhkghayrrodrngswelvpghnrtwanysecvklftnetrerevfdrlGGGSGGGSGG
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 EWTQEWKECPDYVSAGENSCYFNSSFTSIAIPYCIKLTNSGGTVDEKCFVDEIVQDPPIALNWTLLNVS1LTIHAD1QVRW
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图10

a) SEQ ID NO 67
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 AGATGAGCCAA*

b) (SEQ ID NO 13)

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 QMSQ*

图11

a) SEQ ID NO 68
 atggctacaggctccccgacgtccctgctcctggcttttggcctgctctgctgcctggcttcaagagggcagtgccTCTGT
 GAGTGAAATACAGCTTATGCATAACCTGGGAAAACATCTGAACTCGATGGAGAGAGTAGAATGGCTGCGTAAGAGCTGCAGG
 ATGTGCACAATTTGGTGGCGGAGGTAGTGGTGGCGGAGGTAGCGGTGGCGGAGGTTCTGGTGGCGGAGGTTCCgatgaogto
 atgaactaaagaggaacagataottcctgctgcaocgtgctcagggccocagtgogaaaaacggctcaaggaggtcctgacagagcc
 agocagcaataatggaaacagacaagggatggacaototgogtocaocacagggaaagocagggaaagataaggcaotctgggaagc
 totacocctgagctgaggaggacaaggaggcaccactggcagcaggtacogaggggocccctgctcoggaatgggaccac
 atcctgtgctggccgctgggggaccaggtgaggtggtggtgctgocctgtccggactacatttaagactcaatcaacaagg
 coactgctaccgacgctgtgaccgcaatggcagctgggagctggtgctggccacaacaggaogtgggccaactacagogagt
 gtgtcaaatttctcaocaaatgagactogtgaacogggaggtgtttgacogcctgGGTGGCGGAGGTAGTGGTGGCGGAGGTAGC
 GGTGGCGGAGGTTCTGGTGGCGGAGGTTCCTTTTCTGGAAGTGAGGCCACAGCAGCTATCCTTAGCAGAGCACCCCTGGAGTCT
 GCAAAAGTGTAAATCCAGGCCATAAGACAAATTTCTTAAGGAGCCTAAATTCACCAAGTGCCGTTACCTGAGCGAGAGACTT
 TTTCATGCCACTGGACAGATGAGGTTTATCATGGTACAAAGAACCTAGGACCCATACAGCTGTTCTATACCAGAAGGAACACT
 CAAGAATGGACTCAAGAATGGAAAGAATGCCCTGATTATGTTTCTGCTGGGAAAACAGCTGTTACTTTAATTCATCGTTTAC
 CTCCATCGCAATACCTTATGTATCAAGCTAACTAGCAATGGTGGTACAGTGGATGAAAAGTGTCTCTGTGTGATGAAATAG
 TGCAACCAGATCCACCCATTGCCCTCAACTGGACTTTACTGAACGTCAGTTTAACTGGGATTTCATGCAGATATCCAAGTGAGA
 TGGGAAGCACCGCAATGCAGATATTCAGAAAGGATGGATGGTCTGGAGTATGAACTTCAATACAAGAAGTAAATGAAAC
 TAAATGAAAAATGATGGACCCTATATTGACAACATCAGTCCAGTGTACTCATTGAAAGTGGATAAGGAATATGAAGTGCCTG
 TGAGATCCAACAACGAAACTCTGGAATTTATGGCGAGTTCAGTGAGGTGCTCTATGTAACACTTCTCAGATGAGCCAA*

b) (SEQ ID NO 14)
 matgsrtslllafgllclpwlqegsaSVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFGGGSGGGSGGGSGGGSGddv
 mtkeeqifllhraaqcekrllkevlqrpasimesdkwtsastsgkprkdkasgklypeseedkeaptgsryrgrpclpewdh
 ilcwplogevvavpcpdyiydfnhkhayrrrodrngswelvpghnrtnwanysecvklfnetrerevfdrlGGGSGGGSG
 GGGSGGGSGFSGSEATAAILSRAPWSLQSVNPLKTNSSKEPKFTKCRSPERETFSCHWTDVHHGTKNLGPIQLFYTRRNT
 QEWTEWKECPDYVSAGENSCYFNSSFTSIAIPYCIKLTNSGGTVDEKCFVDEIVQPPPIALNWTLLNVSLTGIHADIQVR
 WEAPRNADIQKGMVLEYELQYKEVNETKWKMDPILTTSPVYSLKVDKEYEVRVRSKQRNSGNYGEFSEVLYVTLPQMSQ*

