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(54)发明名称

制备用于制备艾美拉唑钠盐的结晶修饰物的新方法

(57)摘要

本发明涉及制备用于制备艾美拉唑钠盐的结晶修饰物的新方法。此外，本发明也涉及用新的结晶修饰物治疗胃肠道病症，含有它们的药物组合物以及结晶修饰物，等等。

1. 制备艾美拉唑钠盐的方法，基本包括以下步骤：

i) 在甲苯中溶解艾美拉唑中性形式；

ii) 加入额外的合适溶剂，所述溶剂选自甲醇、乙醇和异丙醇；

iii) 加入约 1 摩尔当量的合适的碱 B 的钠盐；

iv) 使艾美拉唑钠盐结晶，并且分离形成的盐。

2. 权利要求 1 的方法，其中 B 是氢氧化物。

3. 权利要求 1 的方法，其中 B 是作为水溶液添加的。

4. 可以通过基本包括以下步骤的方法获得的艾美拉唑钠盐：

i) 在甲苯中溶解艾美拉唑中性形式；

ii) 加入额外的合适溶剂，所述溶剂选自甲醇、乙醇和异丙醇；

iii) 加入约 1 摩尔当量的合适的碱 B 的钠盐；

iv) 使艾美拉唑钠盐结晶，并且分离形成的盐。

5. 权利要求 4 的盐，其中 B 是氢氧化物。

6. 权利要求 4 的盐，其中 B 是作为水溶液添加的。

7. 艾美拉唑钠盐修饰物 C，其特征在于具有 d- 值为 15.7、7.9、6.1、5.3、4.56、3.59、3.49、3.17Å 的峰的 X 线粉末衍射图和 / 或基本如图 1 所定义的 X 线粉末衍射图。

8. 艾美拉唑钠盐修饰物 E，其特征在于具有 d- 值为 15.5、11.8、10.1、6.4、6.2、5.4、5.2、4.28、3.46、3.40、3.12Å 的峰的 X 线粉末衍射图和 / 或基本如图 2 所定义的 X 线粉末衍射图。

9. 艾美拉唑钠盐修饰物 H，其特征在于具有 d- 值为 22.0、18.1、11.1、6.3、5.7、5.3、4.92、4.56、3.73Å 的峰的 X 线粉末衍射图和 / 或基本如图 3 所定义的 X 线粉末衍射图。

10. 一种药物制剂，包含与至少一种药学可接受的赋形剂混合的权利要求 4 － 9 的任意一项所定义的艾美拉唑钠盐。

11. 一种治疗方法，包括给有需要的患者施用治疗有效量的权利要求 4 － 9 的任意一项所定义的艾美拉唑钠盐。

制备用于制备艾美拉唑钠盐的结晶修饰物的新方法

[0001] 本申请是2005年6月20日提交的题为“制备用于制备艾美拉唑钠盐的结晶修饰物的新方法”、国家申请号为200580020874.2(PCT / SE2005 / 000954)的发明专利申请的分案申请。

技术领域

[0002] 本发明涉及制备用于制备艾美拉唑钠盐的结晶修饰物的新方法。进一步,本发明也涉及用新的结晶修饰物(crystal modifications)治疗胃肠病症、含有它们的药物组合物,和结晶修饰物等。

背景技术

[0003] 奥美拉唑,即,化合物5-甲氧基-2-[[(4-甲氧基-3,5-二甲基-2-吡啶基)甲基]亚磺酰]-1H-苯并咪唑及其治疗可接受的盐描述于EP5129。奥美拉唑的一些特定碱性盐公开于EP124495。

[0004] 奥美拉唑是一种亚砜,并且是一种手性化合物,其中硫原子是立体发生中心。因此,奥美拉唑是其两种单对映异构体,即奥美拉唑的R-和S-对映异构体的外消旋混合物,S-对映异构体具有通用名艾美拉唑。艾美拉唑最近作为新一代的质子泵抑制剂而投放市场,其中活性药物成分是艾美拉唑镁盐。与以前的药物相比,艾美拉唑在GERD的治疗中表现出了改进。

[0005] 通过非盐形式的(+)-对映异构体的N-烷基化衍生物的X-线研究确定了奥美拉唑的对映异构体的绝对构型。发现非盐形式的(+)-对映异构体和非盐形式的(-)-对映异构体分别具有R和S构型,也发现镁盐的(+)-对映异构体和镁盐的(-)-对映异构体分别具有R和S构型。对这些对映异构体的每一种进行旋光度测量的条件描述于WO94 / 27988。

[0006] 奥美拉唑的单对映异构体的盐及其制备公开于WO94 / 27988。这些化合物具有改进的药代动力学和代谢特性,将得到改进的治疗谱,如低度的个体间变异。

[0007] WO96 / 02535公开了制备奥美拉唑的单对映异构体及其盐,包括钠盐的方法。

[0008] WO98 / 54171公开了制备三水合奥美拉唑的S-对映异构体的镁盐的方法,其中S-奥美拉唑的钾盐用作中间体。

[0009] WO00 / 44744公开了不含甲醇的S-奥美拉唑的钾盐。

[0010] WO03 / 089408(Sun Pharmaceutical Industries Limited)公开了艾美拉唑的碱金属或碱土金属盐,包括钠盐。

发明内容

[0011] 已经出乎意料地发现,在制备艾美拉唑钠盐的过程中,形成了许多新的的结晶修饰物。这些新的中间体中的一些是稳定的,因此可以分离和表征。其它的寿命太短,以至于不能表征,还有其它一些是晶体,但是处于潮湿状态,但是在干燥后立即转化为多种无水形式,因此难以表征。在干燥过程中,这些修饰物可以经过许多具有较少晶体含量的其它形

式。可以通过本发明的方法获得所有结晶修饰物。

[0012] 本发明的方法通过使新的结晶修饰物能够以更有效和生效的途径制备艾美拉唑钠,最佳利用了新的结晶修饰物和它们的特性。

[0013] 本方法是有利的,因为它使得能够采用具有良好过滤特性的结晶修饰物以高产率和良好质量直接从相应钾盐制备艾美拉唑钠盐。其它优点是高度可再现性,良好的加工能力,包括安全性,和在整个过程中使用一种主要的溶剂体系,所述过程优选包括氧化步骤和随后的步骤和操作。更优选地,在本发明中采用与制备艾美拉唑钾盐中使用的相同溶剂体系。

[0014] 本发明的方法基本包括以下步骤 :

[0015] i) 在合适的溶剂 S_1 中溶解艾美拉唑中性形式 ;

[0016] ii) 加入额外的合适溶剂 S_2 ;

[0017] iii) 加入约 1 摩尔当量的合适的碱 B 的钠盐 ;

[0018] iv) 使艾美拉唑钠盐结晶,并且分离形成的盐。

[0019] 附图简述

[0020] 图 1 是艾美拉唑钠盐修饰物 C 的 X- 线粉末衍射图。

[0021] 图 2 是图 1 的放大版。

[0022] 图 3 是艾美拉唑钠盐修饰物 E 的 X- 线粉末衍射图。

[0023] 图 4 是图 3 的放大版。

[0024] 图 5 是艾美拉唑钠盐修饰物 H 的 X- 线粉末衍射图。

具体实施方式

[0025] 在本发明的一种实施方案中,艾美拉唑中性形式是从相应的艾美拉唑钾盐制备的,并且或多或少地立即用于上文定义的后续步骤。如果如此,可以通过现有技术描述的任何方法制备艾美拉唑钾盐,然后悬浮于溶剂 S_1 中。此后应该调节 pH,以制备中性形式的艾美拉唑。可以通过添加大约 1 摩尔当量的合适酸 HA,优选 HA 水溶液而进行该 pH 调节。所述酸 HA 的实例包括但不限于所有形成水溶性钾盐的矿物酸,如盐酸和乙酸。此后弃去水相,任选用水或盐水洗涤有机相。于是艾美拉唑中性形式可以或多或少地立即用于上文定义的步骤 ii)-iv)。

[0026] 在本发明的另一种实施方案中,艾美拉唑中性形式是从相应的艾美拉唑镁盐制备的,并且或多或少地立即用于上文定义的后续步骤。

[0027] 在本发明的一种实施方案中,溶剂 S_1 是甲苯。

[0028] 在本发明的一种实施方案中,溶剂 S_2 是甲醇。

[0029] 在本发明的一种实施方案中,溶剂 S_2 是乙醇。

[0030] 在本发明的一种实施方案中,溶剂 S_2 是异丙醇 (isopropylalkohol)。

[0031] 在本发明的一种实施方案中,碱 B 是氢氧化物。

[0032] 在本发明的一种实施方案中,碱 B 是作为水溶液添加的。

[0033] 在本发明的一种实施方案中,步骤 iv) 的结晶是通过加入晶种而起始的。

[0034] 在本发明的一种实施方案中,上述步骤 iii) 是在步骤 ii) 之前进行的。

[0035] 在步骤 iv) 中分离的艾美拉唑钠盐将依赖于使用哪一种溶剂 S_2。此后干燥分离的

艾美拉唑钠盐，并且在干燥过程中将大多数溶剂 S_2 和一些额外的水一起除去。根据实施例的分离的艾美拉唑钠盐是晶体，同时处于潮湿和湿润状态，但在干燥后立即转化为各种无水形式。在干燥过程中，分离的结晶修饰物可以经过许多晶体含量较低的其它形式。

[0036] 可以适当地用常规干燥方法干燥可以通过本发明的方法获得的所有艾美拉唑钠盐，以便将它们转化为各种无水形式。干燥过程将略微影响艾美拉唑钠修饰物 C、E 和 H 的 X 线衍射图中峰的位置和强度。为了完全重现图 1-3 的衍射图，重要的是仔细遵照实施例中的程序。对其的微小偏离都可能会影响 X 线衍射图中峰的位置和强度。

[0037] 因此，由于本发明的结晶修饰物的良好过滤特性，它们最适于用作中间体。但是，它们都可以完全干燥，并且配制为药物组合物，用于需要其的患者中。

[0038] 当将甲醇用作溶剂 S2 时，则艾美拉唑钠盐修饰物 C 是分离的结晶修饰物。

[0039] 当将乙醇用作溶剂 S2 时，则艾美拉唑钠盐修饰物 E 是分离的结晶修饰物。

[0040] 当将异丙醇用作溶剂 S2 时，则艾美拉唑钠盐修饰物 H 是分离的结晶修饰物。

[0041] 为了避免疑问，应该理解，在本说明书中，当用“上文定义的”来定义加工步骤或相似活动时，该步骤包括第一次出现的和最宽的定义，以及该步骤的每一个和全部其它定义。

[0042] 应该理解，用于本说明书中的短语“或多或少地立即”表示后续步骤或活动应该在一定时间进行，以避免活性化合物的降解。因此，该后续步骤可以在相当晚的时间进行，前提是必须小心避免活性化合物的降解。

[0043] 合适的溶剂 S_1 包括但不限于甲苯。

[0044] 合适的溶剂 S_2 包括但不限于甲醇、乙醇和异丙醇。

[0045] 合适的碱 B 包括但不限于氢氧化物、甲氧基金属和乙氧基金属，优选是作为水溶液添加的。

[0046] 本发明的另一目的是提供艾美拉唑钠盐的新的稳定的结晶修饰物。艾美拉唑钠盐可以以一种以上的结晶修饰物的形式存在。结晶修饰物或形式在下文中称作艾美拉唑钠盐修饰物 C、E 和 H。符号 C、E 和 H 与产生结晶修饰物的时间相关，而与它们的相对热力学稳定性无关。

[0047] 本发明的一方面是提供艾美拉唑钠盐修饰物 C。

[0048] 艾美拉唑钠盐修饰物 C 的特征在于提供图 1 所示的 X 线粉末衍射图，基本表现出具有以下 d- 值和强度的主峰 ；

[0049]

修饰物 C	
d-值 (Å)	相对强度
15.7	vs
7.9	s
6.1	m
5.3	m
4.56	w
3.59	w
3.49	w
3.17	w

[0050] 用从布拉格公式和强度计算出的 d- 值鉴定的峰是从艾美拉唑钠盐修饰物 C 的衍射图提炼的。仅仅对最特征性的、显著的、独特的和 / 或可再现的主峰进行了制表，但也可用常规方法从衍射图提炼其它峰。在大多数情况下，这些可再现和处于误差限内的主峰的存在足够确定所述结晶修饰物的存在。相对强度的可靠性较低，采用了以下定义代替数字值；

[0051]

vs (非常强):	>15% 相对强度
s (强):	7-15% 相对强度
m (中等):	3-7% 相对强度
w (弱):	1-3% 相对强度
vw (非常弱):	<1% 相对强度

[0052] ＊相对强度是从用可调节的狭缝测量的衍射图得到的。

[0053] 本发明的另一方面是提供艾美拉唑钠盐修饰物 E。

[0054] 艾美拉唑钠盐修饰物 E 的特征在于提供图 3 所示的 X 线粉末衍射图，基本表现出具有以下 d- 值和强度的主峰；

[0055]

修饰物 E	
d-值 (Å)	相对强度
15.5	vs
11.8	w
10.1	w
6.4	w
6.2	m
5.4	w
5.2	m
4.28	w
3.46	w
3.40	w
3.12	w

[0056] 用从布拉格公式和强度计算出的 d- 值鉴定的峰是从艾美拉唑钠盐修饰物 E 的衍射图提炼的。仅仅对最特征性的、显著的、独特的和 / 或可再现的主峰进行了制表，但也可用常规方法从衍射图提炼其它峰。在大多数情况下，这些可再现和处于误差限内的主峰的存在足够确定所述结晶修饰物的存在。相对强度的可靠性较低，采用了以下定义代替数字值；

[0057]

vs (非常强): >15% 相对强度

s (强): 8-15% 相对强度

m (中等): 5-8% 相对强度

w (弱): 1-5% 相对强度

vw (非常弱): <1% 相对强度

[0058] * 相对强度是从用可调节的狭缝测量的衍射图得到的。

[0059] 本发明的另一方面是提供艾美拉唑钠盐修饰物 H。

[0060] 艾美拉唑钠盐修饰物 H 的特征在于提供图 5 所示的 X 线粉末衍射图，基本表现出具有以下 d- 值和强度的主峰；

[0061]

修饰物 H	
d-值 (Å)	相对强度
22.0	vs
18.1	w
11.1	m
6.3	w
5.7	m
5.3	m
4.92	s
4.56	m
3.73	m

[0062] 用从布拉格公式和强度计算出的 d- 值鉴定的峰是从艾美拉唑钠盐修饰物 H 的衍射图提炼的。仅仅对最特征性的、显著的、独特的和 / 或可再现的主峰进行了制表，但也可用常规方法从衍射图提炼其它峰。在大多数情况下，这些可再现和处于误差限内的主峰的存在足够确定所述结晶修饰物的存在。相对强度的可靠性较低，采用了以下定义代替数字值 ;

[0063]

vs (非常强): >50% 相对强度
s (强): 27-50% 相对强度
m (中等): 11-27% 相对强度
w (弱): 3-11% 相对强度
vw (非常弱): <3% 相对强度

[0064] * 相对强度是从用可调节的狭缝测量的衍射图得到的。

[0065] 可以通过溶剂蒸发、降温和 / 或添加反溶剂 (即晶体修饰物在其中难溶的溶剂) 而在溶剂体系中达到超饱和，从而可以实现从包含多种溶剂的合适溶剂体系结晶本发明的结晶修饰物。

[0066] 脱水物还是溶剂合物结晶与特定条件下各个结晶修饰物的动力学和平衡条件相关。因此，如本领域技术人员可以理解的，获得的结晶修饰物依赖于结晶过程的动力学和热力学。在某些热力学条件下 (溶剂体系、温度、压力和本发明化合物的浓度)，一种结晶修饰物可能比另一种 (或实际上其它任何一种) 更稳定。但是，具有相对低的热力学稳定性的结晶修饰物可能是动力学有利的。因此，此外，动力学因素，如时间、杂质谱、搅拌、晶种的存在与否等，也可能影响哪一种结晶修饰物将结晶。

[0067] 为了确保在基本不含其它结晶修饰物的条件下制备特定结晶修饰物，优选通过加

入需要的结晶修饰物的晶种而进行结晶。这特别适用于实施例中描述的每一种特定结晶修饰物。

[0068]　可以根据本发明获得的艾美拉唑钠盐修饰物C、E和H基本不含其它晶体和非晶体形式的艾美拉唑钠盐。应该理解，术语“基本不含其它晶体和非晶体形式的艾美拉唑钠盐形式”表示需要的艾美拉唑晶体形式含有少于15%，优选少于10%，更优选少于5%的任何其它形式的艾美拉唑钠盐形式。

[0069]　本发明的结晶修饰物可有效用作胃酸分泌抑制剂，因此可以用作抗溃疡剂。更广义地，它们可以用于预防和治疗哺乳动物，特别是人的胃酸相关状况，包括，例如，返流性食管炎、胃炎、十二指肠炎、胃溃疡和十二指肠溃疡。此外，它们可以用于治疗需要胃酸抑制作用的其它胃肠道病症，如进行NSAID治疗的患者、患有非溃疡性消化不良的患者，患有有症状的胃－食管返流疾病的患者，和患有胃泌素瘤的患者。它们也可以用于加强监护的患者、患有急性上消化道出血的患者、用于手术前和手术后的患者以预防胃酸吸入、预防和治疗应激性溃疡和哮喘，以及用于改进睡眠。此外，本发明的结晶修饰物可以用于治疗牛皮癣和用于治疗幽门螺杆菌感染和相关疾病。本发明的结晶修饰物也可以用于治疗包括人的哺乳动物的炎性状况。

[0070]　可以用任何合适的施用途径给患者提供有效剂量的结晶修饰物。例如，可以使用口服或肠胃外制剂，包括静脉内注射等。剂型包括胶囊、片剂、分散体、悬浮液、溶液等。

[0071]　进一步提供了包含作为活性成分的本发明的结晶修饰物的药物组合物，所述结晶修饰物与药学可接受的载体、稀释剂或赋形剂组合，并任选与其它活性药物成分组合。包含其它治疗成分的组合物在治疗上文列出的状况中是感兴趣的。本发明也提供了结晶修饰物在制备用于所述状况的药物中的用途，以及治疗胃酸相关状况的方法，该方法包括给患有所述状况的受试者施用药学有效量的结晶修饰物。

[0072]　本发明的组合物包括适于口服、静脉内或肠胃外施用的组合物。最优选的途径是静脉内途径。组合物可以方便地以单位剂型存在，并且可以通过盖伦药学领域的任何方法制备。

[0073]　在本发明的实施中，最合适的施用途径和治疗剂量强度将依赖于要治疗的疾病的性质和严重程度。剂量和给药频率也根据各个患者的年龄、体重和反应而改变。对于具有卓－艾综合征的患者，可能需要特别的要求，如比通常的患者需要更高的剂量。儿童和肝脏疾病患者通常将从在某种程度上低于平均值的剂量受益。因此，在某些状况中，可能必须使用在下文指出的范围之外的剂量，例如，长期治疗可能要求较低的剂量。所述较高和较低剂量在本发明的范围内。所述每日剂量将在5mg-300mg之间改变。