图12

a) SEQ ID NO 69
 atggctacaggctccccgacgtccctgctcctggcttttggcctgctctgctgcctggcttcaagagggcagtgccTCTGT
 GAGTGAAATACAGCTTATGCATAACCTGGGAAAACATCTGAACTCGATGGAGAGAGTAGAATGGCTGCGTAAGAGCTGCAGG
 ATGTGCACAATTTGGTGGCGGAGGTAGTGGTGGCGGAGGTAGCGGTGGCGGAGGTTCTGGTGGCGGAGGTTCCTTTTCTGGA
 AGTGAGGCCACAGCAGCTATCCTTAGCAGAGCACCCCTGGAGTCTGCAAAGTGTAAATCCAGGCCATAAGACAAATTTCTTAA
 GGAGCCTAAATTCACCAAGTGCCGTTACCTGAGCGAGAGACTTTTCATGCCACTGGACAGATGAGGTTTCATCATGGTACAA
 AGAACCTAGGACCCATACAGCTGTTCTATACCAGAAGGAACACTCAAGAATGGACTCAAGAATGGAAAGAATGCCCTGATTAT
 GTTTCTGCTGGGAAAACAGCTGTTACTTTAATTCATCGTTTACCTCCATCGCAATACCTTATTGTATCAAGCTAACTAGCAA
 TGGTGGTACAGTGGATGAAAAGTGTCTCTGTGTGATGAAATAGTGCAACCAGATCCACCCATTGCCCTCAACTGGACTTTAC
 TGAACGTCAGTTTAACTGGGATTCATGCAGATATCCAAGTGGATGGGAAGCACCCAGCAATGCAGATATTCAGAAAGGATGG
 ATGGTCTGGAGTATGAACTTCAATACAAGAAGTAAATGAACTAAATGAAAAATGATGGACCCTATATTGACAACATCAGT
 TCCAGTGTACTCATTGAAAGTGGATAAGGAATATGAAGTGCCTGTGAGATCCAACAACGAAACTCTGGAATTTATGGCGAGT
 TCAGTGAGGTGCTCTATGTAACACTTCTCAGATGAGCCAA*aaagctt*

b) (SEQ ID NO 15)
 matgsrtslllafgllclpwlqegsaSVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFGGGSGGGSGGGSGGGSGFSG
 SEATAAILSRAPWSLQSVNPLKTNSSKEPKFTKCRSPERETFSCHWTDVHHGTKNLGPIQLFYTRRNTQEWTEWKECPDY
 VSAGENSCYFNSSFTSIAIPYCIKLTNSGGTVDEKCFVDEIVQPPPIALNWTLLNVSLTGIHADIQVRWEAPRNADIQKGM
 MVLEYELQYKEVNETKWKMDPILTTSPVYSLKVDKEYEVRVRSKQRNSGNYGEFSEVLYVTLPQMSQ*

图13

a) SEQ ID NO 70
 atggctacaggctcccggagctccctgctcctggcttttggcctgctctgctgcccctggcttcaagagggcagtgccTCTGT
 GAGTGAAATACAGCTTATGCATAACCTGGGAAAACATCTGAACTCGATGGAGAGAGTAGAATGGCTGCGTAAGAAGCTGCAGG
 ATGTGCACAATTTTGGTGGCGGAGGTAGTGGTGGCGGAGGTAGCGGTGGCGGAGGTTCTGGTGGCGGAGGTTCCgatgacgtc
 atgactaaagaggaacagatcttctctgctgcaocgtgctcagggcccagtgcgaaaaacggctcaaggaggtcctgacagagcc
 agccagcataatggaatcagacaagggatggacatctgogtccacatcaggggaagcccaggaagaataaggaatctgggaagc
 tctaccctgagctctgaggaggacaaggaggcacccactggcagcaggtacogaggggocccctgtctgocggaatgggaccac
 atcctgtgctggcogctgggggcaaccaggtgaggtggtggtgctgcccctgtcoggactacattatgactcaatcacaagg
 ccatgcctaccgacgtgtgaccgcaatggcagctgggagctgggtccctgggcacaacaggacgtgggccaactacagcaggt
 gtgtcaaatttctaccaatgagactcgtgaaocgggaggtgtttgaccgcctg
 accggtCATCATCACCATCACCAT*

b) (SEQ ID NO 17)
 matgsrtslllafgllclpwlqegsaSVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFGGGSGGGSGGGSGGGSGddv
 mtkeeqifllhraaqcekrllkevlqrpasimesdkgwtasatgkprkdkasgklypeseedkeaptgsryrgrpclpewdh
 ilcwpplgagpevvavpccdyiydfnhkghayrrcdrngswelvpghnrtwanyscvkfltnetrerevfdrlTGHHHHHH*

图14

a) SEQ ID NO 71
 atggctacaggctcccggagctccctgctcctggcttttggcctgctctgctgcccctggcttcaagagggcagtgccTCTGT
 GAGTGAAATACAGCTTATGCATAACCTGGGAAAACATCTGAACTCGATGGAGAGAGTAGAATGGCTGCGTAAGAAGCTGCAGG
 ATGTGCACAATTTTGGTGGCGGAGGTAGTGGTGGCGGAGGTAGCGGTGGCGGAGGTTCTGGTGGCGGAGGTTCCgatgacgtc
 atgactaaagaggaacagatcttctctgctgcaocgtgctcagggcccagtgcgaaaaacggctcaaggaggtcctgacagagcc
 agccagcataatggaatcagacaagggatggacatctgogtccacatcaggggaagcccaggaagaataaggaatctgggaagc
 tctaccctgagctctgaggaggacaaggaggcacccactggcagcaggtacogaggggocccctgtctgocggaatgggaccac
 atcctgtgctggcogctgggggcaaccaggtgaggtggtggtgctgcccctgtcoggactacattatgactcaatcacaagg
 ccatgcctaccgacgtgtgaccgcaatggcagctgggagctgggtccctgggcacaacaggacgtgggccaactacagcaggt
 gtgtcaaatttctaccaatgagactcgtgaaocgggaggtgtttgaccgcctg*

b) (SEQ ID NO 16)
 matgsrtslllafgllclpwlqegsaSVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFGGGSGGGSGGGSGGGSGddv
 mtkeeqifllhraaqcekrllkevlqrpasimesdkgwtasatgkprkdkasgklypeseedkeaptgsryrgrpclpewdh
 ilcwpplgagpevvavpccdyiydfnhkghayrrcdrngswelvpghnrtwanyscvkfltnetrerevfdrl*