[0074]　通常，本发明的化合物的合适口服剂型可以覆盖每日总剂量为5mg-300mg的剂量范围，以单一剂量或等分剂量施用。优选的剂量范围是10mg-80mg。

[0075]　可以根据常规技术，将本发明的化合物作为活性成分与药物载体紧密混合，如WO96 / 01623和EP0247983中描述的口服剂型，在此全文引入所述文献作为参考。

[0076]　也可以使用包含本发明的化合物和其它活性成分的组合制剂。所述活性成分的实例包括但不限于抗细菌化合物、非甾体类抗炎剂、抗酸剂、藻酸盐和促动力剂。

[0077]　可以在配制为合适的药物制剂前进一步加工本发明的化合物。例如，可以将结晶修饰物碾碎或研磨成更小的颗粒。

[0078] 为了避免疑问,“治疗”包括对状况进行的治疗性处理和预防。

[0079] 样品中其它物质,如药物赋形剂的存在,在通过X线粉末衍射表征时当然会掩盖上述任意表征的结晶修饰物中的一些小峰。单独的这一事实当然不能证明样品中不存在结晶修饰物。在所述情况下,必须采用应有的注意,并且X线粉末衍射图中基本所有主峰的存在可能足够表征结晶修饰物。因此,优选在不存在其它物质的条件下分析本发明的结晶修饰物。

[0080] 通过以下实施例说明本发明,但不以任何方式限制。

[0081] 实施例

[0082] 通用程序

[0083] 在根据标准方法制备的样品上进行X线粉末衍射分析(XRPD),所述方法例如以下文献描述的那些:Giacovazzo,C.et al(1995),Fundamentals of Crystallography,Oxford University Press;Jenkins,R.and Snyder,R.L.(1996),Introduction to X-Ray Powder Diffractometry,John Wiley&Sons,New York;Bunn,C.W.(1948),Chemical Crystallography,Clarendon Press,London;或Klug,H.P.&Alexander,L.E.(1974),X-ray Diffraction Procedures,John Wiley and Sons,New York。用Philips X'Pert MPD进行X线衍射分析16分钟,从1-40° 2θ。在没有内部参照的条件下分析样品,因为加样可能影响制备样品所花费的时间,因此影响X线衍射图中的位置和强度。基于以前的经验(-0.05° 2θ)调节测量的峰值。此后进行d-值的计算。

[0084] XRPD距离值可能在最后一位小数位上以±2的范围改变。

[0085] 实施例1.1

[0086] <u>制备艾美拉唑钠盐修饰物C</u>

[0087] 将艾美拉唑-K(11.89g)溶解于水(50ml),加入甲苯(80ml)。然后,通过加入乙酸(5.89ml,25% v / v)将pH调节为大约7。将两相混合10分钟,然后使其分离。除去水相,用NaCl水溶液(50ml,10%)洗涤剩余的有机相。相分离后,将甲醇(4.24ml)加入甲苯相,然后加入1eq NaOH(1.52ml,aq,45%)。在溶液中加入25mg Eso-Na晶种。搅拌下结晶过夜,真空过滤晶体,用甲苯(2x10ml)迅速洗涤两次。在空气中短暂干燥得到的湿滤饼,如干燥2-5分钟,然后进行分析。

[0088] 实施例1.2

[0089] <u>制备艾美拉唑钠盐修饰物E</u>

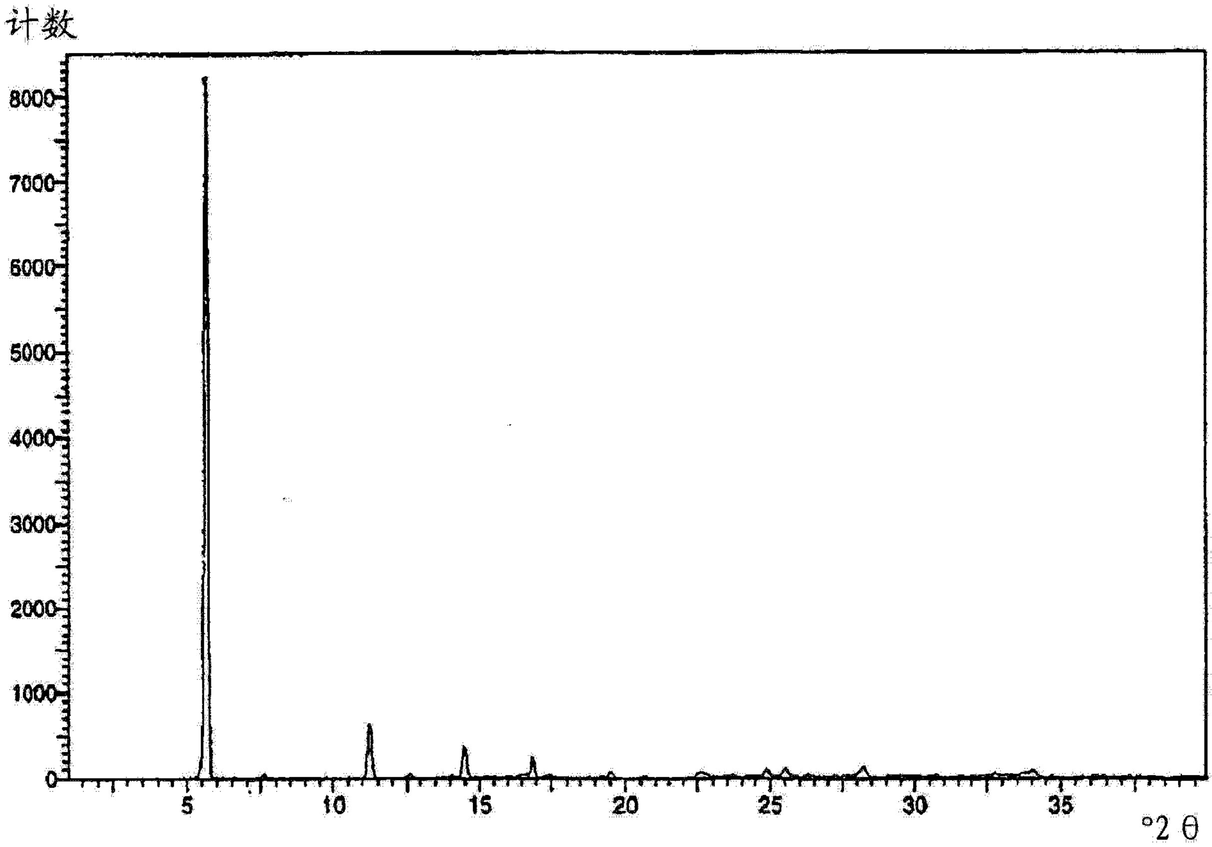
[0090] 将艾美拉唑-K(11.89g)溶解于水(50ml),加入甲苯(80ml)。然后,通过加入乙酸(5.89ml,25% v / v)将pH调节为大约7。将两相混合10分钟,然后使其分离。除去水相,用NaCl水溶液(50ml,10%)洗涤剩余的有机相。相分离后,将乙醇(11.1ml)加入甲苯相,然后加入1eq NaOH(1.52ml,aq,45%)。在溶液中加入55mg Eso-Na晶种。搅拌下结晶过夜,真空过滤晶体,用甲苯(2x10ml)迅速洗涤两次。在空气中短暂干燥得到的湿滤饼,如干燥2-5分钟,然后进行分析。

[0091] 实施例1.3

[0092] <u>制备艾美拉唑钠盐修饰物H</u>

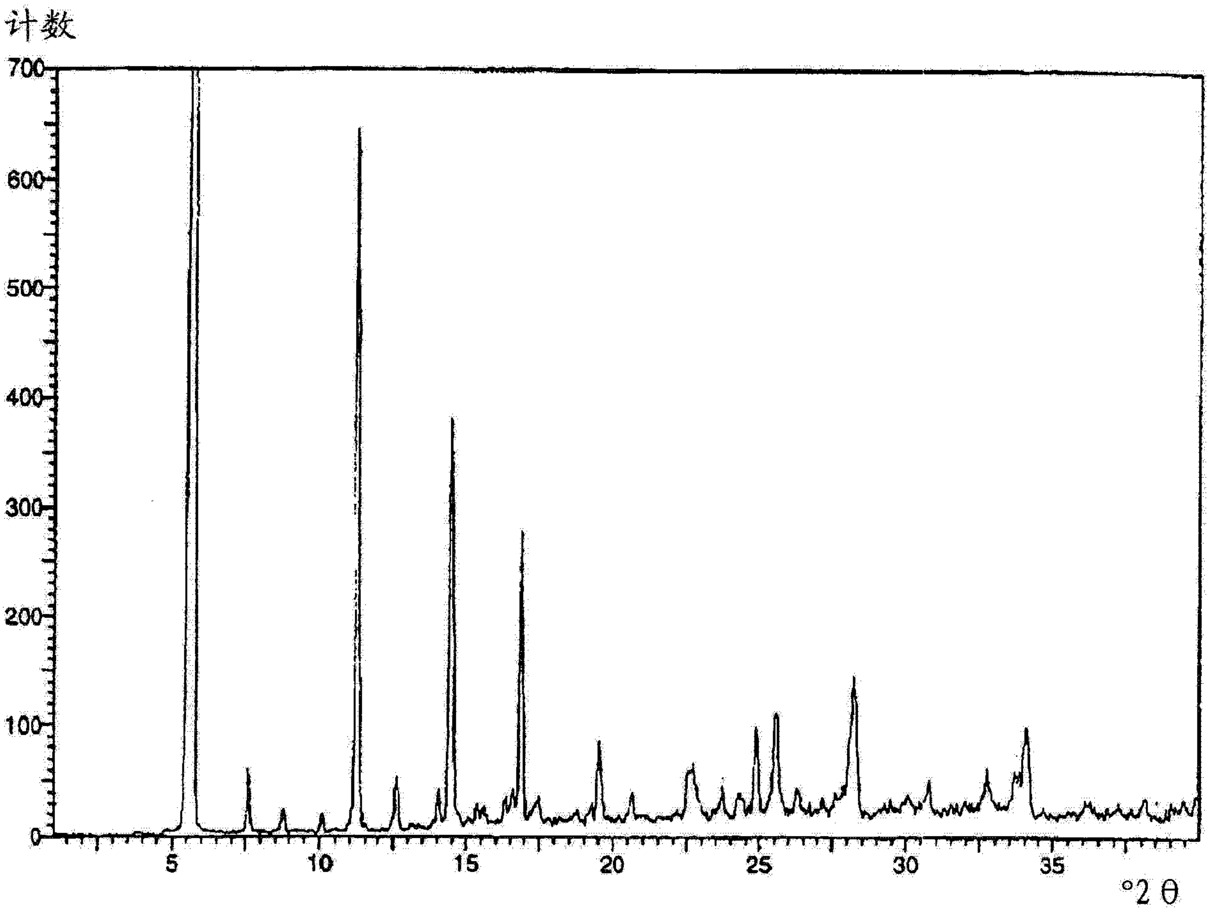
[0093] 将艾美拉唑-K(11.89g)溶解于水(50ml),加入甲苯(80ml)。然后,通过加入乙酸(5.89ml,25% v / v)将pH调节为大约7。将两相混合10分钟,然后使其分离。除去水相,

用 NaCl 水溶液(50ml,10%)洗涤剩余的有机相。相分离后,将 2- 丙醇(3.6ml)加入甲苯相,然后加入 1eqNaOH(1.52ml,aq,45%)。在溶液中加入 53mg Eso-Na 晶种。搅拌下结晶过夜,真空过滤晶体,用甲苯(2x10ml)迅速洗涤两次。在空气中短暂干燥得到的湿滤饼,如干燥 2-5 分钟,然后进行分析。