图15

a) SEQ ID NO 72
 atgatacctgcaaaagacatggctaaagtattgattgtcatgttgcaatttgttttcttcaaaaatcggatgggaaatctgt
 taagaagagaTCTGTGAGTGAAATACAGCTTATGCATAACCTGGGAAAACATCTGAACTCGATGGAGAGAGTAGAATGGCTGC
 GTAAGAAGCTGCAGGATGTGCACAATTTTGGTGGCGGAGGTAGTGGTGGCGGAGGTAGCGGTGGCGGAGGTTCTGGTGGCGGA
 GGTTCGatgacgtcatgactaaagaggaacagatcttctctgctgcaocgtgctcagggcccagtgcgaaaaacggctcaagga
 ggtcctgacagagggccagccagcataatggaatcagacaagggatggacatctgogtccacatcaggggaagcccaggaagaata

**aggcatctgggaagctctaccctgagctctgaggaggacaaggaggcaccactggcagcaggtaocgaggggccccctgtctg
 coggaaatgggaccacatacctgtgctggcogctgggggcaocaggtaggtggtggctgtgcocctgtocggactacatttatga
 cttcaatcacaaggccatgctacccagcgtgtgacccgcaatggcagctgggagctgggtcctgggcacaacaggacgtggg
 ccaactacagcaggtgtgtcaaatctcaccaatgagactcgtgaacgggaggtgtttgacccgctgaccggtCATCATCAC
 CATCACCAT***

b) (SEQ ID NO 18)

**mipakdmakvmivmlaicfltksdgksvkkrsVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFGGGSGGGSGGGSGGG
 GSddvmtkeeqifllhraqaqcekrklevlqrpasimesdkgwtsaatsgkprkdkasgklypeseedkeaptgsryrgrpol
 pedwhilcwpplgaggevvavpcpdyiydfnhkghayrrcdrngswelvpghnrtwanysevcvklfnetrerevfdrlTGHHH
 HHH***

图16

a) SEQ ID NO 73

**atgatacctgcaaaaagacatggctaagttatgattgtcatgttgccaattgttttcttcaaaaatcggatgggaaatctgt
 taagaagagaTCTGTGAGTGAAATACAGCTTATGCATAACCTGGGAAAACATCTGAACTCGATGGAGAGAGTAGAATGGCTGC
 GTAAGAAGCTGCAGGATGTGCACAATTTGGTGGCGGAGGTAGTGGTGGCGGAGGTAGCGGTGGCGGAGGTTCTGGTGGCGGA
 GGTTCGatgaogtcatgactaaagaggaaacagatcttctctgtgcacogtgotcaggccocagtgogaaaaocggctcaagga
 ggtcctgcagagggccagccagcataatggaaacagacaaggatggacatctgogtocaocatcagggaaocccaggaagata
 aggcacatgggaagctctaccctgagctctgaggaggacaaggaggcaccactggcagcaggtaocgaggggococctgtctg
 coggaaatgggaccacatacctgtgctggcogctgggggcaocaggtaggtggtggctgtgcocctgtocggactacatttatga
 cttcaatcacaaggccatgctacccagcgtgtgacccgcaatggcagctgggagctgggtcctgggcacaacaggacgtggg
 ccaactacagcaggtgtgtcaaatctcaccaatgagactcgtgaacgggaggtgtttgacccgctg***

b) (SEQ ID NO 19)

**mipakdmakvmivmlaicfltksdgksvkkrsVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFGGGSGGGSGGGSGGG
 GSddvmtkeeqifllhraqaqcekrklevlqrpasimesdkgwtsaatsgkprkdkasgklypeseedkeaptgsryrgrpol
 pedwhilcwpplgaggevvavpcpdyiydfnhkghayrrcdrngswelvpghnrtwanysevcvklfnetrerevfdrl***

图17

a) SEQ ID NO 74

**atgatacctgcaaaaagacatggctaagttatgattgtcatgttgccaattgttttcttcaaaaatcggatgggaaatctgt
 taagaagagaTCTGTGAGTGAAATACAGCTTATGCATAACCTGGGAAAACATCTGAACTCGATGGAGAGAGTAGAATGGCTGC
 GTAAGAAGCTGCAGGATGTGCACAATTTGGTGGCGGAGGTAGTGGTGGCGGAGGTAGCGGTGGCGGAGGTTCTGGTGGCGGA
 GGTTCCTTTTCTGGAAGTGAGGCCACAGCAGCTATCCTTAGCAGAGCACCCCTGGAGTCTGCAAAGTGTAAATCCAGGCCTAAA
 GACAAATCTTCTAAGGAGCCTAAATTCACCAAGTGCCGTTACCTGAGCGAGAGACTTTTTCATGCCACTGGACAGATGAGG
 TTCATCATGGTACAAAGAACCTAGGACCCATACAGCTGTTCTATACCAGAAGGAACACTCAAGAATGGACTCAAGAATGGAAA
 GAATGCCCTGATTATGTTTCTGCTGGGGAAAACAGCTGTTACTTTAATTCATCGTTTACCTCCATCGCAATACCTTATTGTAT
 CAAGCTAAGTCAATGGTGTACAGTGGATGAAAAGTGTCTCTGTTGATGAAATAGTGCAACCAGATCCACCCATTGCC
 TCAACTGGACTTTACTGAACGTGAGTTAACTGGGATTCATGCAGATATCCAAGTGAAGTGGGAAGCACCACGCAATGCAGAT
 ATTCAGAAAGGATGGATGGTCTGGAGTATGAACTCAATACAAAGAAGTAAATGAACTAAATGGAAAATGATGGACCCTAT
 ATTGACAACATCAGTCCAGTGTACTCATTGAAAGTGGATAAGGAATATGAAGTGCCTGTGAGATCCAAACAACGAAACTCTG
 GAAATATGGCGAGTTCAGTGGGTCTCTATGTAACACTTCTCAGATGAGCCAA***

b) (SEQ ID NO 20)

**mipakdmakvmivmlaicfltksdgksvkkrsVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFGGGSGGGSGGGSGGG
 GSFSGSEATAAILSRAPWSLQSVNPLKTNSSKEPKFTKCRSPERETFSCHWTDEVHHTGNLGPILFYTRRNTQEWTEQWK
 ECPDYVSAGENSCYFNSSFTSIAIPYCIKLTNNGGTVDEKCFVDEIVQPPPIALNWTLLNVSILTGIHADIQVRWEAPRND
 IQKGMVLELEYLQYKEVNETKWKMMDFILTTSVPVYSLKVDKEYEVRVRSKQRNSGNNGYEFSEVLYVTLPQMSQ***

图18

a) SEQ ID NO 75

atgatacctgcaaaaagacatggctaaagtattgattgtcatgttggaatttgtttttcttacaaaatcggatgggaaatctgt
taagaagagaTCTGTGAGTGAAATACAGCTTATGCATAACCTGGGAAAACATCTGAACTCGATGGAGAGAGTAGAATGGCTGC
GTAAGAAGCTGCAGGATGTGCACAATTTGGTGGCGGAGGTAGTGGTGGCGGAGGTAGCGGTGGCGGAGGTTCTGGTGGCGGA
GGTTCGatgacgtcatgactaaagaggaacagatcttctgtctgcacgtgctcaggccagtgogaaaaacggctcaagga
ggtcctgcagaggccagccagcataatggaatcagacaagggatggacatctgcgtccacatcaggggaagccaggaagata

aggcatctgggaagctctaccctgagctctgaggaggacaaggaggaacccactggcagcaggtacogagggogccoctgtctg
coggaatgggaccacatctgtgtctggcogctgggggcaaccaggtgaggtggtggctgtgcctgtcoggactacaagtatga
cttcaatcacaaggccatgctaccgacgctgtgacogcaatggcagctgggagctggtgcctgggcacaacaggaagctggg
ccaactacagcaggtgtgtcaaatctcaccacatgagactogtgaacgggaggtgtttgaccgctgGGTGGCGGAGGTAGT
GGTGGCGGAGGTAGCGGTGGCGGAGGTTCTGGTGGCGGAGGTTCTCTGGAAGTGAGGCCACAGCAGCTATCCTTAGCAG
AGCACCTGGAGTCTGCAAAGTGTAAATCCAGGCCTAAAGACAAATCTCTAAGGAGCCTAAATTCACCAAGTGCCGTTTAC
CTGAGCGAGAGACTTTTTCATGCCACTGGACAGATGAGGTTTCATCATGGTACAAAGAACCTAGGACCATACAGCTGTTCTAT
ACCAGAAGGAACACTCAAGAATGGACTCAAGAATGGAAAGAATGCCCTGATTATGTTTCTGCTGGGAAAACAGCTGTTACTT
TAATTCATCGTTTACCTCCATCGCAATACCTTATTGTATCAAGCTAACTAGCAATGGTGGTACAGTGGATGAAAAGTGTCTT
CTGTTGATGAAATAGTGAACCCAGATCCACCCATTGCCCTCACTGGACTTFACTGAACGTCAGTTTAACTGGGATTATGCA
GATATCCAAGTGAGATGGGAAGCACCAGCAATGCAGATATTCAGAAAAGGATGGATGGTCTGGAGTATGAACTTCAATACAA
AGAAGTAAATGAACTAAATGAAAATGATGGACCCTATATTGACAACATCAGTCCAGTGTACTCATTGAAAGTGGATAAGG
AATATGAAGTGCCTGTGAGATCCAACAACGAAACTCTGGAATATGGCGAGTTCAGTGGGTGCTCTATGTAACACTTCT
CAGATGAGCCAA*

b) (SEQ ID NO 21)

mipakdmakvmivmlaicfltksdgksvkkkrSVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFSGGGSGGGSGGGSGGG
GSddvntkeeqifllhraaqcekrklevlqrpasimesdkgwtsastsgkprkdkasgklypeseedkeaptgsryrgrpcl
pewdhilcwlpgapgevvavpdpdykydfnhkghayrrcdrngswelvpghnrtwanysecvklfnetrerevfdrlGGGGS
GGGGSGGGSGGGSGFSGSEATAAILSRAFWLSQSVNPGLKTNSSKEPKFTKCRSPERETFCHWTVDEHHGKTNLGPQLFY
TRRNTQEWTEWKECPDYVSAGENSCYFNSSFTSIAI PYCIKLT SNGGTVDEKCFVDEIVQDPPIALNWTLNLVSLTGIHA
DIQVRWEAPRNADIQKGMVLEYELQYKEVNETKWKMDPIITTSVPVYSLKVDKEYEVRVRSKQRNSGNYGEFSEVLYVTLF
QMSQ*