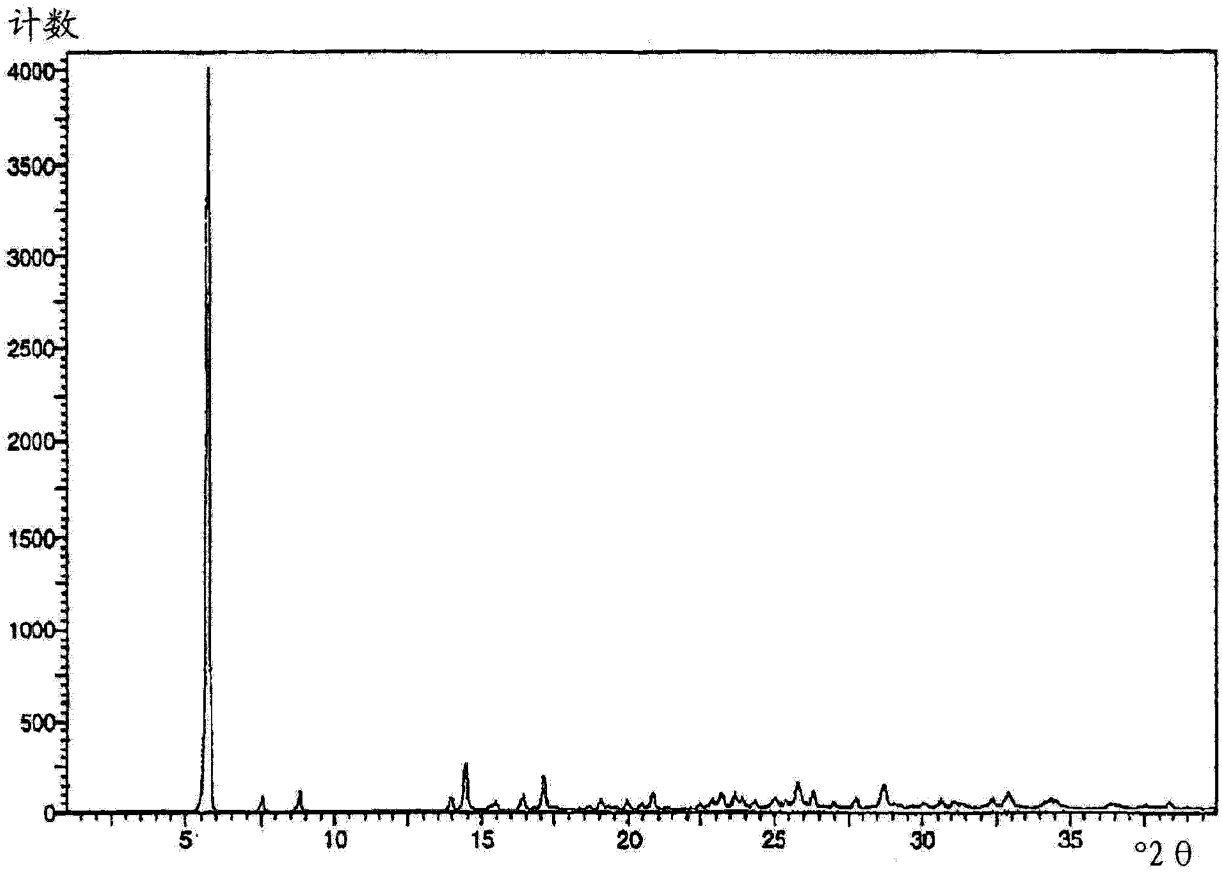
用可调节的狭缝测量的艾美拉唑钠盐修饰物C的
X线粉末衍射图

图 1



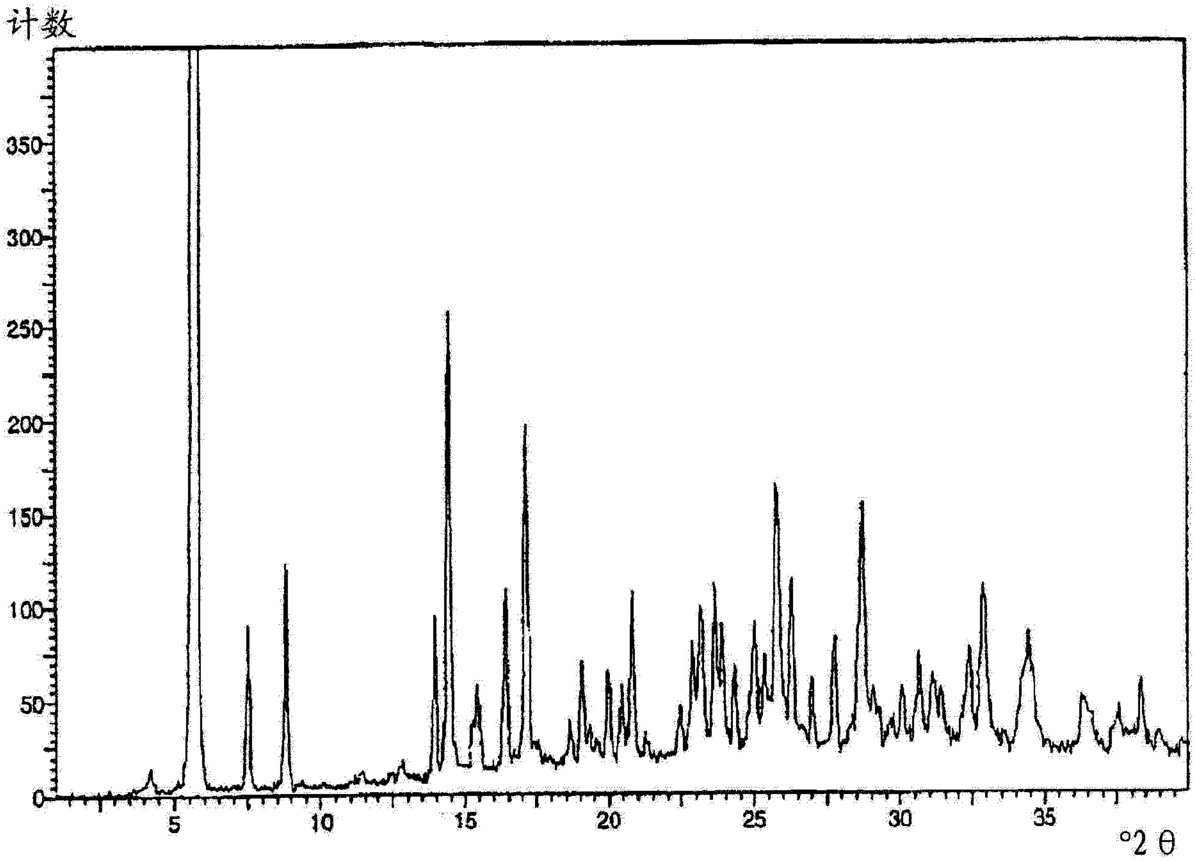
用可调节的狭缝测量的艾美拉唑钠盐修饰物C的
X线粉末衍射图,图1的放大版

图2



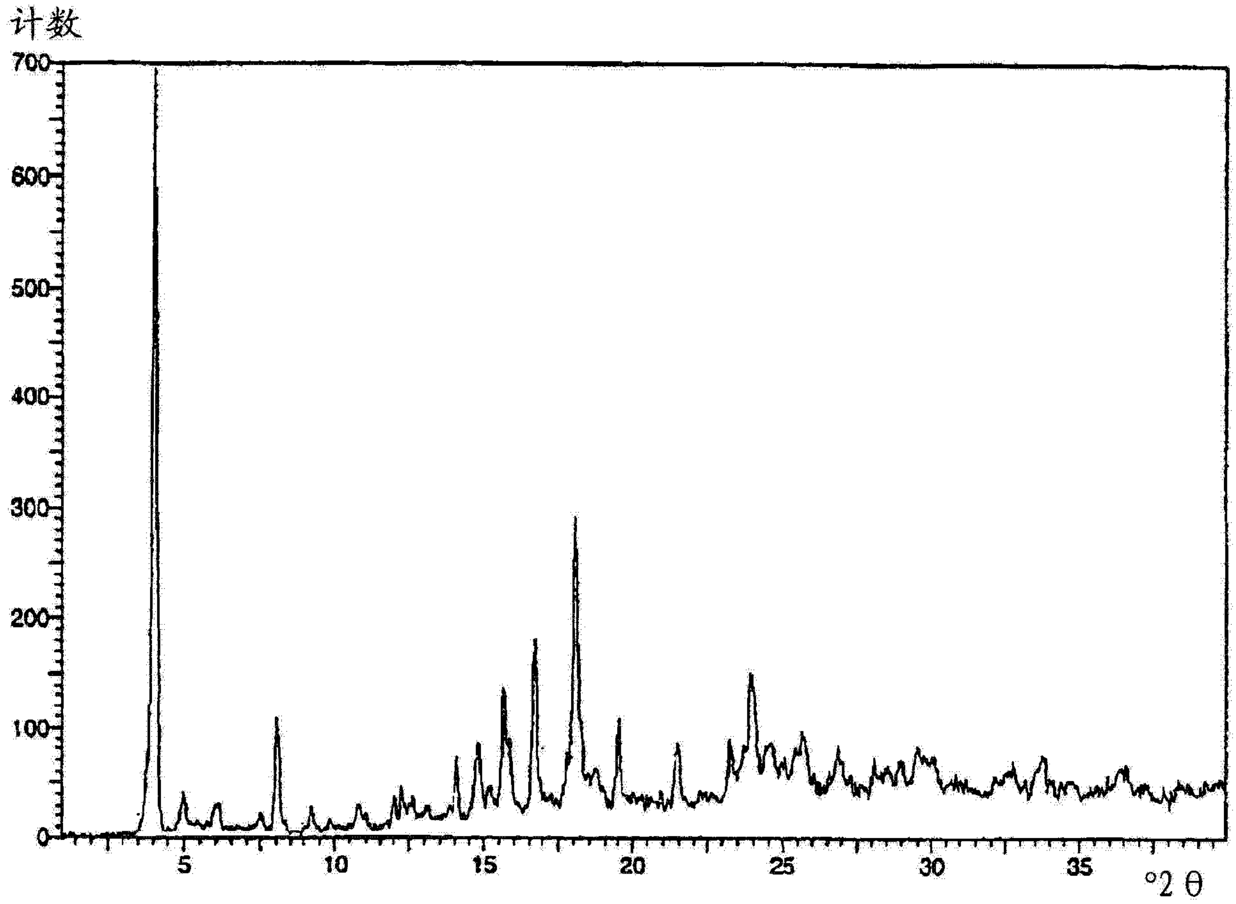
用可调节的狭缝测量的艾美拉唑钠盐修饰物E的
X线粉末衍射图

图 3



用可调节的狭缝测量的艾美拉唑钠盐修饰物C的
X线粉末衍射图，图3的放大版

图 4



用可调节的狭缝测量的艾美拉唑钠盐修饰物H的
X线粉末衍射图

图 5

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权利要求书2页 说明书34页
序列表277页 附图10页

(54)发明名称

通过递送人工转录因子调节受体表达

(57)摘要

本发明涉及人工转录因子,其包含融合至抑制或激活蛋白结构域、核定位序列和蛋白质转导结构域的特异性靶向受体基因启动子的多指锌指蛋白。在具体的实例中,这些受体基因启动子调节内皮素受体A、内皮素受体B、Toll 样受体4或高亲和力 IgE 受体的表达。指向内皮素A或B受体的人工转录因子用于治疗由内皮素调节的疾病,诸如心血管疾病和尤其是眼疾病,例如视网膜静脉阻塞、视网膜动脉阻塞、黄斑水肿、视神经病变、中心性浆液性脉络膜视网膜病变、视网膜色素变性、Leber 遗传性视神经病变等。指向Toll 样受体4或IgE 受体的人工转录因子分别用于治疗自身免疫病症等,和变应性病症。

CN 103998609 A

1. 人工转录因子，其包含融合至抑制或激活蛋白结构域、核定位序列和蛋白质转导结构域的特异性靶向受体基因启动子的多指锌指蛋白。

2. 人工转录因子，其中受体基因启动子是内皮素受体 A 启动子。

3. 人工转录因子，其中受体基因启动子是内皮素受体 B 启动子。

4. 人工转录因子，其中受体基因启动子是 Toll 样受体 4 启动子。

5. 人工转录因子，其中受体基因启动子是 FCER1A 启动子。

6. 权利要求 1、2、3、4 或 5 的人工转录因子，其包含六聚锌指蛋白。

7. 权利要求 2、3、4 或 5 的人工转录因子，其包含具有选自以下的蛋白序列的锌指蛋白：SEQ ID NO:31 至 SEQ ID NO:37、SEQ ID NO:39 至 SEQ ID NO:43、SEQ ID NO:45 至 SEQ ID NO:50、SEQ ID NO:52、SEQ ID NO:54 至 SEQ ID NO:57、SEQ ID NO:59 至 SEQ ID NO:64、SEQ ID NO:66 至 SEQ ID NO:80、SEQ ID NO:82 至 SEQ ID NO:95、SEQ ID NO:97 至 SEQ ID NO:118、SEQ ID NO:120 至 SEQ ID NO:136、SEQ ID NO:138 至 SEQ ID NO:143、SEQ ID NO:145 至 SEQ ID NO:153、SEQ ID NO:155 至 SEQ ID NO:164、SEQ ID NO:166 至 SEQ ID NO:173、SEQ ID NO:175 至 SEQ ID NO:181、和 SEQ ID NO:183 至 SEQ ID NO:191。

8. 权利要求 2、3、4 或 5 的人工转录因子，其包含具有选自以下蛋白序列的锌指蛋白：SEQ ID NO 56、83、85、101、114、118、127、133、140、142、146、147、156、159、175、和 181。

9. 权利要求 2、3、4 或 5 的人工转录因子，其包含 SEQ ID NO 118、133、156、或 175 的锌指蛋白。

10. 权利要求 1-9 中任一项的人工转录因子，其中所述锌指蛋白融合至抑制蛋白结合域。

11. 权利要求 10 的人工转录因子，其中所述抑制蛋白结构域是 SEQ ID NO: 1 的 N- 末端 KRAB、SEQ ID NO: 2 的 C- 末端的 KRAB、SEQ ID NO: 3 的 SID、或 SEQ ID NO: 4 的 ERD。

12. 权利要求 1-9 中任一项的人工转录因子，其中所述锌指蛋白融合至激活蛋白结合域。

13. 权利要求 12 的人工转录因子，其中所述激活蛋白结构域是 SEQ ID NO: 5 的 VP16 或 SEQ ID NO: 6 的 VP64。

14. 权利要求 1-13 中任一项的人工转录因子，其中所述核定位序列是含有 K-K/R-X-K/R 共有序列的碱性氨基酸簇或 SEQ ID NO: 196 的 SV40 NLS。

15. 权利要求 1-14 中任一项的人工转录因子，其中所述蛋白质转导结构域是 SEQ ID NO: 7 的 HIV 衍生的 TAT 肽、HSV-1 VP22 肽、SEQ ID NO: 192 的合成肽 mT02、SEQ ID NO: 193 的合成肽 mT03、SEQ ID NO: 194 的 R9 肽、ANTP 结构域、或保护性抗原 / 致死因子 N 末端 PTD。

16. 人工转录因子，其包含融合至抑制或激活蛋白结构域和核定位序列的特异性靶向内皮素受体 A 启动子的多指锌指蛋白。

17. 人工转录因子，其包含融合至抑制或激活蛋白结构域和核定位序列的特异性靶向内皮素受体 B 启动子的多指锌指蛋白。

18. 人工转录因子，其包含融合至抑制或激活蛋白结构域和核定位序列的特异性靶向 Toll 样受体 4 启动子的多指锌指蛋白。

19. 人工转录因子，其包含融合至抑制或激活蛋白结构域和核定位序列的特异性靶向 FCER1A 启动子的多指锌指蛋白。

20. 药物组合物，其包含权利要求 1-19 的人工转录因子。

21. 权利要求 1-19 的人工转录因子，其用于调节细胞对外界刺激和对其他可溶性信号分子的反应。

22. 权利要求 1-19 的人工转录因子，其用于治疗由特异性效应物与受体的结合所调节的疾病，为此所述多指锌指蛋白特异性靶向所述受体基因启动子。

23. 权利要求 2 或 6-16 的人工转录因子，其用于影响对内皮素的细胞应答，以降低或提高内皮素受体 A 水平，并且用于治疗由内皮素调节的疾病。

24. 权利要求 3、6-15 或 17 的人工转录因子，其用于影响对内皮素的细胞应答，以降低或提高内皮素受体 B 水平，并且用于治疗由内皮素调节的疾病。

25. 权利要求 4、6-15 或 18 的人工转录因子，其用于影响对脂多糖的细胞应答，以降低或提高 Toll 样受体 4 水平，并且用于治疗由脂多糖调节的疾病。

26. 权利要求 5-15 或 19 的人工转录因子，其用于影响对 IgE 的细胞应答，以降低或提高 IgE 受体水平，并且用于治疗由 IgE 调节的疾病。

27. 治疗疾病的方法，其包括向有其需要的患者施用治疗有效量的权利要求 1-26 的人工转录因子，其中待治疗疾病由特异性效应物与受体的结合所调节，为此所述多指锌指蛋白特异性靶向所述受体基因启动子。

28. 治疗由内皮素调节的疾病的方法，其包括向有其需要的患者施用治疗有效量的权利要求 2、3 或 6-17 的人工转录因子。

通过递送人工转录因子调节受体表达

发明领域

[0001] 本发明涉及人工转录因子，其包含融合至抑制或激活结构域、核定位序列和蛋白质转导结构域的特异性靶向受体基因启动子的多指锌指蛋白，以及它们在治疗由特异性效应物与此类受体的结合所调节的疾病中的用途。

背景技术

[0002] 提出人工转录因子（ATF）是用于调节基因表达的有用工具（Sera T.，2009，*Adv Drug Deliv Rev* 61，513-526）。许多天然存在的转录因子通过抑制或激活基因转录来影响表达，具有识别某一DNA序列的复杂的特定结构域。如果技术人员意在修饰它们的特异性和一个或多个靶基因，则这使得它们对于操作而言是无吸引力的目标。然而，某一类转录因子含有几个所谓锌指（ZF）结构域，它们是模块化的，并因此使得它们可以进行遗传工程。锌指是几乎独立靶向三个DNA碱基对的短（30个氨基酸）DNA结合基序。含有几个此类锌指的蛋白因此能够识别更长的DNA序列。六聚锌指蛋白（ZFP）识别18个碱基对（bp）的DNA靶，其在整个人基因组中几乎是唯一的。最初认为是完全背景独立的，但更深入的分析显示对于锌指的某些背景特异性（Klug A.，2010，*Annu Rev Biochem* 79，213-231）。突变在锌指识别表面中的某些氨基酸改变ZF模块的结合特异性产生对于大部分的5’-GNN-3’、5’-CNN-3’、5’-ANN-3’和某些5’-TNN-3’密码子的确定的ZF结构单元（例如所谓的Barbas模块，见Dreier B.，Barbas C.F. 3rd等，2005，*J Biol Chem* 280，35588-35597）。尽管关于人工转录因子的早期工作集中于基于组合预先选择的锌指与已知的3 bp靶序列的合理设计，但意识到锌指的某一背景特异性需要产生大的锌指文库，其使用复杂方法诸如细菌或酵母单杂交、噬菌体展示、区室化核糖体展示（compartmentalized ribosome display）或使用FACS分析的体内选择来询问。

[0003] 使用此类人工锌指蛋白，可以以高特异性靶向在人基因组内的DNA基因座。因此，这些锌指蛋白是将具有转录调节活性的蛋白结构域转运至特定启动子序列以产生目标基因表达的调节的理想工具。用于转录沉默的合适结构域是Krueppel相关的结构域（KRAB）如N-末端（SEQ ID NO：1）或C-末端（SEQ ID NO：2）KRAB结构域、Sin3相互作用结构域（SID，SEQ ID NO：3）和ERF阻抑蛋白结构域（ERD，SEQ ID NO：4），而基因转录的激活通过单纯疱疹病毒VP16（SEQ ID NO：5）或VP64（VP16的四聚体重复，SEQ ID NO：6）结构域来完成（Beerli R.R.等，1998，*Proc Natl Acad Sci USA* 95，14628-14633）。此外，考虑通过基因本体论GO:0001071（http://amigo.geneontology.org/cgi-bin/amigo/term_details?term=GO:0001071）确定的蛋白的转录活性结构域实现靶蛋白的转录调节。

[0004] 所有已知药物靶的很大百分比是受体分子，其被具有时常相当大的脱靶（off-target）活性的小分子药物的作用而刺激或阻断。此类受体的实例是组胺H1受体或α和β肾上腺素受体，但通常是通过基因本体论GO:0004888和GO:0004930确定的蛋白。

[0005] 尽管由于特定特征的高保守性，小分子药物并非总能选择性靶向给定蛋白家族的某一成员，但如基于抗体的新药物所显示出的，生物制剂提供了巨大的特异性。然而，实际

上所有生物制剂到目前为止均在细胞外起作用。

[0006] 尤其是上文提及的人工转录因子将适合于以治疗上有用的方式影响基因转录。然而，此类因子向作用位点－细胞核－的递送并不容易实现，因而妨碍了治疗性人工转录因子方法的有效性，例如通过依赖于逆转录病毒递送具有该方法的所有缺点，诸如免疫原性和细胞转化的潜能 (Lund C.V. 等 , 2005, *Mol Cell Biol* 25, 9082-9091)。

[0007] 所谓的蛋白质转导结构域(PTD)显示促进蛋白经质膜易位至细胞溶胶 / 核质中。短肽诸如 HIV 来源的 TAT 肽 (SEQ ID NO: 7) 和其他显示出诱导不依赖于细胞类型的货物蛋白质的大胞饮摄取 (Wadia J.S. *et al.* , 2004, *Nat Med* 10, 310-315)。当到达细胞溶胶中时，此类融合蛋白显示出具有生物活性。有趣的是，在蛋白转导后，极可能是通过胞内蛋白伴侣的作用，即使错误折叠的蛋白也能够变得有功能。

[0008] 血管活性内皮素系统在多种疾病的发病中起重要作用。内皮素一方面参与调节血液供给，并且另一方面是由低氧诱导的事件级联中的主要参与者。内皮素例如参与血脑或血视网膜屏障的破坏和参与新血管形成。此外，内皮素参与神经变性以及调节痛觉或甚至口渴感觉的阈值。内皮素还参与调节眼内压。

[0009] 内皮素作用通过它的同族受体来介导，主要是内皮素受体 A，其通常位于环绕血管的平滑肌细胞上。影响内皮素系统－全身地或局部地－是治疗许多疾病诸如蛛网膜下腔或脑出血所关注的。内皮素还影响多发性硬化的病程。内皮素是(肺动脉)高血压的原因，而且也是低动脉压、心肌病和雷诺综合征、变异型心绞痛和其他心血管疾病的原因。内皮素参与糖尿病性肾病和糖尿病性视网膜病变。在眼中，它还对青光眼性神经变性、视网膜静脉阻塞、巨细胞性关节炎、视网膜色素变性、年龄相关性黄斑变性、中心性浆液性脉络膜视网膜病变、Morbus Leber、Susac 综合征、眼内出血、视网膜前神经胶质增生和某些其他病理学病况起作用。

[0010] 眼是精密器官，其强烈依赖于平衡的且充足的灌注以达到它的高需氧量。无法提供充足且稳定的供氧会引起局部缺血 - 再灌注损伤，导致神经胶质活化和神经元损害，如在患有渐进性疾病的青光眼患者中所观察到的，尽管其具有正常或标准化的眼内压。如在糖尿病性视网膜病变或湿性年龄相关性黄斑变性中显而易见的，不充足的血液供给还导致低氧，引起具有进一步视网膜损害潜能的失控的(run-away)新血管形成。眼组织灌注在复杂控制之下并且依赖于血压、眼内压以及调节血管直径的局部因子。此类局部因子例如提及的内皮素、具有强血管收缩活性的短肽。内皮素的三种同工型 (ET-1、ET-2 和 ET-3) 由内皮素转化酶从位于血管壁中的内皮细胞分泌的前体分子来产生。成熟 ET 的两个同族受体是已知的，ETRA 和 ETRB。尽管 ETRA 位于形成血管壁的平滑肌细胞中并促进血管收缩，但 ETRB 主要表达于内皮细胞中，并且通过促进一氧化氮的释放来使血管舒张，因而引起平滑肌松弛。ETRA 和 ETRB 属于 G 蛋白偶联的七跨膜螺旋受体的大类。ET 与 ETRA 或 ETRB 的结合导致 G 蛋白活化，因而引发胞内钙浓度的升高，并由此引起一大批的细胞反应。

[0011] 药理学上影响 ET 系统可能证明在其中 ET 水平升高并且 ET 以有害形式起作用的病例中，诸如在视网膜静脉阻塞、青光眼性神经变性、视网膜色素变性、巨细胞性关节炎、中心性浆液性脉络膜视网膜病变、多发性硬化、视神经炎、类风湿性关节炎、Susac 综合征、辐射性视网膜病变、视网膜前神经胶质增生、纤维肌痛和糖尿病性视网膜病变过程中是有用的。为此目的，下调 ETRA 将有助于调节疾病结果。但在某些情况下，上调 ETRA 并因此对 ET

提高的敏感性可能是希望的，例如以促进在从角膜外伤或角膜溃疡恢复过程中的角膜伤口愈合。

[0012] 此外，ETRB 介导的信号传递例如在癌症干细胞维持和肿瘤生长过程中与病例生理学过程有关。此外，上调 ETRB 与青光眼性神经变性有关，而抑制 ETRB 则显示出在青光眼过程中起神经保护作用。此外，ETRB 在炎症过程中被上调。因此，通过特异性人工转录因子药理学上调节 ETRB 将可用于治疗癌症，预防神经变性和调节炎症过程。

[0013] 细菌细胞壁组分诸如脂多糖(LPS)在多种疾病的发病中起重要作用。体内存在 LPS 指向需要由免疫系统针对的细菌感染。由于 LPS 是革兰氏阴性细菌的一般组分，因此 LPS 构成了能够激活免疫系统的所谓的危险信号。LPS 由 Toll 样受体 4 (TLR4)所识别，所述 Toll 样受体 4 是参与识别多种危险信号或与细菌或病毒感染相关的病原体相关分子模式(PAMP)的 Toll 样受体的更大家族的成员。尽管识别 LPS 为危险信号是先天免疫的重要部分，但 TLR4 受体的过度刺激或延长的刺激与多种与慢性炎症有关的病理学病况相关。实例是多种肝疾病，诸如酒精性肝病、非酒精性脂肪性肝病、非酒精性脂肪性肝炎、慢性乙型肝炎或丙型肝炎病毒(HCV)感染、和 HIV-HCV 共感染。其他与 TLR4 信号传递相关的疾病是类风湿性关节炎、动脉粥样硬化、银屑病、克罗恩氏病、葡萄膜炎、接触镜相关性角膜炎和角膜炎症。此外，TLR4 介导的信号传递参与癌症进展(cancer progression)和对化学疗法的抗性。

[0014] 药理学上影响 LPS 识别和 TLR4 信号传递可能证明对于与由于 TLR4 的不恰当活化而导致的慢性炎症有关的疾病是有用的。因此，通过靶向 TLR4 启动子的特异性负调节的人工转录因子的作用来下调 TLR4 蛋白，会有助于通过破坏由 LPS 导致的慢性炎症的恶性循环来调节疾病结果。

[0015] 免疫球蛋白同种型 E(IgE)是适应性免疫系统的部分，并且同样参与针对感染以及致瘤性转化的保护。IgE 通过位于肥大细胞和嗜碱细胞上的高亲和力 IgE 受体(FCER1)来结合。IgE 与 FCER1 的结合及随后经称为变应原的特异性抗原交联这些复合体导致多种因子从肥大细胞和嗜碱细胞中释放，引起变应性应答。在这些因子中有组胺、白细胞三烯类、多种细胞因子以及溶菌酶、类胰蛋白酶或 β - 己糖胺酶。这些因子的释放与变应性疾病诸如变应性鼻炎、哮喘、湿疹和过敏反应相关。

[0016] 发明概述

本发明涉及人工转录因子，其包含融合至抑制或激活蛋白结构域、核定位序列和蛋白质转导结构域的特异性靶向受体基因启动子的多指锌指蛋白，并且涉及包含此类人工转录因子的药物组合物。此外，本发明涉及此类人工转录因子用于调节细胞对外界刺激和对其他可溶性信号分子的反应的用途，以及在治疗由特异性效应物与此类受体的结合所调节的疾病中的用途。

[0017] 在一个具体的实施方案中，受体基因启动子是内皮素受体 A 启动子。在另一个具体的实施方案中，本发明涉及此类人工转录因子，其用于影响对内皮素的细胞应答，以降低或提高内皮素受体水平，并且用于治疗由内皮素调节的疾病，尤其用于治疗此类眼疾病。同样，本发明涉及治疗由内皮素调节的疾病的方法，其包括向有其需要的患者施用治疗有效量的本发明的人工转录因子。

[0018] 在另一个具体的实施方案中，本发明涉及人工转录因子中间体，其包含融合至抑

制或激活蛋白结构域和核定位序列的特异性靶向内皮素受体 A 启动子的多指锌指蛋白。

[0019] 在另一个具体的实施方案中，受体基因启动子是内皮素受体 B 启动子。在另一个具体的实施方案中，本发明涉及此类人工转录因子，其用于影响对内皮素的细胞应答，以降低或提高内皮素受体 B 水平，并且用于治疗由内皮素调节的疾病，尤其用于治疗此类眼疾病。同样，本发明涉及治疗由内皮素调节的疾病的方法，其包括向有其需要的患者施用治疗有效量的本发明的人工转录因子。

[0020] 在另一个具体的实施方案中，本发明涉及人工转录因子中间体，其包含融合至抑制或激活蛋白结构域和核定位序列的特异性靶向内皮素受体 B 启动子的多指锌指蛋白。

[0021] 在另一个具体的实施方案中，受体基因启动子是 Toll 样受体 4 启动子。在另一个具体的实施方案中，本发明涉及此类人工转录因子，其用于影响对脂多糖的细胞应答，以降低或提高 Toll 样受体 4 水平，并且用于治疗由脂多糖调节的疾病，尤其用于治疗眼疾病。同样，本发明涉及治疗由脂多糖调节的疾病的方法，其包括向有其需要的患者施用治疗有效量的本发明的人工转录因子。

[0022] 在另一个具体的实施方案中，本发明涉及人工转录因子中间体，其包含融合至抑制或激活蛋白结构域和核定位序列的特异性靶向 Toll 样受体 4 启动子的多指锌指蛋白。

[0023] 在另一个具体的实施方案中，受体基因启动子是高亲和力免疫球蛋白 ε 受体亚基 α 启动子。在另一个具体的实施方案中，本发明涉及此类人工转录因子，其用于影响对免疫球蛋白 E（IgE）的细胞应答，以降低或提高高亲和力 IgE 受体水平，并且用于治疗由 IgE 调节的疾病，尤其用于治疗眼疾病。同样，本发明涉及治疗由 IgE 调节的疾病的方法，其包括向有其需要的患者施用治疗有效量的本发明的人工转录因子。

[0024] 在另一个具体的实施方案中，本发明涉及人工转录因子中间体，其包含融合至抑制或激活蛋白结构域和核定位序列的特异性靶向高亲和力免疫球蛋白 ε 受体亚基 α 启动子的多指锌指蛋白。

[0025] 附图简述

图 1：通过调节受体表达改变细胞敏感性

通过蛋白质转导结构域（PTD）诸如 TAT 或其他的作用将人工转录因子转运至细胞中，所述人工转录因子含有融合至抑制 / 激活结构域（RD= 调节域）以及核定位序列（NLS）的特异性靶向受体基因（RG）启动子（P）的六聚锌指（ZF）蛋白。根据转录调节域，受体基因表达提高（+）或抑制（-），分别产生增强的或减少的对受体（R1、R2 或 R3）激动剂（A）的细胞敏感性。

[0026] 图 2：人内皮素受体 A（ETRA）启动子区

显示了含有假定的 ETRA 启动子的 ETRA 基因的 5' 非翻译区。突出显示的是转录起始（用 +1 标记）和人工转录因子潜在的 15bp 和 18 bp 靶位点（TS）（下划线表示并标记为 TS-855、TS-555、TS-487、TS-447、TS-306、TS-230、TS-103、TS-37、TS+74）。

[0027] 图 3：人 Toll 样受体 4（TLR4）启动子区

显示了含有 TLR4 启动子的 TLR4 基因的 5' 区。突出显示的是转录起始（用 +1 标记）、第一外显子的起始密码子和可读框（粗体字母）和特异性人工转录因子潜在的 18 bp 靶位点（下划线表示并标记为 TS-276、TS-55、TS+113）。

[0028] 图 4：高亲和力 IgE 受体 A（FCER1A）启动子区

显示了含有邻近的、组成型启动子的 FCER1A 基因的 5' 区。突出显示的是转录起始（用 +1 标记）、第一外显子的起始密码子和可读框（粗体字母）和特异性人工转录因子潜在的 18 bp 靶位点（下划线表示并标记为 TS-147 和 TS+17）。

[0029] 图 5：人内皮素受体 B（ETRB）启动子区

显示了含有 ETRB 启动子的 ETRB 基因的 5' 区。突出显示的是翻译起始（用 +1 标记）和特异性人工转录因子潜在的 18 bp 靶位点（下划线表示并标记为 TS-1149 和 TS-487）。由于报道了几个可变转录起始位点（Arai H. 等，1993，*J Biol Chem* 268，3463-70；Tsutsumi M. 等，1999，*Gene* 4，43-9），选择翻译起始位点作为命名靶位点的参考点。

[0030] 图 6：人工转录因子

A）将多种锌指蛋白克隆入三个不同质粒中。显示唯一的限制酶位点以突出多种表达质粒的模块设计。产生的 DNA 构建体编码以下融合蛋白：KRAB-NLS-6ZFP-3xmyc（SEQ ID NO：8）、SID-NLS-6ZFP-3xmyc、

NLS-6ZFP-GGSGGS（SEQ ID NO：9）接头 -KRAB A-3xmyc 和

NLS-6ZFP-GGSGGS 接头 -VP64-3xmyc。

[0031] 图 7：通过人工转录因子 A074A、A074E、A074R 和 A074V 调节人内皮素受体 A（ETRA）活性

（A）ETRA 启动子驱动的蛋白表达的人工转录因子依赖的阻抑。显示了表达指向 ETRA 启动子内的靶位点的 A074A（SEQ ID NO：10）、A074E（SEQ ID NO：11）、A074R（SEQ ID NO：12）和 A074V（SEQ ID NO：13）后的萤光素酶报道基因测定（RLuA = 相对萤光素酶活性，相对于对照 C，以％计）的结果。C = 作为对照的黄色荧光蛋白（YFP）。

（B）A074Vp（SEQ ID NO：14），转导的 A074V 蛋白，相比于对照 B（缓冲液处理的细胞）不抑制 HeLa 细胞增殖。RP = 以对照的％计的相对增殖。

（C）A074Vp 相比于对照 B（缓冲液处理的细胞）不抑制人子宫平滑肌细胞（hUtSMC）的增殖。

（D）A074Vp 阻断了 hUtSMC 的 ET-1 依赖性收缩。将 hUtSMC 植入三维胶原网格。C = 作为对照的用缓冲液处理的细胞。B = 用缓冲液和 ET-1 处理的细胞。A074Vp = 用 A074Vp 和 ET-1 处理的细胞。RLA = 以对照 C 的％计的相对网格面积。细节描述于下文。

[0032] 图 8：通过人工转录因子 A074Ra 和 A074Va 驱动的 ETRA 启动子活性的增强

（A）激活人工转录因子 A074Ra（SEQ ID NO：15）和 A074Va（SEQ ID NO：16）表达后，ETRA 启动子驱动的萤光素酶报道基因的表达升高。RLuA = 相对萤光素酶活性，以相对于对照 C（YFP）的％计。

（B）用 A074Vap（SEQ ID NO：17）处理并不抑制 hUtSMCs 细胞增殖。作为蛋白递送的 A074Vp 对 hUtSMCs 细胞没有毒性，并且并不负面影响细胞增殖。B = 缓冲液处理的细胞。RP = 以对照的％计的相对增殖。

[0033] 图 9：通过 A01149N 和 A01149P 的人内皮素受体 B（ETRB）启动子的阻抑

在萤光素酶报道基因测定中，人工转录因子 A01149N（SEQ ID NO：18）和 A01149P（SEQ ID NO：19）的表达相对于 YFP（对照 C）阻抑了 ETRB 启动子活性。RLuA = 相对萤光素酶活性，以相对于对照 C 的％计。

[0034] 图 10：通过 A055B 和 A055E 的人 Toll 样受体 4（TLR4）活性的调节

(A) 在萤光素酶报道基因测定中，A055B (SEQ ID NO: 20) 和 A055E (SEQ ID NO: 21) 的表达相对于 YFP (对照 C)阻断了 TLR4 启动子活性。RLuA = 相对萤光素酶活性，以相对于对照 C 的％计。

(B) 在巨噬细胞样 U937 细胞中表达 A055B 后，TLR4 依赖性的、LPS 诱导的白细胞介素(IL)-6 的分泌变弱(blunted)。

(C) 用 A055Bp (SEQ ID NO:22) 处理并不抑制 HeLa 细胞增殖。RP = 以对照的％计的相对增殖。B = 缓冲液处理的细胞。RP = 以对照的％计的相对增殖。

[0035] 图 11：高亲和力 IgE 受体通过 A0147A 调节

(A) A0147A (SEQ ID NO: 23) 表达后，高亲和力 IgE 受体 α 亚基 (FCER1A) 启动子驱动的萤光素酶报道基因的表达在大鼠嗜碱 RBL-2H3 细胞中被抑制。RLuA = 相对萤光素酶活性，以相对于对照 C (YFP) 的％计。

(B) A0147Ap (SEQ ID NO:24) 并不抑制 HeLa 细胞增殖。B = 缓冲液处理的细胞。RP = 以对照的％计的相对增殖。

C). 用 A0147Ap 处理抑制人 IgE 与人嗜碱 KU812F 细胞的结合为 80％左右。IgEB = 使用人 IgE 和用 FITC 标记的小鼠抗人 IgE 通过流式细胞术测定的 IgE 对 FCER1 的结合能力，以相对于作为对照的缓冲液处理的细胞(B)的％计。

[0036] 发明详述

本发明涉及人工转录因子，其包含融合至抑制或激活蛋白结构域、核定位序列和蛋白质转导结构域的特异性靶向受体基因启动子的多指锌指蛋白，并且涉及包含此类人工转录因子的药物组合物。

[0037] 许多疾病的治疗基于调节细胞受体信号传递。实例是高血压(其中 β 阻断剂抑制 β 肾上腺素能受体的功能)、抑郁(其中 5- 羟色胺摄取阻断剂增加激动剂浓度和因此的 5- 羟色胺受体信号传递)、或青光眼(其中前列腺素类似物活化前列腺素受体，继而降低眼内压)。传统上，为了治疗目的，使用以受体激动剂或拮抗剂形式的小分子来影响受体信号传递。然而，细胞受体信号传递还能够被受体蛋白表达的直接调节所影响。

[0038] 顺从于受体表达水平的直接调节的病理学过程例如为以下：患有由于先天性心脏病的充血性心力衰竭的患者将受益于 β 肾上腺素受体的上调，这是由于该受体在心肌中的下调与手术后心力衰竭风险相关。在帕金森氏病中，用多巴胺能药疗法的治疗抑制多巴胺受体的可利用性，因此，多巴胺受体的上调将改善多巴胺能药疗法的效力。在癫痫中，海马中大麻素受体表达不足涉及疾病病因学，因此，大麻素受体的上调将是癫痫患者的可行疗法。

[0039] 对于由受体蛋白的单倍剂量不足引起的遗传疾病，诸如引起生长迟缓的胰岛素样生长因子 I 受体，但还有其他的，额外激活剩余的有功能的受体基因将有益于患者。此外并在其他中，病理性自身免疫的诱导和永续性(perpetuation)与从 Toll 样受体的不恰当信号传递相关联。因此，下调 Toll 样受体破坏多种自身免疫疾病的恶性循环。在变应性疾病中，通过高亲和力 IgE 受体防止 IgE 介导的信号传递用于操纵变应性反应。在癌症中，下调生长因子受体或上调胞外基质受体对于防止肿瘤进展是有利的。

[0040] 在此类受体分子中的是来自所谓的七跨膜或 G 蛋白偶联受体(GPCR)蛋白家族的蛋白，其特征在于将受体锚定在质膜中的七跨膜结构域和 G 蛋白依赖性信号级联放大。此

类蛋白的实例是内皮素的受体A和B。其他受体蛋白经单跨膜区锚定,例如脂多糖的受体、Toll样受体4或多种细胞因子受体诸如IL-4受体。其他受体由多聚蛋白复合体组成,例如由α、β和γ链组成的IgE抗体的高亲和力受体,或者由α、β、γ、δ、ε和ζ链组成的T细胞受体。因此,在术语"受体分子"下包含的是来自不同蛋白家族具有非常不同的作用模式的蛋白。

[0041] 本发明中考虑的受体是人受体分子,其由以下编码:

HTR1A, HTR1B, HTR1D, HTR1E, HTR1F, HTR2A, HTR2B, HTR2C, HTR4, HTR5A, HTR5BP, HTR6, HTR7, CHRM1, CHRM2, CHRM3, CHRM4, CHRM5, ADORA1, ADORA2A, ADORA2B, ADORA3, ADRA1A, ADRA1B, ADRA1D, ADRA2A, ADRA2B, ADRA2C, ADRB1, ADRB2, ADRB3, AGTR1, AGTR2, APLNR, GPBAR1, NMBR, GRPR, BRS3, BDKRB1, BDKRB2, CNR1, CNR2, CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6, CXCR7, CX3CR1, XCR1, CCKAR, CCKBR, C3AR1, C5AR1, GPR77, DRD1, DRD2, DRD3, DRD4, DRD5, EDNRA, EDNRB, GPER, FPR1, FPR2, FPR3, FFAR1, FFAR2, FFAR3, GPR42, GALR1, GALR2, GALR3, GHSR, FSHR, LHCGR, TSHR, GNRHR, GNRHR2, HRH1, HRH2, HRH3, HRH4, HCAR1, HCAR2, HCAR3, KISS1R, LTB4R, LTB4R2, CYSLTR1, CYSLTR2, OXER1, FPR2, LPAR1, LPAR2, LPAR3, LPAR4, LPAR5, S1PR1, S1PR2, S1PR3, S1PR4, S1PR5, MCHR1, MCHR2, MC1R, MC2R, MC3R, MC4R, MC5R, MTNR1A, MTNR1B, MLNR, NMUR1, NMUR2, NPFFR1, NPFFR2, NPSR1, NPBWR1, NPBWR2, NPY1R, NPY2R, PPYR1, NPY5R, NPY6R, NTSR1, NTSR2, OPRD1, OPRK1, OPRM1, OPRL1, HCRTR1, HCRTR2, P2RY1, P2RY2, P2RY4, P2RY6, P2RY11, P2RY12, P2RY13, P2RY14, QRFPR, PTAFR, PROKR1, PROKR2, PRLHR, PTGDR, PTGDR2, PTGER1, PTGER2, PTGER3, PTGER4, PTGFR, PTGIR, TBXA2R, F2R, F2RL1, F2RL2, F2RL3, RXFP1, RXFP2, RXFP3, RXFP4, SSTR1,