图19

a) SEQ ID NO 39
 atggtctacaggctcccggaagctccctgctcctggcttttggcctgctctgctgcctgacctggettaagagggcagtgccTCTGT
 GAGTGAATACAGCTTATGCATAACCTGGGAAAACATCTGAACTCGATGGAGAGAGTAGAATGGCTGCGTAAGAAGCTGCAGG
 ATGTGCACAATTTGGTGGCGGAGGTAGTGGTGGCGGAGGTAGCGGTGGCGGAGGTTCTGGTGGCGGAGGTTCCGatgacgctc
 atgactaaagaggaacagatcttctgctgcaaccgtgctcagggccagtgogaaaaacggctcaaggaggtcctgcaaggcc
 agccagcataatggaatcagacaaggatggacatctgctgctccacatcagggaaagccaggaagataaggcatctggaagc
 tctacccctgagctctgaggaggacaaggaggcaccacatggcagcaggtaaccgagggcgccccctgctgcccgaatgggaccac
 atcctgtgctggccgctggggggcaccaggtgaggtggggctgctgcoctgtcoggactacaagtatgacttoaatcaaaaag
 ccatgcoctacagcagctgtgaccgcaatggcagctgggagctggctggccacaacaggacgtgggccaactacagcaggt
 gtgtcaaatctcaccatgagactcgtgaacgggaggtgtttgacccctgGGTGGCGGAGGTAGTGGTGGCGGAGGTAGC
 GGTGGCGGAGGTTCTGGTGGCGGAGGTTCCCTTTCTGGAAGTGAGGCCACAGCAGCTATCCTTAGCAGAGCACCTGGAGTCT
 GCAAAGTGTAAATCCAGGCCTAAAGACAAATCTTCTAAGGAGCCTAAATTCACCAAGTGCCGTTACCTGAGCGAGAGACTT
 TTTTCATGCCACTGGACAGATGAGGTTTCATCATGGTACAAAGAACCTAGGACCCATACAGCTGTCTATACAGAAGGAACACT
 CAAGAATGGACTCAAGAATGGAAGAATGCCCTGATTATGTTTCTGCTGGGAAAACAGCTGTTACTTTAATTCATCGTTTAC
 CTCCATCGCAATACCTTATTGTATCAAGCTAACTAGCAATGGTGGTACAGTGGATGAAAAGTGTCTCTGTGTGATGAAATAG
 TGCAACCAGATCCACCCATTGCCCTCAACTGGACTTTACTGAACGTCAGTTAACTGGGATTTCATGCAGATATCCAAGTGAGA
 TGGGAAGCACCAAGCAATGCAGATATTCAGAAAGGATGGATGGTCTGGAGTATGAACTTCAATACAAAGAAGTAAATGAAAC
 TAAATGGAAGATGATGGACCCTATATGACAACATCAGTTCAGTGTACTCATTGAAAGTGGATAAGGAATATGAAGTGCCTG
 TGAGATCCAACAACGAAACTCTGGAATATATGGCGAGTTCAGTGGGTGCTCTATGTAACACTTCTCAGATGAGCCAA*

b) (SEQ ID NO 22)
 matgsrtslllafgllclpwlqegsaSVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNF~~GGGSGGGSGGGSGGGSGGG~~ddv
 mtkeeqifllhraqaqcekrklevlqrpasimesdkgwtsastsgkprkdkasgklypeseedkeaptgsryrgrpclpewdh
 ilcwpलगवववपपdykydfnhkghayrrodrngswelvpghnrtwanysecvklfnetrerevfdrlGGGSGGGSGGG
 GGGSGGGSGGFSGSEATAILSRAPWSLQSVNPGLKTNSSKEPKFTKCRSPERETF SCHWTDEVHHTKLNLPQLFYTRRNT
 QEWTEWKECPDVSAGENSCYFNSSFTSIAIPYCIKLTNSGGTVDEKCFVDEIVQDPPIALNWTLLNVS LTIHADIQVR
 WEAPRNADIQKGMVLEYELQYKEVNETKWKMDPILTT SVPVYSLKVDKEYEVRVRSKQRNSGNYGEFSEVLYVTLPQMSQ*

图20

a) SEQ ID NO 38
 atgataacctgcaaaaagacatggctaaagtattgattgtcatgttgcaattgttttcttcaaaaatcggatgggaaatctgt
 taagaagagaTCTGTGAGTGAATACAGCTTATGCATAACCTGGGAAAACATCTGAACTCGATGGAGAGAGTAGAATGGCTGC
 GTAAGAAGCTGCAGGATGTGCACAATTTGGTGGCGGAGGTAGTGGTGGCGGAGGTAGCGGTGGCGGAGGTTCTGGTGGCGGGA
 GGTTCGatgacgctcactgactaaagaggaacagatcttctgctgcaaccgtgctcagggcccagtgogaaaaacggctcaagga
 ggtcctgcaaggccagccagcataatggaatcagacaaggatggacatctgctgctccacatcagggaaagccaggaagata
 aggcatactgggaagctctaccctgagctctgaggaggacaaggaggcaccacatggcagcaggtaaccgagggcgccccctgctct

cgggaatgggaccacatcctgtgctggccgctggggggcaccaggtgaggtggggctgtgcoctgtcoggactacaagatga
 ctcaaatcaaaaaggccatgctaccgacgctgtgaccgcaatggcagctgggagctggctgcoctgggcaaacaggacgtggg
 ccaactacagcaggtgtgtcaaatctcaccatgagactcgtgaacgggaggtgtttgacccctgaccgggtCATCATCAC
 CATCACCAT*

b) (SEQ ID NO 23)
 mipakdmakvmlaifltsdgsksvkrSVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNF~~GGGSGGGSGGGSGGGSGGG~~
 GSDdvm~~mtkeeqifllhraqaqcekrklevlqrpasimesdkgwtsastsgkprkdkasgklypeseedkeaptgsryrgrpcl~~
 pwhdhilcwpलगवववपपdykydfnhkghayrrodrngswelvpghnrtwanysecvklfnetrerevfdrlTGH
 HHH

图21

a) SEQ ID NO 6
 atggctacaggctccccggacgtccctgctcctggcttttggcctgctctgctgcccctggcttcaagagggcagtgccTCTGT
 GAGTGAAATACAGCTTATGCATAACCTGGGAAAACATCTGAACTCGATGGAGAGAGTAGAATGGCTGCGTAAGAAGCTGCAGG
 ATGTGCACAATTTTGGTGGCGGAGGTAGTGGTGGCGGAGGTAGCGGTGGCGGAGGTTCTGGTGGCGGAGGTCCgatgagctc
 atgactaaagaggaaacagatcttctctgctgcaocgtgtcagggccagtgogaaaaacggotcaaggaggctctgcagaggcc
 agccagcataatggaatcagacaagggaatggacatctgctgcccacatcaggggaagcccaggaaaagataaggcatctgggaagc
 tctaccctgagctgaggaggacaaggaggcacccactggcagcaggtaccgaggggcccctgtctgocggaaatgggaccac
 atcctgtgtggcogctggggcaccaggtgaggtgggtgctgtgcoctgtccggactacaagtatgacttcaatcacaagg
 ccatgcctaccgacgctgtgacogcaatggcagctgggagctgggtgcoctgggcacaacaggacgtgggccaactacagcgagt
 gtgtcaaatctcaccaatgagactcgtgaacgggaggtgtttgaccgctgaccggtCATCATCACCATCACCAT*

b) (SEQ ID NO 24)
 matgsrtslllafgllclpwlqeqsaSVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFGGGSGGGGSGGGGSGGGGSDdv
 mtkeeqifllhraqaqcekrllkevlqrpasinesdkwtsastsgkprkdkasgklypeseedkeaptgsryrgrpclpewdh
 ilcwplgapgevavpccpdykydfnhkghayrrcdrngswelvpghnrtwanysecvklftnetrerevfdrlTGHHHHHH*

图22

(SEQ ID NO 9)

SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNFVALGAPLAPRDAGSQRPKKEDNVLVESHEKSLGE
 ADKADVNVLTAKASQ

图23

(SEQ ID NO 40): PTHrP (1-36)

AVSEHQLLHDKGKSIQDLRRRFFLHHLIAEIHTAEI

图24

(SEQ ID NO 41): PTHrP信号序列

MQRRLVQQWSVAVFLLSYAVPSCG

图25

(SEQ ID NO 4): PTHrP前肽

rsveglsrri

图26

A

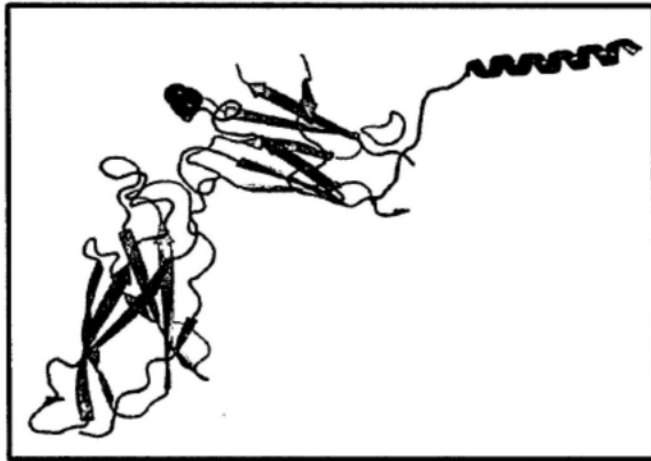
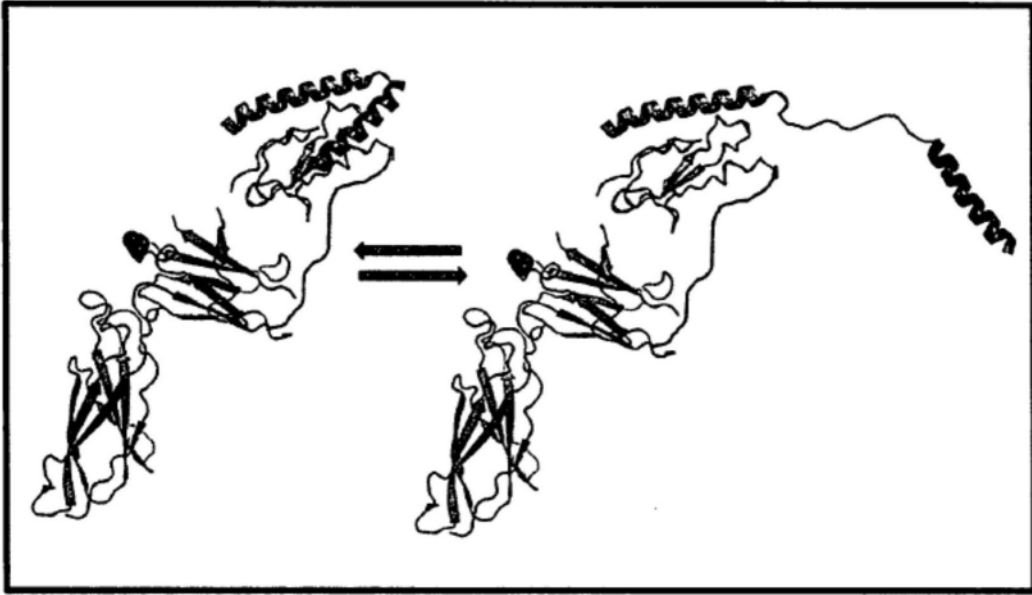