SSTR2, SSTR3, SSTR4, SSTR5, TACR1, TACR2, TACR3, TRHR, TAAR1, UTS2R, AVPR1A, AVPR1B, AVPR2, OXTR, CCRL2, CMKLR1, GPR1, GPR3, GPR4, GPR6, GPR12, GPR15, GPR17, GPR18, GPR19, GPR20, GPR21, GPR22, GPR25, GPR26, GPR27, GPR31, GPR32, GPR33, GPR34, GPR35, GPR37, GPR37L1, GPR39, GPR42, GPR45, GPR50, GPR52, GPR55, GPR61, GPR62, GPR63, GPR65, GPR68, GPR75, GPR78, GPR79, GPR82, GPR83, GPR84, GPR85, GPR87, GPR88, GPR101, GPR119, O3FAR1, GPR132, GPR135, GPR139, GPR141, GPR142, GPR146, GPR148, GPR149, GPR150, GPR151, GPR152, GPR153, GPR160, GPR161, GPR162, GPR171, GPR173, GPR174, GPR176, GPR182, GPR183, LGR4, LGR5, LGR6, LPAR6, MAS1, MAS1L, MRGPRD, MRGPRE, MRGPRF, MRGPRG, MRGPRX1, MRGPRX2, MRGPRX3, MRGPRX4, OPN3, OPN5, OXGR1, P2RY8, P2RY10, SUCNR1, TAAR2, TAAR3, TAAR4P, TAAR5, TAAR6, TAAR8, TAAR9, CCBP2, CCRL1, DARC, CALCR, CALCRL, CRHR1, CRHR2, GHRHR, GIPR, GLP1R, GLP2R, GCGR, SCTR, PTH1R, PTH2R, ADCYAP1R1, VIPR1, VIPR2, BAI1, BAI2, BAI3, CD97, CELSR1, CELSR2, CELSR3, ELTD1, EMR1, EMR2, EMR3, EMR4P, GPR56, GPR64, GPR97, GPR98, GPR110, GPR111, GPR112, GPR113, GPR114, GPR115, GPR116, GPR123, GPR124, GPR125, GPR126, GPR128, GPR133, GPR144, GPR157, LPHN1, LPHN2, LPHN3, CASR, GPRC6A, GABBR1, GABBR2, GRM1, GRM2, GRM3, GRM4, GRM5, GRM6, GRM7, GRM8, GPR156, GPR158, GPR179, GPRC5A, GPRC5B, GPRC5C, GPRC5D, TAS1R1, TAS1R2, TAS1R3, FZD1, FZD2, FZD3, FZD4, FZD5, FZD6, FZD7, FZD8, FZD9, FZD10, SMO, GPR107, GPR137, OR51E1, TPRA1, GPR143, THRA, THRB, RARA, RARB, RARG, PPARA, PPARD, PPARG, NR1D1, NR1D2, RORA, RORB, RORC, NR1H4, NR1H5P, NR1H3, NR1H2, VDR, NR1I2, NR1I3, HNF4A, HNF4G, RXRA, RXRB, RXRG, NR2C1, NR2C2, NR2E1, NR2E3, NR2F1, NR2F2, NR2F6, ESR1, ESR2, ESRRA, ESRRB, ESRRG, AR, NR3C1, NR3C2, PGR, NR4A1, NR4A2, NR4A3, NR5A1, NR5A2, NR6A1, NR0B1, NR0B2, HTR3A, HTR3B, HTR3C, HTR3D, HTR3E, GABRA1, GABRA2, GABRA3, GABRA4, GABRA5, GABRA6, GABRB1, GABRB2, GABRB3, GABRG1, GABRG2, GABRG3, GABRD, GABRE, GABRQ, GABRP, GABRR1, GABRR2, GABRR3, GLRA1, GLRA2, GLRA3, GLRA4, GLRB, GRIA1, GRIA2, GRIA3, GRIA4, GRID1, GRID2, GRIK1, GRIK2, GRIK3, GRIK4, GRIK5, GRIN1, GRIN2A, GRIN2B, GRIN2C, GRIN2D, GRIN3A, GRIN3B, CHRNA1, CHRNA2, CHRNA3, CHRNA4, CHRNA5, CHRNA6, CHRNA7, CHRNA9, CHRNA10, CHRNB1, CHRNB2, CHRNB3, CHRNB4, CHRNG, CHRND, CHRNE, P2RX1, P2RX2, P2RX3, P2RX4, P2RX5, P2RX6, P2RX7, ZACN, AGER, TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10, TLR11, LILRA1, LILRA2, LILRA3, LILRA4, LILRA5, LILRA6, LILRB1, LILRB2, LILRB3a ,LILRB4, LILRB5 ,LILRB6, LILRB7, EGFR, ERBB2, ERBB3, ERBB4, GFRa1, GFRa2, GFRa3, GFRa4, NPR1, NPR2, NPR3, NPR4, NGFR, NTRK1, NTRK2, NTRK3, EGFR, ERB2, ERB3, ERB4, INSR, IRR, IG1R, PDGFalpha, PDGFbeta, Fms, Kit, Flt3, FGFR1, FGFR2, FGFR3, FGFR4, BFR2, VGR1, VGR2, VGR3, EPA1, EPA2, EPA3, EPA4, EPA5, EPA7, EPA8, EPB1, EPB2, EPB3, EPB4, EPB6, TrkA, TrkB, TrkC, UFO, TYRO3, MERK, TIE1, TIE2, RON, MET, DDR1, DDR2, RET, ROS, LTK, ROR1, ROR2, RYK, PTK7,和 *KIT*。

[0042] 考虑的进一步的受体是人受体,其识别白细胞介素(IL)-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, IL-21, IL-22, IL-23, IL-24, IL-25, IL-26, IL-27, IL-28, IL-29, IL-30, IL-31, IL-32, IL-33, IL-34, IL-35, IL-36, IL-37, IL-38,瘦蛋白,干扰素-α,干扰素-β,干扰素-γ,肿瘤坏死因子 α,淋巴毒素,促乳素,制瘤素 M,白血病抑制因子,集落刺激因子,免疫球蛋白 A,免疫球蛋白 D,免疫球蛋白 G,免疫球蛋白 M,免疫球蛋白 E,人白细胞抗原(HLA)A, HLA-B,HLA-C,HLA-E,HLA-F,HLA-G,HLA-DP,HLA-DQ,HLA-DR,转化生长因子 α,转化生长因子 β,神经生长因子,脑源性神经营养因子,神经营养因子-3,神经营养因子-4,肾上腺髓质素,血管生成素,自分泌运动因子,骨形态发生蛋白,促红细胞生成素,成纤维细胞生长因子,神经胶质细胞源性神经营养因子,粒细胞集落刺激因子,粒细胞巨噬细胞集落刺激因子,生长分化因子-9,肝细胞生长因子,肝癌衍生生长因子,胰岛素样生长因子,胰岛素,迁移刺激因子,肌肉生长抑制素(myostatin),血小板衍生生长因子,血小板生成素,血管内皮生长因子,胎盘生长因子和生长激素。

[0043] 进一步考虑的是由同源非人基因编码的受体,例如由猪、马、牛、猫、犬或鼠基因编码的受体;和由同源植物受体基因编码的受体,例如在作物植物诸如小麦、大麦、玉米、稻、黑麦、燕麦、大豆、花生、向日葵、红花、亚麻、豆类、烟草、或生活饲料草中发现的基因,和在水果植物诸如苹果、梨、香蕉、柑橘类水果、葡萄等中发现的基因。

[0044] 逆转录病毒具有特别高的免疫原性潜能,因而限制了它们在某一治疗的重复应用中的使用。由于锌指模块的高保守性,这样的免疫反应在应用本发明的人工转录因子后将较小或不存在,或者可能通过消除免疫原性同时仍保留靶位点结合及因此的功能的对整体结构的小改变来避免或进一步降到最低。此外,考虑用聚乙二醇修饰本发明的人工转录因子以降低免疫原性。此外,应用本发明的人工转录因子到免疫赦免器官诸如眼或脑,将避免任何免疫反应,并降低全身对人工转录因子的耐受。对于治疗免疫赦免器官外的慢性疾病,考虑经在前眼球内注射诱导免疫耐受。

[0045] 调节受体活性的小分子的鉴定主要依赖于在来自不同种类物质的多种多样的不同分子中广泛且耗时的筛选程序。尤其是,对于给定受体分子的此类小分子药物的快速、合理设计是非常有挑战的。相反,本发明的人工转录因子均属于同一物质种类,具有高度确定的总体组成。靶向两条非常不同的启动子序列的两个基于六聚锌指蛋白的人工转录因子仍具有 85%的最小氨基酸序列同一性和总体相似的三级结构,并且能够经标准化方法(如下文所述)以快速且经济的方式来生成。因此,本发明的人工转录因子在一类分子中组合了对非常广泛且不同的组的靶格外高的特异性与总体相似的组成。此外,将本发明的人工转录因子配制到药物中可以依赖于进一步加速药物开发进程的先前经验。

[0046] 人工转录因子的蛋白质转导结构域(PTD)介导的胞内递送是以新方式利用生物制

剂对靶受体分子的高选择性的新方法。尽管常规药物调节某些受体的活性，但人工转录因子改变这些蛋白的可利用性。并且由于人工转录因子被设计为特异性作用于此类受体基因的启动子区，因此本发明允许选择性地靶向甚至密切相关的蛋白。这基于甚至密切相关的蛋白的启动子区的仅松散的保守性。蛋白质转导结构域介导的人工转录因子的递送用于调节细胞对外界刺激的反应，所述外界刺激包括但不限于激素如例如胰岛素、内皮素或免疫调节肽诸如白细胞介素、趋化因子和细胞因子，但还有抗体、抗原和分子模式。而且对其他可溶性信号分子诸如谷氨酸或 γ-氨基丁酸和其他神经递质的细胞应答可以通过该方法调节。利用本发明的人工转录因子的高选择性，基于给定受体蛋白家族的某些成员的时常组织特异性表达，甚至药物作用的组织特异性靶向也是可能的。

[0047] 本发明还涉及此类人工转录因子在治疗由特异性效应物与受体的结合所调节的疾病中的用途，为此多指锌指蛋白特异性靶向受体基因启动子。同样，本发明涉及治疗疾病的方法，其包括向有其需要的患者施用治疗有效量的人工转录因子，其中待治疗疾病由特异性效应物对受体的结合所调节，为此多指锌指蛋白特异性靶向受体基因启动子。

[0048] 所考虑的多指锌指蛋白是四聚的、五聚的、六聚的或七聚的锌指蛋白。“四聚的”、“五聚的”、“六聚的”和“七聚的”表示锌指蛋白分别由四个、五个、六个和七个部分蛋白结构组成，其每一个具有对特定核苷酸三联体的结合特异性。优选地，人工转录因子包含六聚锌指蛋白。

[0049] *在给定启动子区内选择靶位点*

靶位点选择对于成功产生有功能的人工转录因子是至关重要的。对于人工转录因子体内调节靶基因表达，它必须在靶基因的基因组背景中结合它的靶位点。这需要 DNA 靶位点的可接近性，表示该区域中的染色体 DNA 并未被围绕组蛋白紧密包装成核小体，并且没有 DNA 修饰诸如甲基化干扰人工转录因子结合。尽管大部分的人基因组被紧密包装并且是转录无活性的，但活跃转录基因的转录起始位点的紧挨的附近 (-1000 至 +200bp) 必须对于内源转录因子和转录机诸如 RNA 聚合酶是可接近的。因此，在任何给定靶基因的该区域中选择靶位点将极大增强产生具有体内期望功能的人工转录因子的成功率。

[0050] *在人内皮素受体 A (ETRA) 启动子区内选择靶位点*

通过如下分析人 ETRA 基因确定特异性靶向内皮素受体 A 启动子的六聚锌指蛋白 (6ZFP)：

人 ETRA 基因 (含启动子区 SEQ ID NO: 25、编码区 SEQ ID NO: 26 的基因组区) 由被七个内含子分隔的八个外显子构成 (Hosoda K. 等 , 1992, *J Biol Chem* 267, 18797-18804)。外显子 1 和内含子 1 位于 5' 非编码区，转录起始位点在 ATG 翻译起始密码子上游 502 bp。

[0051] 分析相对于转录起始位点从 -1000 bp 至 +100 bp 的 ETRA 启动子区的 $(GNN)_6$ 靶位点(图 2 和表 1)。使用 ZiFiT 软件 (Sander J.D. 等 , 2010, *Nucleic Acids Res* 38, W462-468), 鉴定到 TS-855 和 TS+74，并且选择 Barbas 组的 GNN 锌指模块来设计 ZFP-855A 和 ZFP+74A。

[0052] 尽管基于预先选择的锌指模块的锌指蛋白的合理设计是已知的，但基于含有无偏向 ZFP 的文库的筛选方法证明对于鉴定高亲和力锌指蛋白是优秀的。因此，选择最初被 ZiFiT 程序排除的另外的 $(GNN)_6$ 序列 (TS-103)。此外，在 TS-855 和 TS+74 之间选择含有 GNN 或 CNN 三联体的其他 18 bp 靶位点。此外，在 TS-855 和 TS-306 之间选择 15 bp 靶位点

用于筛选 6ZFP 文库。

[0053] *在人内皮素受体 B(ETRB)启动子区内选择靶位点*

如下选择用于调节 ETRB 表达的人工转录因子的结合位点:ETRB 基因的 5' 区 (SEQ ID NO: 27) 在翻译起始位点上游的 -1195、-817、-229 和 -258 bp 处含有假定的转录起始位点。因此,在 -1149 bp 和 -487 bp 之间选择由 GNN 或 CNN 三联体组成的 18bp 靶位点(见图 5)。

[0054] *在人 Toll 样受体 4(TLR4)启动子区内选择靶位点*

在 TLR4 基因的 5' 区 (SEQ ID NO: 28) 中在相对于转录起始位点的 -276 bp 和 +113 bp 之间选择由六个 G/CNN 三联体组成的调节 TLR4 表达人工转录因子的 18 bp 潜在结合位点(见图 3)。

[0055] *在人高亲和力 IgE 受体 A(FCER1A)启动子区内选择靶位点*

在 FCER1A 基因的 5' 区 (SEQ ID NO: 29) 中选择 FCER1A 表达调节人工转录因子的结合位点。人 FCER1A 启动子含有在转录起始位点上游 200 bp 左右的近侧调节区以及进一步上游的含有 IL-4 应答元件的远侧区 (Nishiyama C., 2006, *Biosci Biotechnol Biochem* 70(1), 1-9)。在远侧调节区中相对于转录起始位点的 -147 bp 和 +17 bp 处选择调节 FCER1A 人工转录因子的潜在结合位点。

[0056] *用于选择六聚锌指蛋白的改良的酵母单杂交 (Y1H) 筛选*

基于由 Gonzalez B. 等, 2010, *Nat Protoc* 5, 791-810 发表的文库克隆方案,将酵母穿梭载体 pGAD10 (pAN1025) 改良以允许锌指蛋白编码文库有效产生。为了改进克隆效力,在 pBluescript 中完成锌指蛋白编码文库的最初装配,随后将文库转移至 pAN1025 中。使用连续消化和 DNA 去磷酸化,防止形成头-头或尾-尾连接的锌指模块,因而改进了有效的文库覆盖度。

[0057] 常规 Y1H 筛选旨在从天然存在蛋白相对小的库中鉴定出给定 DNA 序列的转录因子。本文的目的在于从均具有结合所用靶位点的潜力的蛋白的非常大的库($16*10^6$ 个左右)中选择六聚锌指蛋白(6ZFP)。这需要使用额外的选择压力以鉴定具有最高靶位点亲和力的 6ZFP。尽管一般将 200 ng/ml 的金担子素 A (AbA) 浓度用于常规 Y1H 分析,但将高至 4000 ng/ml AbA 用于改进上文用所利用的 Y1H 系统通常实现的选择 (MatchMaker Gold, Clontech)。

[0058] 为了进一步提高选择压力并因而鉴定对给定靶位点具有高得多的结合能力的 6ZFP,进一步改良 Y1H 系统。对于第一轮选择,将人工转录因子文库包含在基于 2μ 复制起点的酵母载体中。此类载体在酵母细胞中独立复制至约 50 个拷贝,导致 6ZFP 的强力产生。对于第二轮选择,将人工转录因子文库包含在基于具有 1-2/ 细胞的拷贝数的低拷贝 ARS/CEN 载体的酵母载体中。由于文库锌指蛋白的较低表达水平,组合有 4000 ng/ml 的 AbA 的基于 ARS/CEN 的 Y1H 筛选更为灵敏,并且产生对其同族靶序列具有更高结合亲和力的 6ZFP。

[0059] 表 1:ETRA 启动子区内的靶位点和 Y1H 筛选的结果

靶位点DNA序列 5'-3' [a])	来自Y1H筛选的ZFP [b])	分离的ZFP的ZF模块 (F1-F2-F3-F4-F5-F6) [c])	SEQ ID NO[d])
-855 TCCTCCAGCCCCTGCTAC (SEQ ID NO: 30)	ZFP-855A	GM03-GM03-GM14-GM11-GM02-GM04	31
	ZFP-855B	GM15-GM03-GM04-GM15-GM02-GM04	32
	ZFP-855C	GM15-GM11-GM08-GM11-GM02-GM04	33
	ZFP-855D	GM02-GM02-GM02-GM15-GM11-GM16	34
	ZFP-855E	GM03-GM15-GM03-GM08-GM11-GM04	35
	ZFP-855F	GM03-GM07-GM16-GM15-GM02-GM04	36
	ZFP-855G	GM15-GM03-GM06-GM10-GM04-GM04	37
-555 CTCCTCTCCCACCCC (SEQ ID NO: 38)	ZFP-555A	GM15-GM11-GM03-GM12-GM11-GM15	39
	ZFP-555B	GM09-GM03-GM11-GM11-GM10-GM06	40
	ZFP-555C	GM15-GM02-GM12-GM02-GM09-GM06	41
	ZFP-555D	GM09-GM07-GM12-GM03-GM12-GM06	42
	ZFP-555E	GM08-GM03-GM09-GM03-GM11-GM09	43
-487 AAGGTCGGCTTCTTC (SEQ ID NO: 44)	ZFP-487A	CM04-GM13-GM12-GM02-GM16-GM09	45
	ZFP-487B	CM15-GM16-GM06-GM01-GM01-GM13	46
	ZFP-487C	CM12-GM13-GM06-GM01-GM01-GM16	47
	ZFP-487D	CM13-GM10-GM01-GM01-GM14-GM05	48
	ZFP-487E	CM15-GM06-GM06-GM01-GM01-GM16	49
	ZFP-487F	CM11-GM09-GM16-GM05-GM04-GM04	50
-447 CGGAGCCACGCGCTG (SEQ ID NO: 51)	ZFP-447A	GM16-CM14-GM10-GM13-CM09-CM11	52
-306 CGGCTCCTCAACGGCCTC (SEQ ID NO: 53)	ZFP-306A	CM15-GM04-GM09-GM16-GM05-GM04	54
	ZFP-306B	CM11-GM04-GM03-GM09-GM04-GM05	55
	ZFP-306C	CM13-GM04-GM03-GM09-GM01-GM06	56
	ZFP-306D	CM05-GM04-GM03-GM09-GM01-GM06	57
-230 CCACCCGTGGGCCCTGGC (SEQ ID NO: 58)	ZFP-230A	GM03-CM09-GM09-GM05-CM11-CM15	59
	ZFP-230B	GM12-CM11-GM04-GM07-CM03-CM08	60
	ZFP-230C	GM03-CM07-GM03-GM02-CM15-CM11	61
	ZFP-230D	GM12-CM11-GM04-GM07-CM07-CM12	62
	ZFP-230E	GM13-CM09-GM13-GM13-CM11-CM12	63
	ZFP-230F	GM13-CM09-GM07-GM04-CM11-CM12	64

-103 CTCCTCCACATCCCCCAC (SEQ ID NO: 65)	ZFP-103A	GM15-GM08-GM14-GM13-GM11-GM16	66
	ZFP-103B	GM07-GM12-GM13-GM11-GM02-GM07	67
	ZFP-103C	GM06-GM15-GM12-GM13-GM11-GM07	68
	ZFP-103D	GM10-GM12-GM13-GM11-GM16-GM08	69
	ZFP-103E	GM15-GM07-GM12-GM13-GM11-GM06	70
	ZFP-103F	GM03-GM06-GM12-GM13-GM11-GM05	71
	ZFP-103G	GM14-GM10-GM13-GM11-GM11-GM07	72
	ZFP-103H	GM01-GM12-GM10-GM14-GM11-GM10	73
	ZFP-103I	GM07-GM06-GM12-GM13-GM11-GM16	74
	ZFP-103J	GM05-GM10-GM13-GM11-GM08-GM06	75
	ZFP-103K	GM07-GM10-GM13-GM11-GM11-GM08	76
	ZFP-103L	GM10-GM12-GM13-GM11-GM16-GM06	77
	ZFP-103M	GM10-GM12-GM13-GM11-GM04-GM06	78
	ZFP-103N	GM03-GM07-GM10-GM13-GM11-GM08	79
	ZFP-103O	GM05-GM04-GM13-GM11-GM08	80
-37 GGCCTGGAAGGGGGCGGC (SEQ ID NO: 81)	ZFP-37A	GM14-GM04-GM04-GM12-CM11-GM07	82
	ZFP-37B	GM02-GM02-GM12-GM13-CM11-GM12	83
	ZFP-37C	GM08-GM13-GM04-GM06-CM11-GM09	84
	ZFP-37D	GM04-GM04-GM06-GM11-CM03-GM04	85
	ZFP-37E	GM02-GM02-GM13-GM11-CM14-GM07	86
	ZFP-37F	GM11-GM01-GM12-GM07-CM15-GM06	87
	ZFP-37G	GM02-GM02-GM02-GM11-CM06-GM07	88
	ZFP-37H	GM12-GM16-GM04-GM06-CM11-GM09	89
	ZFP-37I	GM03-GM07-GM11-GM13-CM14-GM06	90
	ZFP-37J	GM06-GM13-GM04-GM06-CM11-GM09	91
	ZFP-37K	GM15-GM07-GM12-GM13-CM11-GM15	92
	ZFP-37L	GM15-GM14-GM02-GM10-CM11-GM08	93
	ZFP-37M	GM08-GM02-GM10-GM11-CM14-GM06	94
	ZFP-37N	GM02-GM02-GM12-GM13-CM11-GM03	95
+74 GGAGGAGACGGGGAGGAC (SEQ ID NO: 96)	ZFP+74A	GM05-GM09-GM11-GM05-GM03-GM03	97
	ZFP+74B	GM01-GM12-GM07-GM05-GM03-GM07	98
	ZFP+74C	GM09-GM11-GM08-GM05-GM11-GM07	99
	ZFP+74D	GM09-GM09-GM04-GM02-GM12-GM09	100
	ZFP+74E	GM12-GM11-GM11-GM05-GM03-GM13	101
	ZFP+74F	GM16-GM09-GM07-GM05-GM04-GM07	102
	ZFP+74G	GM09-GM15-GM05-GM02-GM07-GM06	103
	ZFP+74H	GM09-GM07-GM05-GM15-GM03-GM06	104
	ZFP+74I	GM09-GM07-GM08-GM03-GM03-GM10	105
	ZFP+74J	GM09-GM12-GM06-GM03-GM03-GM07	106
	ZFP+74K	GM08-GM09-GM06-GM05-GM03-GM07	107
	ZFP+74L	GM16-GM05-GM06-GM09-GM11-GM06	108
	ZFP+74M	GM08-GM09-GM12-GM14-GM05-GM12	109
	ZFP+74N	GM15-GM09-GM08-GM07-GM03-GM03	110
	ZFP+74O	GM09-GM11-GM07-GM05-GM13-GM16	111
	ZFP+74P	GM11-GM05-GM12-GM12-GM04-GM03	112
	ZFP+74Q	GM05-GM12-GM09-GM05-GM16-GM07	113
	ZFP+74R	GM09-GM10-GM05-GM03-GM07-GM07	114
	ZFP+74S	GM05-GM12-GM15-GM05-GM12-GM16	115
	ZFP+74T	GM01-GM13-GM12-GM15-GM07-GM12	116
	ZFP+74U	GM09-GM11-GM06-GM03-GM07-GM08	117
	ZFP+74V	GM09-GM12-GM15-GM05-GM04-GM14	118

[a]) 第 1 栏中显示 ETRA 启动子靶位点(根据它们与转录起始位点的距离来命名)。

[b]) 第 2 栏对在 Y1H 筛选中鉴定到结合 ETRA 启动子靶位点的 ZFP 命名。命名方案如下 :ZFP,随后为靶位点的名称和指明在筛选中分离到的不同 ZFP 的字母。

[c]) 第 3 栏根据它们的确定的结合偏好通过详述各个锌指模块显示了 ZFP 的构成。GM01 指明优选结合至 GAA 三联体的锌指模块，GM02 指明优选结合至 GCA，GM03 指明优选结合至 GGA，GM04 指明优选结合至 GTA，GM05 指明优选结合至 GAC，GM06 指明优选结合至 GCC，GM07 指明优选结合至 GGC，GM08 指明优选结合至 GTC，GM09 指明优选结合至 GAG，GM10 指明优选结合至 GCG，GM11 指明优选结合至 GGG，GM12 指明优选结合至 GTG，GM13 指明优选结合至 GAT，GM14 指明优选结合至 GCT，GM15 指明优选结合至 GGT，GM16 指明优选结合至 GTT，并且此外，CM01 指明优选结合至 CAC，CM02 指明优选结合至 CAA，CM03 指明优选结合至 CAG，CM04 指明优选结合至 CAT，CM05 指明优选结合至 CCA，CM06 指明优选结合至 CCC，CM07 指明优选结合至 CCG CM08 指明优选结合至 CCT，CM09 指明优选结合至 CGA，CM10 指明优选结合至 CGC，CM11 指明优选结合至 CGG，CM12 指明优选结合至 CGT，CM13 指明优选结合至 CTA，CM14 指明优选结合至 CTG，和 CM15 指明优选结合至 CTT。

[d]) 第 4 栏指鉴定到的结合各个靶位点序列的 ZFP 的序列 ID。

[0060] 表 2 :ETRB 启动子内的靶位点和 Y1H 筛选的结果

靶位点DNA序列 5'-3' [a])	来自Y1H筛选的ZFP [b])	分离的ZFP的ZF模块 (F1-F2-F3-F4-F5-F6) [c])	SEQ ID NO[d])
-1149 CTCGGGCAACTACTACTG (SEQ ID NO: 119)	ZEB-1149A	CM14-CM12-CM13-CM06-GM09-CM11	120
	ZEB -1149B	CM14-CM08-CM11-CM11-GM09-CM11	121
	ZEB -1149C	CM12-CM14-CM11-CM11-GM09-CM11	122
	ZEB -1149D	CM06-CM04-CM11-CM11-GM09-CM11	123
	ZEB -1149E	CM11-CM12-CM08-CM08-GM06-CM06	124
	ZEB -1149F	CM11-CM08-CM12-CM11-GM09-CM11	125
	ZEB -1149G	CM15-CM11-CM08-CM06-GM09-CM11	126
	ZEB -1149H	CM14-CM15-CM04-CM15-GM13-CM11	127
	ZEB -1149I	CM08-CM12-CM11-CM11-GM09-CM11	128
	ZEB -1149J	CM02-CM10-CM11-CM11-GM09-CM11	129
	ZEB -1149K	CM14-CM04-CM11-CM11-GM09-CM11	130
	ZEB -1149L	CM15-CM12-CM11-CM11-GM09-CM11	131
	ZEB -1149M	CM08-CM12-CM11-CM11-GM09-CM11	132
	ZEB -1149N	CM15-CM08-CM11-CM11-GM09-CM11	133
	ZEB -1149O	CM06-CM08-CM04-CM11-GM07-CM08	134
	ZEB -1149P	CM09-CM11-CM11-GM09-CM11	135
	ZEB -1149Q	CM15-CM14-CM12-CM12-GM04-CM08	136
-487 GAGGTTCCCCTGCGGGGC (SEQ ID NO: 137)	ZEB -487A	GM03-CM11-CM14-CM12-GM16-GM13	138
	ZEB -487B	GM07-CM11-CM14-CM06-GM16-GM09	139
	ZEB -487C	GM15-CM11-CM08-CM12-GM16-GM13	140
	ZEB -487D	GM03-CM11-CM15-CM12-GM16-GM09	141
	ZEB -487E	GM15-CM11-CM14-CM12-GM04-GM09	142
	ZEB -487F	GM03-CM11-CM14-CM12-GM04-GM13	143

[a]) 第 1 栏中显示 ETRB 启动子靶位点(根据它们与翻译起始位点的距离来命名)。

[b]) 第 2 栏对在 Y1H 筛选中鉴定到结合 ETRB 启动子靶位点的 ZFP 命名。命名方案如下：ZEP,随后为靶位点的名称和指明在筛选中分离到的不同 ZFP 的字母。

[c]) 第 3 栏根据它们的确定的结合偏好通过详述各个锌指模块显示了 ZFP 的构成。GM01 指明优选结合至 GAA 三联体的锌指模块，GM02 指明优选结合至 GCA，GM03 指明优选结合至 GGA，GM04 指明优选结合至 GTA，GM05 指明优选结合至 GAC，GM06 指明优选结合至 GCC，GM07 指明优选结合至 GGC，GM08 指明优选结合至 GTC，GM09 指明优选结合至 GAG，GM10 指

明优选结合至 GCG，GM11 指明优选结合至 GGG，GM12 指明优选结合至 GTG，GM13 指明优选结合至 GAT，GM14 指明优选结合至 GCT，GM15 指明优选结合至 GGT，GM16 指明优选结合至 GTT，并且此外，CM01 指明优选结合至 CAC，CM02 指明优选结合至 CAA，CM03 指明优选结合至 CAG，CM04 指明优选结合至 CAT，CM05 指明优选结合至 CCA，CM06 指明优选结合至 CCC，CM07 指明优选结合至 CCG CM08 指明优选结合至 CCT，CM09 指明优选结合至 CGA，CM10 指明优选结合至 CGC，CM11 指明优选结合至 CGG，CM12 指明优选结合至 CGT，CM13 指明优选结合至 CTA，CM14 指明优选结合至 CTG，和 CM15 指明优选结合至 CTT。

[d]）第 4 栏指鉴定到的结合各个靶位点序列的 ZFP 的序列 ID。

[0061] 表 3：TLR4 启动子内的靶位点和 Y1H 筛选的结果

靶位点DNA序列 5'-3' a)	来自Y1H筛选的ZFP b)	分离的ZFP的ZF模块 (F1-F2-F3-F4-F5-F6) c)	SEQ ID NOd)
-276 CACCAAGCCCAGGCAGAG (SEQ ID NO: 144)	ZFP-276A	GM09-GM04-CM03-GM13-CM02-CM08	145
	ZFP-276B	GM09-GM02-CM03-GM04-CM08-CM03	146
	ZFP-276C	GM09-GM04-CM03-GM04-CM02-CM15	147
	ZFP-276D	GM09-GM02-CM14-GM04-CM02-CM14	148
	ZFP-276E	GM09-GM02-CM03-GM13-CM08-CM12	149
	ZFP-276F	GM09-GM02-CM03-GM16-CM02-CM02	150
	ZFP-276G	GM09-GM02-CM03-GM16-CM08-CM12	151
	ZFP-276H	GM11-GM02-CM03-GM16-CM02-CM12	152
	ZFP-276I	GM09-GM04-CM14-GM14-CM02-CM12	153
-55 GCTGTGGGGCGGCTCGAG (SEQ ID NO: 154)	ZFP-55A	GM07-CM15-CM12-GM09-GM01-GM13	155
	ZFP-55B	GM03-CM09-CM04-GM16-GM09-GM07	156
	ZFP-55C	GM07-CM15-CM06-GM14-GM06-GM12	157
	ZFP-55D	GM13-CM11-CM04-GM14-GM04-GM07	158
	ZFP-55E	GM06-CM03-CM12-GM09-GM01-GM16	159
	ZFP-55F	GM07-CM08-CM05-GM01-GM09-GM06	160
	ZFP-55G	GM13-CM11-CM11-GM06-GM02-GM06	161
	ZFP-55H	GM04-CM14-CM05-GM09-GM09-GM13	162
	ZFP-55I	GM07-CM04-CM15-GM02-GM12-GM09	163
	ZFP-55J	GM06-CM13-CM04-GM16-GM09-GM13	164
+113 ATGGCCTTCCTCTCCTGC (SEQ ID NO: 165)	ZFP+113A	CM13-GM07-GM09-GM03-GM02-GM06	166
	ZFP+113B	CM06-GM13-GM12-GM02-GM03-GM12	167
	ZFP+113C	CM11-GM03-GM09-GM03-GM08-GM06	168
	ZFP+113D	CM06-GM13-GM07-GM01-GM11-GM07	169
	ZFP+113E	CM06-GM07-GM03-GM09-GM07-GM02	170
	ZFP+113F	CM04-GM07-GM02-GM09-GM07-GM02	171
	ZFP+113G	CM14-GM07-GM03-GM09-GM07-GM16	172
	ZFP+113H	CM12-GM13-GM09-GM15-GM02-GM06	173

[a]）第 1 栏中显示 TLR4 启动子靶位点（根据它们与转录起始位点的距离来命名）。

[b]）第 2 栏对在 Y1H 筛选中鉴定到结合 TLR4 启动子靶位点的 ZFP 命名。命名方案如下：ZFP，随后为靶位点的名称和指明在筛选中分离到的不同 ZFP 的字母。

[c]）第 3 栏根据它们的确定的结合偏好通过详述各个锌指模块显示了 ZFP 的构成。GM01 指明优选结合至 GAA 三联体的锌指模块，GM02 指明优选结合至 GCA，GM03 指明优选结合至 GGA，GM04 指明优选结合至 GTA，GM05 指明优选结合至 GAC，GM06 指明优选结合至 GCC，GM07 指明优选结合至 GGC，GM08 指明优选结合至 GTC，GM09 指明优选结合至 GAG，GM10 指明优选结合至 GCG，GM11 指明优选结合至 GGG，GM12 指明优选结合至 GTG，GM13 指明优选

结合至 GAT，GM14 指明优选结合至 GCT，GM15 指明优选结合至 GGT，GM16 指明优选结合至 GTT，并且此外，CM01 指明优选结合至 CAC，CM02 指明优选结合至 CAA，CM03 指明优选结合至 CAG，CM04 指明优选结合至 CAT，CM05 指明优选结合至 CCA，CM06 指明优选结合至 CCC，CM07 指明优选结合至 CCG CM08 指明优选结合至 CCT，CM09 指明优选结合至 CGA，CM10 指明优选结合至 CGC，CM11 指明优选结合至 CGG，CM12 指明优选结合至 CGT，CM13 指明优选结合至 CTA，CM14 指明优选结合至 CTG，和 CM15 指明优选结合至 CTT。

d) 第 4 栏指鉴定到的结合各个靶位点序列的 ZFP 的序列 ID。

[0062] 表 4 :FCER1A 启动子内的靶位点和 Y1H 筛选的结果

靶位点DNA序列 5'-3' a)	来自Y1H筛选的ZFP b)	分离的ZFP的ZF模块 (F1-F2-F3-F4-F5-F6) c)	SEQ ID NO d)
-147 GCCCAGTTGGGCACCATC (SEQ ID NO: 174)	ZFP-147A	GM07-CM14-CM02-GM16-GM15-GM13	175
	ZFP-147B	GM04-CM14-CM02-GM16-GM16-GM13	176
	ZFP-147C	GM04-CM14-CM09-GM16-GM16-GM13	177
	ZFP-147D	GM16-CM14-CM09-GM16-GM15-GM13	178
	ZFP-147E	GM15-CM14-CM09-GM16-GM03-GM13	179
	ZFP-147F	GM15-CM09-CM02-GM01-GM15-GM13	180
	ZFP-147G	GM03-CM14-CM09-GM04-GM15-GM13	181
+17 GTCCATGAAGAAGATGGC (SEQ ID NO: 182)	ZFP+17A	GM15-GM16-GM06-GM13-CM11-GM04	183
	ZFP+17B	GM14-GM12-GM10-GM13-CM11-GM04	184
	ZFP+17C	GM12-GM04-GM06-GM13-CM11-GM04	185
	ZFP+17D	GM05-GM11-GM06-GM13-CM11-GM04	186
	ZFP+17E	GM10-GM13-GM11-GM04-CM15-GM04	187
	ZFP+17F	GM05-GM12-GM06-GM13-CM11-GM04	188
	ZFP+17G	GM02-GM12-GM06-GM13-CM03-GM04	189
	ZFP+17H	GM05-GM01-GM01-GM13-CM11-GM04	190
	ZFP+17I	GM02-GM12-GM02-GM13-CM11-GM11	191

a) 第 1 栏中显示 FCER1A 启动子靶位点(根据它们与转录起始位点的距离来命名)。

b) 第 2 栏对在 Y1H 筛选中鉴定到结合 FCER1A 启动子靶位点的 ZFP 命名。命名方案如下 :ZFP,随后为靶位点的名称和指明在筛选中分离到的不同 ZFP 的字母。

c) 第 3 栏根据它们的确定的结合偏好通过详述各个锌指模块显示了 ZFP 的构成。GM01 指明优选结合至 GAA 三联体的锌指模块，GM02 指明优选结合至 GCA，GM03 指明优选结合至 GGA，GM04 指明优选结合至 GTA，GM05 指明优选结合至 GAC，GM06 指明优选结合至 GCC，GM07 指明优选结合至 GGC，GM08 指明优选结合至 GTC，GM09 指明优选结合至 GAG，GM10 指明优选结合至 GCG，GM11 指明优选结合至 GGG，GM12 指明优选结合至 GTG，GM13 指明优选结合至 GAT，GM14 指明优选结合至 GCT，GM15 指明优选结合至 GGT，GM16 指明优选结合至 GTT，并且此外，CM01 指明优选结合至 CAC，CM02 指明优选结合至 CAA，CM03 指明优选结合至 CAG，CM04 指明优选结合至 CAT，CM05 指明优选结合至 CCA，CM06 指明优选结合至 CCC，CM07 指明优选结合至 CCG CM08 指明优选结合至 CCT，CM09 指明优选结合至 CGA，CM10 指明优选结合至 CGC，CM11 指明优选结合至 CGG，CM12 指明优选结合至 CGT，CM13 指明优选结合至 CTA，CM14 指明优选结合至 CTG，和 CM15 指明优选结合至 CTT。

d) 第 4 栏指鉴定到的结合各个靶位点序列的 ZFP 的序列 ID。

[0063] 本发明的人工转录因子包含基于表 1-4 第 3 栏中显示的锌指模块组成的锌指蛋白，其中高至三个单独的锌指模块与具有可选结合特征的其他锌指模块交换，以调节人工

转录因子与它的靶序列的结合。

[0064] 本发明的人工转录因子包含基于表 1-4 第 3 栏中显示的锌指模块组成的锌指蛋白，其中交换单独的氨基酸以将潜在的免疫原性降到最低，同时保留对预期靶位点的结合亲和力。