图27

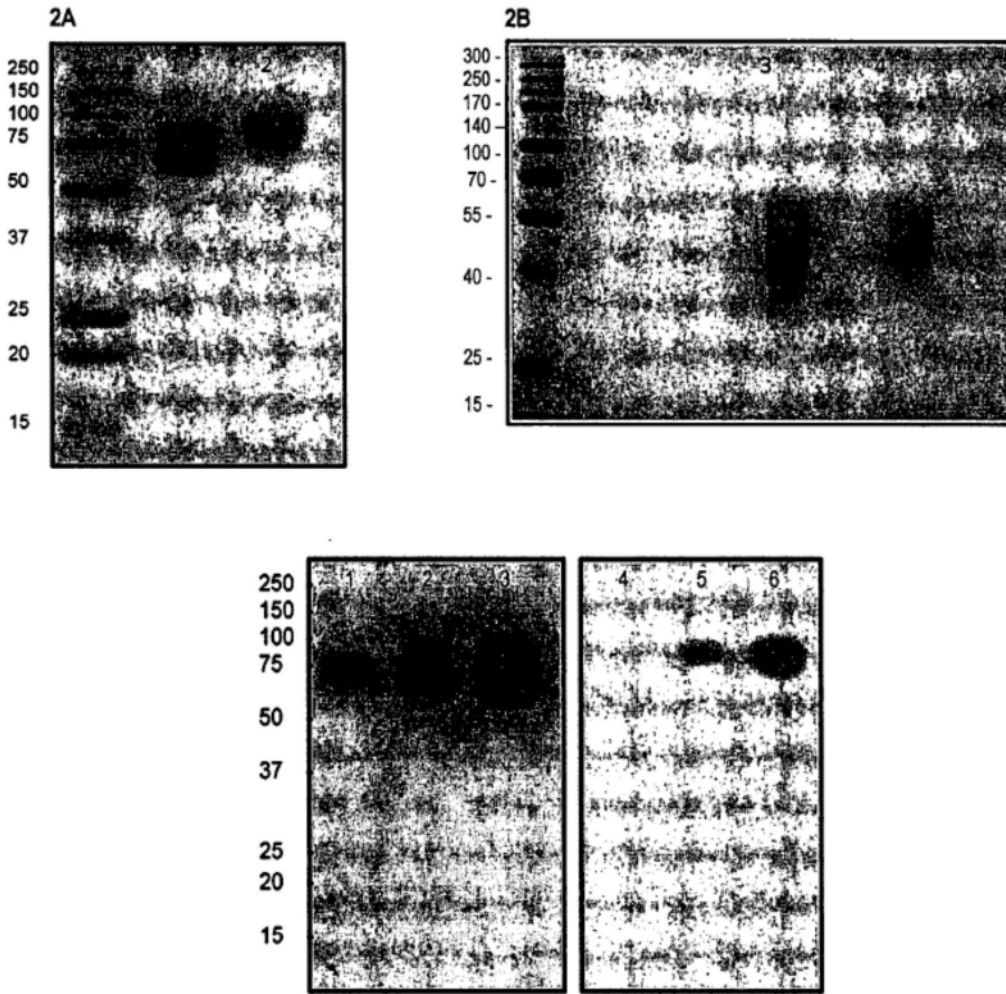
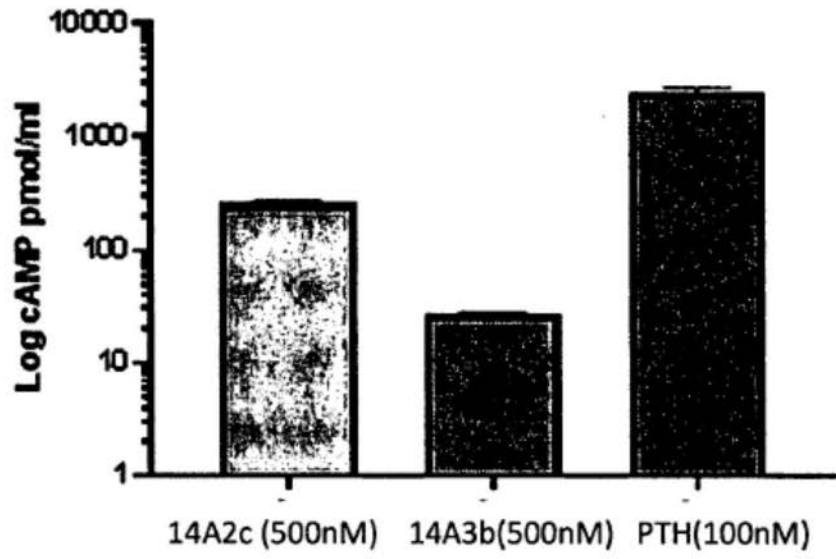


图28

A



B

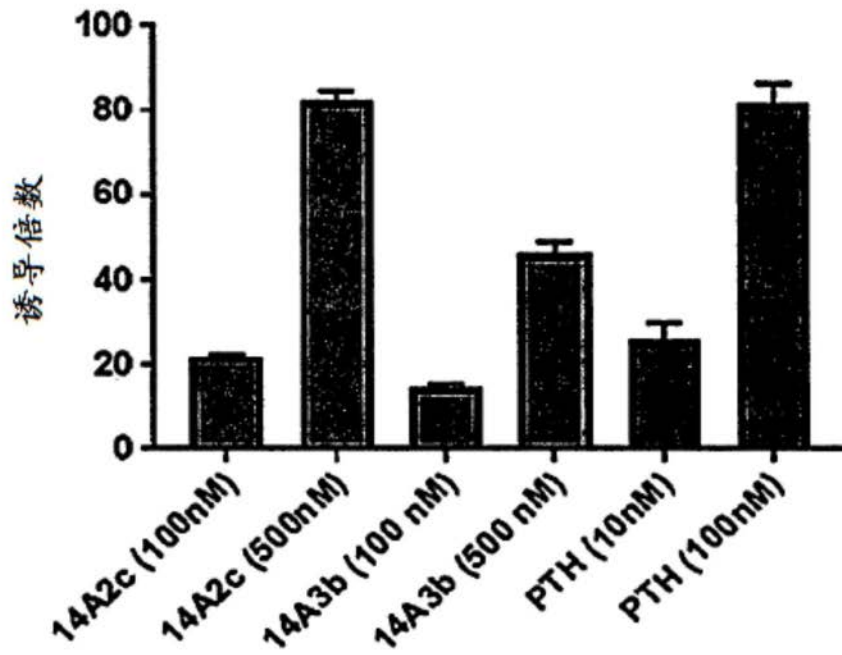
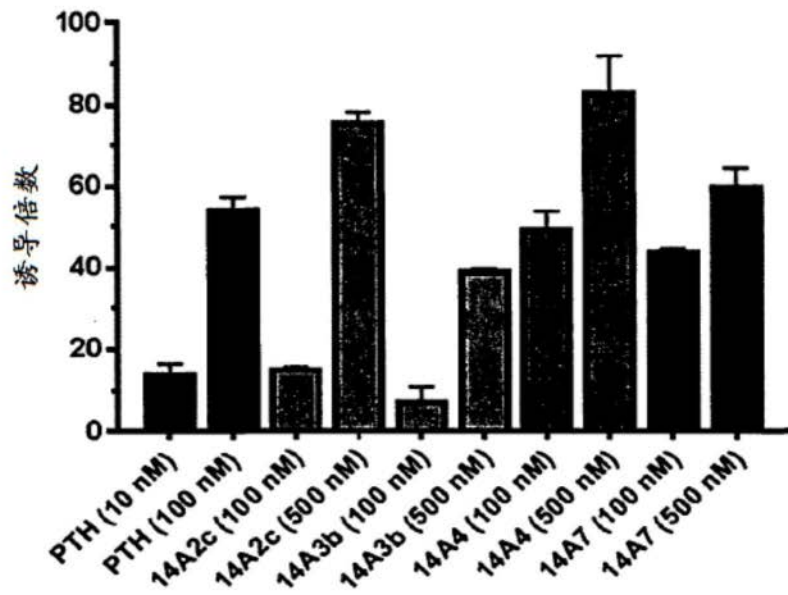


图29

C



D

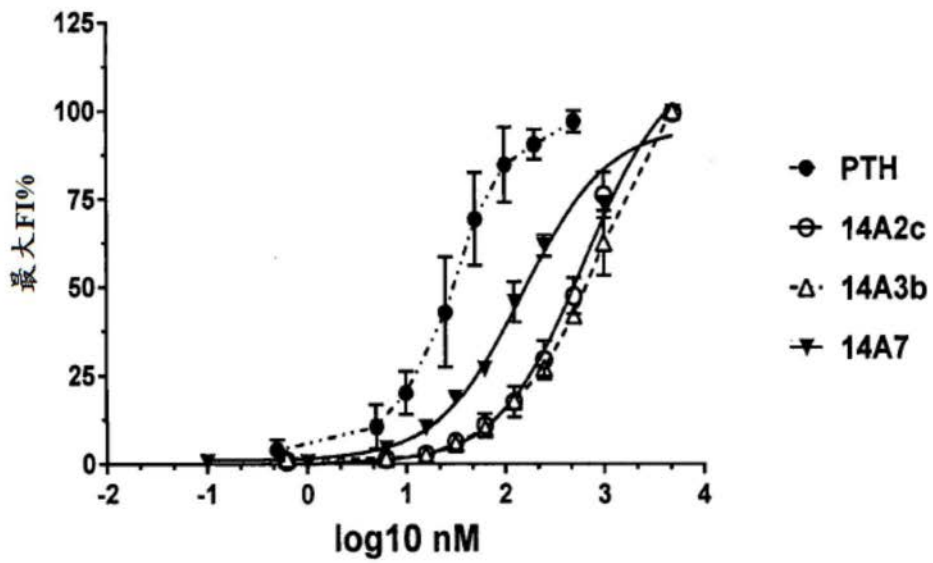


图29续