[0065] 优选地，本发明的人工转录因子包含具有选自以下的蛋白序列的锌指蛋白 :SEQ ID NO:31 至 SEQ ID NO:37, SEQ ID NO:39 至 SEQ ID NO:43, SEQ ID NO:45 至 SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54 至 SEQ ID NO:57, SEQ ID NO:59 至 SEQ ID NO:64, SEQ ID NO:66 至 SEQ ID NO:80, SEQ ID NO:82 至 SEQ ID NO:95, SEQ ID NO:97 至 SEQ ID NO:118, SEQ ID NO:120 至 SEQ ID NO:136, SEQ ID NO:138 至 SEQ ID NO:143, SEQ ID NO:145 至 SEQ ID NO:153, SEQ ID NO:155 至 SEQ ID NO:164, SEQ ID NO:166 至 SEQ ID NO:173, SEQ ID NO:175 至 SEQ ID NO:181, 和 SEQ ID NO:183 至 SEQ ID NO:191。

[0066] 更优选地，本发明的人工转录因子包含具有 SEQ ID NO 135 的五聚锌指蛋白或具有选自以下蛋白序列的六聚锌指蛋白 :SEQ ID NO 33, 54, 56, 64, 68, 83, 84, 85, 97, 101, 114, 118, 122, 127, 133, 140, 142, 146, 147, 156, 159, 169, 171, 173, 175, 181, 184, 187, 189, 和 191。

[0067] 甚至更优选的是人工转录因子，其包含具有 SEQ ID NO 135 的五聚锌指蛋白或具有选自以下蛋白序列的六聚锌指蛋白 :SEQ ID NO 56, 83, 85, 101, 114, 118, 127, 133, 140, 142, 146, 147, 156, 159, 175, 和 181。

[0068] 甚至更优选的是人工转录因子，其包含具有 SEQ ID NO 118, 127, 146, 156, 或 175 的六聚锌指蛋白。

[0069] 甚至更优选的是人工转录因子，其包含具有 SEQ ID NO 118, 127, 156, 或 175 的六聚锌指蛋白。

[0070] 最优选的是人工转录因子，其包含具有 SEQ ID NO 118, 156, 或 175 的六聚锌指蛋白。

[0071] 将多指锌指蛋白融合至调节域，其是抑制或激活蛋白结构域。考虑的抑制蛋白结构域是由基因本体论 GO:0001071 确定的蛋白的转录活性结构域，诸如 N- 末端 KRAB、C- 末端 KRAB、SID 和 ERD 结构域、优选 KRAB 或 SID。考虑的激活蛋白结构域是由基因本体论 GO:0001071 确定的蛋白的转录活性结构域，诸如 VP16 或 VP64 (VP16 的四聚体重复)，优选 VP64。

[0072] 进一步对于融合至抑制或激活蛋白结构域的多指锌指蛋白，本发明的人工转录因子包含核定位序列(NLS)。考虑的核定位序列是通过结合至由基因本体论 GO:0008139 确定的蛋白而赋予核输入的氨基酸基序，例如碱性氨基酸的簇，其包含赖氨酸残基，随后为赖氨酸或精氨酸残基，随后为任何氨基酸，随后为赖氨酸或精氨酸残基 (K-K/R-X-K/R 共有序列 , Chelsky D. 等 , 1989 *Mol Cell Biol* 9, 2487-2492) 或 SV40 NLS，并且 SV40 NLS 是优选的。

[0073] 本发明的人工转录因子进一步任选包含蛋白质转导结构域(PTD)。考虑的蛋白质转导结构域是 HIV 衍生的 TAT 肽、HSV-1 VP22 肽、合成肽 mT02 (PVRRPRRRRRRK, SEQ ID NO: 192, Yoshikawa T. 等 2009 *Biomaterials* 30, 3318-23)、合成肽 mT03 (THRLPRRRRRRK, SEQ ID NO: 193)、R9 肽 (RRRRRRRRR, SEQ ID NO: 194)、ANTP 结构域和保护性抗原 / 致死因子 N

末端 PTD，优选 TAT PTD。

[0074] 指向受体基因启动子但不具有蛋白质转导结构域的人工转录因子也是本发明的主题。它们是如上文确定的本发明的人工转录因子的中间体。

[0075] 指向 ETRA 但不具有蛋白质转导结构域的人工转录因子也是本发明的主题。它们是如上文确定的本发明的人工转录因子的中间体。

[0076] 指向 ETRB 启动子但不具有蛋白质转导结构域的人工转录因子也是本发明的主题。它们是如上文确定的本发明的人工转录因子的中间体。

[0077] 指向 TLR4 启动子但不具有蛋白质转导结构域的人工转录因子也是本发明的主题。它们是如上文确定的本发明的人工转录因子的中间体。

[0078] 指向 FCER1A 启动子但不具有蛋白质转导结构域的人工转录因子也是本发明的主题。它们是如上文确定的本发明的人工转录因子的中间体。

[0079] 本发明的人工转录因子的结构域可以通过短的柔性接头连接。短的柔性接头具有 2-8 个氨基酸，优选甘氨酸和丝氨酸。考虑的具体接头是 GGSGGS (SEQ ID NO:9)。人工转录因子还可以包含标志物以便于它们的检测和加工。

[0080] *人工转录因子在调节受体启动子活性中的活性*

根据图 6 中显示的方案从使用 Y1H 筛选选择的特异性结合受体启动子的某些靶位点的 ZFP（见表 1-4）构建基于锌指模块的人工转录因子。这些人工转录因子包含不同的转录活性结构域诸如 N- 末端 KRAB、C- 末端 KRAB、SID 或 VP64。根据发表的数据 (Beerli R.R. 等，1998 *Proc Natl Acad Sci USA* 95, 14628-14633)，预测 KRAB 以及 SID 结构域作为转录阻抑蛋白起作用，而 VP64 介导转录激活。为了评估人工转录因子（6ZFP 和转录活性结构域之间的融合体）影响由受体启动子驱动的转录的潜力，使用萤光素酶报道基因测定。为此目的，用人工转录因子表达质粒与双报道基因质粒一同共转染能够从某一启动子驱动表达的细胞。双报道基因质粒包含在所讨论的受体启动子的控制下的分泌型 *Gaussia* 萤光素酶基因以及在基于 NEG-PG04 和 EF1a-PG04 质粒 (GeneCopoeia, Rockville, MD) 的组成型 CMV 启动子的控制下的分泌型碱性磷酸酶 (SEAP) 的基因。

[0081] 许多启动子展示出细胞类型特异性表达模式，在一些细胞类型中实际上无表达，并且在其他细胞类型中高水平表达。因此，对于启动子调节研究选择合适细胞模型依赖于给定受体启动子的组织特异性。在本文显示的例子中，子宫颈癌细胞系 HeLa 细胞能够从 ETRA、ETRB 或 TLR4 启动子表达萤光素酶报道基因。由于 FCER1A 启动子的组织特异性，因此在该启动子的控制下萤光素酶的表达在 HeLa 细胞中是不可能的。因此，利用大鼠嗜碱细胞性白血病 RBL-2H3 细胞来评估针对 FCER1A 启动子的人工转录因子功能。该细胞系支持 FCER1A 启动子驱动的萤光素酶报道基因的表达，并可以使用核转染以 50％左右的效力转染。

[0082] 以 3:1 的 ATF: 报道基因质粒的比例完成共转染，以确保在用报道基因质粒和萤光素酶转染的细胞中人工转录因子（ATF）表达的存在，并且根据制造商建议 (GeneCopoeia, Rockville, MD) 测量 SEAP 活性。将萤光素酶值对 SEAP 活性进行归一化，并与设定为 100％的表达黄色荧光蛋白（YFP）的对照细胞进行比较。通过测量经转染的细胞的上清液中萤光素酶与 SEAP 活性之间的比例，仅在转染有人工转录因子质粒的细胞中受体启动子驱动的萤光素酶表达对 SEAP 表达的归一化是可能的。该方法证明对于计算并归一化不同实验之

间的转染效力中的差异是有用的，并且允许定量人工转录因子介导的给定受体启动子的调节。

[0083] 将所有萤光素酶表达研究（图 7A-11A）进行至少三次，一式三份，进行平均化，与对照转染细胞比较，表示为以对照的%计的相对萤光素酶活性（RLuA），并作图，其具有表示 SEM 的误差棒。

[0084] 人工转录因子的命名约定如下：将这样的人工转录因子用字母 AO 随后为代表靶位点的数字和辨识使用 Y1H 筛选鉴定的某一 ZFP 的字母来指定，所述人工转录因子使用哺乳动物表达载体表达于哺乳动物细胞中，并由锌指蛋白（ZFP）、核定位序列和负调节结构域诸如 SID 或 KRAB（N- 或 C- 末端）组成。向该名称添加的小写的“a”指代含有激活 VP64 结构域的人工转录因子。添加的小写“p”指代纯化的人工转录因子蛋白，其产生于异源表达系统中，并且除了上述结构域之外，还含有蛋白质转导结构域 TAT 和 HA 标签（SEQ ID NO:195）。

[0085] 图 7A 显示了 ETRA 启动子依赖性萤光素酶表达的人工转录因子依赖性下调。用如上所述的 ETRA 启动子萤光素酶 / 组成型 SEAP 报道基因构建体和 AO74A、AO74E、AO74R、AO74V 或作为对照（标记为 C）的黄色荧光蛋白（YFP）的表达质粒共转染 HeLa 细胞。这些人工转录因子指向 ETRA 启动子的 TS+74，并且含有负调节的 SID 结构域。尽管 AO74A 和 AO74E 抑制 ETRA 启动子驱动的表达约 70%，但 AO74R 和 AO74V 能够阻断 ETRA 启动子至背景水平。

[0086] 图 8A 突出显示了用于生成靶向受体启动子的转录因子的方法的多样性。通过简单交换 AO74V 或 AO74R 中的抑制结构域 SID 为激活结构域 VP64，可以产生能够增强 ETRA 启动子的转录活性至 400%左右的激活转录因子。

[0087] 使用相同方法，构建靶向 ETRB 受体启动子的人工转录因子。图 9A 显示了由含有指向 ETRB 启动子的靶位点 TS-1149 的 ZFP（见图 2）以及抑制 SID 结构域的 AO1149N 和 AO1149P 的 ETRB 启动子活性的抑制。用 ETRB 启动子萤光素酶 /SEAP 报道基因构建体和 AO1149N、AO1149P 或作为对照的 YFP 的表达质粒共转染 HeLa 细胞。AO1149N 抑制 ETRB 启动子活性 80%左右，而 AO1149P 阻断 ETRB 启动子几乎至背景水平。

[0088] 为了分析由指向 TLR4 启动子中的靶位点 TS-55 的 ZFP（见图 3）和在 C- 末端的抑制 KRAB 结构域组成的 TLR4 特异性人工转录因子 AO55B 和 AO55E 的活性，使用 *Gaussia* 萤光素酶 /SEAP 报道基因测定。如图 10 中显示，在 HeLa 细胞中 AO55B 或 AO55E 的表达抑制 TLR4 启动子驱动的表达，并且相比于表达 YFP 的对照转染的细胞，AO55B 完全阻断了萤光素酶表达。

[0089] 为了评估指向 FCER1A 启动子的人工转录因子的活性，将 AO147A 与 FCER1A 启动子驱动的 *Gaussia* 萤光素酶和如上的 CMV 驱动的 SEAP 一同表达于大鼠嗜碱 RBL-2H3 细胞中。该人工转录因子指向靶位点 TS-147，并且含有 N- 末端 KRAB 结构域。基于 FCER1A 启动子的组织特异性和使用核穿孔（nucleoporation）转染的方便性，选择 RBL-2H3 细胞。如图 11 所示，在产生 AO147A 的 RBL-2H3 细胞中 FCER1A 驱动的表达相比于表达 YFP 的对照细胞（C）降低 80%左右。

[0090] 总之，依赖于用于人工转录因子构建的调节结构域，受体启动子驱动的调节的人工转录因子介导的调节是可行的，并且能够上调表达高至 400%，或者完全阻断表达，这开发了以几乎两个数量级的级别的可能调节范围。

[0091] *评估人工转录因子的潜在毒性作用*

尽管对于给定的靶序列选择人工转录因子，并且尽管所选的靶位点在人基因组内是唯一的，但人工转录因子可能通过结合类似序列而具有脱靶作用，由此产生毒性作用。此类毒性作用可能潜在地干扰此类人工转录因子的功能测定。对于任何给定的唯一的 18 bp 靶位点，可以鉴定到具有一个、两个或三个取代的任何数目的高度相似序列。尽管这些序列可能允许人工转录因子的结合并且可能导致脱靶作用，但大部分此类脱靶位点位于其他位置而非活跃转录基因的调控序列内，极大地改善了人工转录因子处理的脱靶作用的潜力。对于以下实验，用 1 μM 转导的人工转录因子蛋白处理细胞，并使用 MTS 测定评估细胞增殖作为测量潜在毒性。每一实验进行一式三份至少三次；将人工转录因子处理后的细胞的增殖进行平均化，并表示为用相应缓冲液处理的对照的百分比。值得注意的是，向人工转录因子指代中加入“p”表示含有 TAT 蛋白质转导结构域、锌指蛋白和调节结构域诸如 SID、KRAB 或 VP64 的蛋白，而非编码不具有蛋白质转导结构域的人工转录因子的表达质粒。

[0092] 如图 7B 中显示，用 1 μM 的 A074Vp 蛋白（A074V 的转导版本）处理 HeLa 细胞两天，相对于用缓冲液处理的细胞并未引起增殖损失。类似地，用 A074Vp 处理 hUtSMC 对于这些细胞没有毒性，并且不抑制它们的增殖（图 7C）。此外，基于 ZFP-74V 的激活人工转录因子蛋白 A074Vap 不展示出对 hUtSMC 增殖的任何毒性作用（图 8B）。这些数据与含有 ZFP-74V 的人工转录因子在人基因组中的可忽略的脱靶结合是一致的。类似地，用 TLR-4 特异性人工转录因子 A055Bp（图 10C）或 FCER1A 特异性的 A0147Ap（图 11B）处理 HeLa 细胞不会导致增殖损失。总之，所有检测的人工转录因子对于它们预期靶位点是高度特异性的，并且不会引起可能导致细胞死亡或增殖降低的脱靶作用。

[0093] *使用细胞应答测定的人工转录因子功能分析*

为了确定基于 TAT 的蛋白递送后人工转录因子对内源受体启动子的功能，观察人工转录因子和对照处理的细胞之间对受体激动剂处理的细胞应答。

[0094] *人工转录因子处理后 ETRA 下调的评估*

平滑肌细胞（SMC）表达 ETRA 并且能够在暴露于 ET-1 后收缩。为了测量抗 ETRA 启动子人工转录因子 A074V 的有效性，使用人子宫平滑肌细胞（hUtSMC）作为模型系统。为此目的，将 hUtSMC 植入三维胶原网格并在暴露于 0 或 100 nM ET-1 之前用 1 μM A074Vp 或缓冲液对照处理三天。每 24 小时重复蛋白或缓冲液处理。在网格从它们的支持物上脱离下并加入 ET-1 后，观察到网格的收缩。如图 7D 中所示，相比于未用 ET-1 处理的网格，暴露于 ET1 的对照网格收缩约 78％。相反，当与未用 ET-1 处理的对照网格相比时，A074V 处理的网格在 ET-1 存在的情况下没有明显收缩。这与用 A074Vp 处理后完全阻断 ET-1 诱导的 hUtSMC 的收缩是一致的。图 7D 中显示的数据代表一式六份完成的三次独立实验的加入 ET-1 后 9 小时的平均网格面积。使用 SPSS 软件包利用一般线性单变量模型的统计学分析揭示了 A074Vp 的阻断作用的高显著性（** 代表 $p<0.001$）。

[0095] *人工转录因子处理后 TLR4 下调的评估*

巨噬细胞表达 TLR4 并且响应 LPS 结合至 TLR4 来产生促炎性细胞因子诸如 IL-6。佛波醇 -12- 肉豆蔻酸酯 -13- 乙酸酯（PMA）刺激的 U937 细胞是人巨噬细胞样细胞的广泛接受的模型。为了测量抗 TLR4 启动子人工转录因子 A055B 的有效性，用 0.5 ng/ml LPS 攻击表达 A055B 或作为对照的 YFP 的 PMA 刺激的 U937 细胞 8 小时，并且使用 ELISA 测量 IL-6 的

产生。如图 10B 中所示，相比于对照细胞，A055B 的表达显著降低 ($p< 0.005$) IL-6 的分泌 25％左右。考虑到 U937 核转染效力约为 50％，表示 A055B 在这些实验中仅在约 50％的细胞中表达，由 A055B 对 IL-6 产生的实际抑制在 50％的级别内。

[0096]　*人工转录因子处理后 FCER1 功能的评估*

IgE 抗体结合巨噬细胞表面上的异源三聚的高亲和力 IgE 受体 FCER1 时，肥大细胞和嗜碱细胞是在特应性个体中引发变应性应答的第一步。遇到变应原导致 IgE 装载的 FECR1 分子的交联，引发胞内信号级联放大，导致变应性介体和细胞因子的释放。因此，IgE 结合例如嗜碱细胞的能力是变应性过程中的一个关键步骤。为了评估用指向 FCER1 的 α 亚基启动子的人工转录因子处理后 IgE 的结合能力，用 1 μM 的 A0147Ap 或缓冲液日常处理人嗜碱 KU812F 细胞 48 小时。处理后，使用流式细胞术测量 IgE 结合能力。三次独立实验的 A0147A 处理后的 KU812F 细胞的平均 IgE 结合能力(IgEB)显示在图 11C 中。相比于对照处理后的细胞，用 A0147Ap 处理降低嗜碱细胞的 IgE 结合能力约 80％。有趣的是，尽管人工转录因子 A0147Ap 仅指向 FCER1 受体复合体的 α 亚基，但整个受体在结合 IgE 能力方面的功能极大降低。因此，预期变应原诱导的 FCER1 交联极大降低，提高了变应性介体释放的阈值。与一些其他受体不同，FCER1 是由 α、β 和 γ 亚基构成的多聚蛋白复合体，所述亚基由三个不同遗传基因座编码。只有含有一个 α、一个 β 和两个 γ 链(并且 α 链提供 IgE 结合位点)的正确装配的 FCER1 能够引发变应性应答。因此，例如用合适的人工转录因子下调 FCER1 α 链 (FCER1A) 的表达将阻止作为整体的 FCER1 的正确装配和功能。这种观点被其中消除了过敏反应的 FCER1A-/- 小鼠支持 (Dombrowicz D., 1993, *Cell* 75, 969-976)。因此，使用人工转录因子技术靶向 FCER1A 表达适合于根除变应性反应。此外，尽管人工转录因子对于一种靶基因是高度特异性的，但多聚受体通常顺从于人工转录因子介导的敲低。

[0097]　*药物组合物*

本发明还涉及包含如上定义的人工转录因子的药物组合物。考虑的药物组合物是向温血动物尤其是人肠胃外全身施用的组合物，尤其是静脉内施用的组合物，吸入的组合物，和局部施用的组合物，尤其是眼局部使用，例如作为滴眼剂，或玻璃体内、结膜下、眼球侧(parabulbar)或眼球后施用。尤其优选的是滴眼剂和玻璃体内、结膜下、眼球侧或眼球后施用的组合物。组合物包含单独的活性组分，或者优选与药学上可接受的载体一同的活性组分。进一步考虑的是缓释制剂。活性组分的剂量依赖于待治疗的疾病并依赖于物种、它的年龄、体重和个体病况、个体药代动力学数据以及施用方式。

[0098]　进一步考虑的是用于口腔递送的药物组合物，尤其是包含合适地装入胶囊的活性组分的或者另外针对消化道降解进行保护的组合物。例如，此类药物组合物可以包含膜透性增强剂、蛋白酶抑制剂，并且由肠溶包衣包封。

[0099]　药物组合物包含大约 1％至大约 95％的活性成分。单位剂量形式例如是安瓿、药瓶、吸入器、滴眼剂等。

[0100]　本发明的药物组合物以本身已知的方式制备，例如通过常规混合、溶解或冷冻干燥方法。

[0101]　优选给予使用活性组分的溶液、以及悬浮液或分散液，尤其是等渗水溶液、分散液或悬浮液，其例如在含有单独的活性组分或者与载体例如甘露醇一同的活性组分的冷冻干燥的组合物的情况下，可以在使用前配制。药物组合物可以进行灭菌和/或可以包含赋形

剂，例如防腐剂、稳定剂、湿润剂和／或乳化剂、增溶剂、用于调节渗透压的盐类和／或缓冲液，并且以本身已知的方式制备，例如通过常规溶解和冷冻干燥方法。所述溶液或悬浮液可以包含增粘剂，具体为羧甲基纤维素钠、羧甲基纤维素、葡聚糖、聚乙烯吡咯酮或明胶、或还有增溶剂，例如 Tween 80®（聚氧乙烯 (20) 脱水山梨醇单油酸酯）。

[0102] 油中悬浮液包含习惯用于注射目的的植物油、合成油或半合成油作为油组分。关于这一点，可以特别提及液体脂肪酸酯，其包含具有 8-22 个、尤其 12-22 个碳原子的长链脂肪酸作为酸组分。这些脂肪酸酯的醇组分具有最多 6 个碳原子，并且是一价醇或多价醇，例如一价、二价或三价醇，尤其是乙二醇和丙三醇。作为脂肪酸酯的混合物，植物油诸如棉子油、杏仁油、橄榄油、蓖麻油、芝麻油、大豆油和花生油尤其有用。

[0103] 可注射制剂的制造通常在无菌条件下进行，如例如装入安瓿或药瓶和容器的密封。

[0104] 对于肠胃外使用，以水可溶性形式的活性组分的水溶液，例如水可溶性盐的水溶液，或者含有增粘物质例如羧甲基纤维素钠、山梨醇和／或葡聚糖(并且如需要的话含有稳定剂)的含水注射悬浮液，是尤其合适的。活性组分任选与赋形剂一同还可以以冷冻干燥剂的形式，并且可以在肠胃外施用前通过加入合适的溶剂配制入溶液中。

[0105] 用于吸入的组合物可以以气溶胶形式如喷雾剂、雾或以滴剂的形式施用。气溶胶从溶液或悬浮液制备，其可以用剂量测定的吸入器或雾化器(即使用合适的推进剂例如二氯二氟甲烷、三氯氟甲烷、二氯四氟乙烷、二氧化碳或其他合适气体向呼吸道或肺递送特定量的药剂的装置）以由患者吸入的气溶胶化的药物的短爆发（short burst）的形式来递送。还可以提供具有合适粉末基质（base）诸如乳糖或淀粉的用于吸入的粉末喷剂。

[0106] 滴眼剂优选是含有合适的试剂以使组合物与泪液等渗 (295-305 mOsm/1) 的活性组分的等渗水溶液。考虑的试剂是氯化钠、柠檬酸、甘油、山梨醇、甘露醇、乙二醇、丙二醇、葡萄糖等。此外，组合物包含缓冲剂，例如磷酸盐缓冲剂、磷酸盐－柠檬酸盐缓冲剂或 Tris 缓冲剂(三（羟甲基）氨基甲烷)，以保持 5-8 的 pH，优选 7.0-7.4。组合物还可以含有抗菌性防腐剂，例如对羟基苯甲酸酯类、季铵盐类、诸如苯扎氯铵、聚六亚甲基双胍 (PHMB) 等。滴眼剂还可以含有黄原胶以产生凝胶样滴眼剂，和／或其他增粘剂，诸如透明质酸、甲基纤维素、聚乙烯醇或聚乙烯吡咯酮。

[0107] *人工转录因子在治疗方法中的用途*

此外，本发明涉及如上所述的指向内皮素受体 A 启动子的人工转录因子，其用于影响对内皮素的细胞应答，以降低或提高内皮素受体水平，并且用于治疗由内皮素调节的疾病，尤其用于治疗此类眼疾病。同样，本发明涉及治疗由内皮素调节的疾病的方法，其包括向有其需要的患者施用治疗有效量的指向内皮素受体 A 启动子的人工转录因子。

[0108] 由内皮素调节的疾病例如是心血管疾病，诸如原发性高血压、肺动脉高压、慢性心脏衰竭以及慢性肾衰竭。此外，通过将内皮素应答变弱来实现在不透射线材料应用之前、过程中和之后的肾保护。此外，多发性硬化受内皮素系统负面影响。

[0109] 进一步的由内皮素调节的疾病是糖尿病性肾疾病或眼疾病，诸如青光眼性神经变性、眼部血液循环中的血管功能失调、视网膜静脉阻塞、视网膜动脉阻塞、黄斑水肿、年龄相关性黄斑变性、视神经病变、中心性浆液性脉络膜视网膜病变、视网膜色素变性、Susac 综合征和 Leber 遗传性视神经病变。

[0110] 同样，本发明涉及治疗由内皮素调节的疾病的方法，其包括向有其需要的患者施用治疗有效量的本发明的人工转录因子。尤其是本发明涉及治疗青光眼性神经变性、眼部血液循环中的血管功能失调的方法，尤其是涉及治疗视网膜静脉阻塞、视网膜动脉阻塞、黄斑水肿、视神经病变、中心性浆液性脉络膜视网膜病变、视网膜色素变性和 Leber 遗传性视神经病变的方法，其包括向有其需要的患者施用有效量的本发明的人工转录因子。本发明的人工转录因子的有效量依赖于待治疗的疾病的具体类型并依赖于物种、它的年龄、体重和个体病况、个体药代动力学数据以及施用方式。对于向眼中施用，优选 0.5-1 mg 的每月玻璃体注射。对于全身应用，优选 10mg/kg 的每月注射。此外，还优选将缓释沉积物（slow release deposits）植入眼的玻璃体中。

[0111] 此外，本发明涉及如上所述的指向内皮素受体 B 启动子的人工转录因子，其用于影响对内皮素的细胞应答，以降低或提高内皮素受体水平，并且用于治疗由内皮素调节的疾病，尤其用于治疗此类眼疾病。同样，本发明涉及治疗由内皮素调节的疾病的方法，其包括向有其需要的患者施用治疗有效量的指向内皮素受体 B 启动子的人工转录因子。

[0112] 由 ET-1 依赖性的、ETRB 介导的人工转录因子调节的疾病是某些癌症、神经变性和炎症相关病症。

[0113] 此外，本发明涉及如上所述的指向 TLR4 启动子的人工转录因子，其用于影响对 LPS 的细胞应答，以降低或提高 TLR4 水平，并且用于治疗由 LPS 调节的疾病，尤其用于治疗此类眼疾病。同样，本发明涉及治疗由 LPS 调节的疾病的方法，其包括向有其需要的患者施用治疗有效量的指向 TLR4 启动子的人工转录因子。由 LPS 调节的疾病是类风湿性关节炎、动脉粥样硬化、银屑病、克罗恩病、葡萄膜炎、接触镜相关性角膜炎、角膜炎症、癌症对化学疗法的抗性等。

[0114] 此外，本发明涉及如上所述的指向 FCER1A 启动子的人工转录因子，其用于影响对 IgE 或 IgE- 抗原复合体的细胞应答，以降低或提高 FCER1 水平，并且用于治疗由 IgE 或 IgE- 抗原复合体调节的疾病，尤其用于治疗此类眼疾病。

[0115] 同样，本发明涉及治疗由 IgE 或 IgE- 抗原复合体调节的疾病的方法，其包括向有其需要的患者施用治疗有效量的指向 FCER1A 启动子的人工转录因子。由 IgE 或 IgE- 抗原复合体调节的疾病是变应性鼻炎、哮喘、湿疹和过敏反应等。

[0116] *人工转录因子在植物中的用途*

此外，本发明涉及靶向植物受体的人工转录因子的用途。优选地，将编码人工转录因子的 DNA 克隆入用于转化植物定居微生物或植物的载体中。或者，将人工转录因子以用于向植物局部应用的合适组合物直接应用。

实施例

[0117] <u>DNA 质粒的克隆</u>

对于所有克隆步骤，限制性内切核酸酶和 T4 DNA 连接酶均购自 New England Biolabs。虾碱性磷酸酶(SAP)来自 Promega。将高保真 Platinum *Pfx* DNA 聚合酶 (Invitrogen) 用于所有标准 PCR 反应中。DNA 片段和质粒按照制造商说明书使用 NucleoSpin Extract II 试剂盒、NucleoSpin Plasmid 试剂盒或 NucleoBond Xtra Midi Plus 试剂盒 (Macherey-Nagel) 来分离。寡核苷酸购自 Sigma-Aldrich。新生成质粒的所有相关 DNA 序列通过测序

(Microsynth)来验证。

[0118] *两种六聚锌指蛋白(ZFP-855A 和 ZFP+74A)的设计和克隆*

为了生成调节 ETRA 表达的人工转录因子,设计由 TAT-KRAB-ZFP 组成的融合蛋白,并通过基因合成获得对应的、密码子优化的 DNA 序列。对于融合蛋白的 ZFP 部分,使用具有对"模块装配"的参数集的 ZiFiT 软件 (Sander J.D. 等, 2010, *Nucleic Acids Res* 38, W462-468; 2007, *Nucleic Acids Res* 35, W599-605) 用所谓的"Barbas 模块"集来筛选人 ETRA 启动子区(相对于转录起始位点的 -1000 bp 至 +100 bp; RefSeq DNA NG_013343)的潜在的 $(GNN)_6$ 6ZFP 靶位点。对于旨在结合靶位点 -855 (在相对于转录起始位点的 -855 bp 处开始)的 ZFP-855A,按照 Wright D.A. 等, 2006, *Nat Protoc* 1, 1637-1652 构建 ZF59-ZF59-ZF72-ZF58-ZF71-ZF67。类似地,对于旨在结合靶位点 +74 (相对于转录起始位点的 +74 bp)的 ZFP+74A 装配 ZF65-ZF62-ZF58-ZF65-ZF59-ZF59。

[0119] 作为人工转录因子的阻抑蛋白结构域,选择由人 KOX1 蛋白的氨基酸 1-97 组成的 KRAB 结构域 (Beerli, R.R. 等, 1998, *Proc Natl Acad Sci USA* 95, 14628-14633)。对于核靶向,将氨基酸 PKKKRKV (SEQ ID NO: 196)(对应于 SV40 NLS)以及 YKDDDDK (SEQ ID NO: 197)(FLAG 标签)整合入融合蛋白中。将编码 *Xho*I-*Nco*I-KRAB-NLS-FLAG-*Spe*I-ZFP-855A-*Hin*dIII 和 *Spe*I-ZFP+74A-*Hin*dIII(以用 ZFP+74A 代替 ZFP-855A)的合成基因进行密码子优化并由 GenScript 合成。在用 *Xho*I/*Hin*dIII 切割插入片段和载体后,将 KRAB-NLS-FLAG-ZFP-855A 和 KRAB-NLS-FLAG- ZFP+74A 插入 pcDNA3(-) (Invitrogen) 中,分别产生 pAN1021 和 pAN1022。

[0120] *六聚锌指蛋白文库向猎物质粒的克隆*

按照 Gonzalez B. 等,. 2010, *Nat Protoc* 5, 791-810 并具有以下改进来克隆几个含有结合 GNN 和/或 CNN 的锌指 (ZF) 模块的六聚锌指蛋白文库。合成编码 GNN 和 CNN ZF 模块的 DNA 序列并插入 pUC57 (GenScript) 中,分别产生 pAN1049 和 pAN1073。在 pBluescript SK (+) 载体中完成 ZFP 文库的逐步装配。为了避免在每一单独克隆步骤中插入多个 ZF 模块导致无功能的蛋白,将 pBluescript(及其含有 1ZFP、2ZFP 或 3ZFP 的衍生产物)和 pAN1049 或 pAN1073 首先与一种限制酶孵育,并随后用 SAP 处理。在加入第二种限制性内切核酸酶之前,通过 NucleoSpin Extract II 试剂盒将酶去除。

[0121] 通过用 *Xho*I、SAP 并随后用 *Spe*I 处理 5 μg pBluescript 完成 pBluescript-1ZFPL 的克隆。通过将 10 μg pAN1049 (16 种不同 GNN ZF 模块的释放物)或 pAN1073 (15 种不同 CNN ZF 模块的释放物)与 *Spe*I、SAP 并随后与 *Xho*I 孵育来生成插入片段。为了生成 pBluescript-2ZFPL 和 pBluescript-3ZFPL,将 7 μg pBluescript-1ZFPL 或 pBluescript-2ZFPL 用 *Age*I 切割,去磷酸化,并用 *Spe*I 切割。通过分别向 10 μg pAN1049 或 pAN1073 应用 *Spe*I、SAP 和随后 *Xma*I 来获得插入片段。通过用 *Age*I、SAP 并随后用 *Spe*I 处理 6 μg 的 pBluescript-3ZFPL 以获得切割后的载体,来完成 pBluescript-6ZFPL 的克隆。通过用 *Spe*I、SAP 和随后 *Xma*I 孵育从 pBluescript-3ZFPL 释放 3ZFPL 插入片段。

[0122] 使用 200 ng 切割后的载体、400 U T4 DNA 连接酶在 20 μl 总体积中在 RT (室温)下过夜并以 3:1 摩尔比的插入片段:载体设定含有一个、两个和三个 ZFP 的文库的连接反应。六聚锌指蛋白文库的连接反应包括在 200 μl 总体积中的 2000 ng pBluescript-3ZFPL、500 ng 3ZFPL 插入片段、4000 U T4 DNA 连接酶,将所述总体积分为 10 个 20 μl,并分别在

RT 下孵育过夜。根据每一文库所需的克隆数通过几种方法将连接反应的部分转化入大肠杆菌(*Escherichia coli*)中。为了生成 pBluescript-1ZFPL 和 pBluescript-2ZFPL，将 3 μl 的连接反应直接用于大肠杆菌 NEB 5-α 的热激转化。在转化入电感受态大肠杆菌 NEB 5-α(来自 EquiBio 的 EasyjecT Plus 电穿孔仪，2.5 kV 和 25 μF，来自 Bio-Rad 的 2 mm 电穿孔杯)前，通过使用 0.05 μm VMWP 滤器 (Millipore) 对 DNA 级 H_2O 透析 1 小时将 pBluescript-3ZFPL 的连接反应脱盐。将 pBluescript-6ZFP 文库的连接反应应用于 NucleoSpin Extract II 试剂盒，并将 DNA 洗脱在 15 μl 去离子水中。将约 60 ng 脱盐的 DNA 与 50 μl NEB 10-β 电感受态大肠杆菌 (New England Biolabs) 混合，并如制造商建议使用 EasyjecT Plus、2.5 kV、25 μF 和 2 mm 电穿孔杯进行电穿孔。对每一文库进行多次电穿孔，并随后直接合并细胞以提高文库大小。热激转化或电穿孔后，向细菌应用 SOC 培养基，并在 37℃和 250 rpm 下孵育 1 小时后，将 30 μl 的 SOC 培养物用于连续稀释，并铺至含有氨苄青霉素的 LB 平板上。第二天，测定获得文库克隆的总数。此外，选择每一文库的十个克隆以分离质粒 DNA 并通过限制酶消化检查插入片段的整合。对这些质粒中的至少三个进行测序以验证文库的多样性。将剩余的 SOC 培养物转移至 100 ml 含氨苄青霉素的 LB 培养基中并在 37℃和 250 rpm 下培养过夜。将那些细胞用于制备每一文库的质粒 Midi DNA。

[0123] 对于酵母单杂交筛选，将六聚锌指蛋白文库转移到相容的猎物载体中。为此目的，通过用 *Xho*I/*Eco*RI 切割载体并插入到退火的寡核苷酸 OAN971 (TCGACAGGCCCAGGCGGCCCTCGAGGATATCATGATGACTAGTGGCCAGGCCGGCCC, SEQ ID NO: 198) 和 OAN972 (AATTGGGCCGGCCTGGCCACTAGTCATCATGATATCCTCGAGGGCCGCCTGGGCCTG, SEQ ID NO: 199) 中来修饰 pGAD10 (Clontech) 的多克隆位点。将获得的载体 pAN1025 切割并去磷酸化，6ZFP 文库插入片段通过 *Xho*I/*Spe*I 从 pBluescript-6ZFPL 中释放。如上所述对 pBluescript-6ZFP 文库完成连接反应和电穿孔入 NEB 10-β 电感受态大肠杆菌中。

[0124] 对于灵敏度提高的酵母单杂交筛选，将 6ZFP 文库转移到另一个相容的猎物载体中。为此目的，将 pAN1025 的 1460bp *Sph*I 片段连接入 pAN1373 (修饰的 pRS315) 中 (Sikorski, R.S. 和 Hieter, P., 1989, *Genetics* 122(1), 19-27)，其中用退火的寡核苷酸 OAN1143 (CGCCGCATGCATTCATGCAGGCC, SEQ ID NO: 200) 和 OAN1144 (TGCATGAATGCATGCGG, SEQ ID NO: 201)代替 *Apa*I, *Nar*I 片段。这种修饰导致含有相比于与上文概述的文库克隆方案相容的高拷贝 2 μ 复制起点的低拷贝 ARS/CEN 的酵母单杂交载体。

[0125] 用于组合的分泌型萤光素酶和碱性磷酸酶测定的受体启动子区的克隆

将含有 ETRA、ETRB、TLR4 或 FCER1A 启动子区的 DNA 片段克隆入 pAN1485 (NEG-PG04, GeneCopeia) 或 pAN1486 (EF1a-PG04, GeneCopeia) 中，产生含有在受体启动子控制下的分泌型 *Gaussia* 萤光素酶和在组成型 CMV 启动子控制下的分泌型碱性磷酸酶并允许萤光素酶信号对碱性磷酸酶信号归一化的报道基因质粒。详细而言，使用 OAN981 (AATCGCGAGCTCCTTAAGAAACTGGCAGCTTCCACTT, SEQ ID NO: 202) 和 OAN982 (AATCGCCTCGAGCTGCCGGGTCCGCGCGGCG, SEQ ID NO: 203) 从人基因组 DNA 扩增 ETRA 启动子，并经 *Sac*I/*Xho*I 克隆入 pBluescript 中，

产生 pAN1031。将 ETRA 启动子使用 *Xho*I/Klenow/*Bam*HI 从 pAN1031 中切出，并克隆入 *Hind*III/Klenow/*Bgl*II 切割的 pAN1486 中，产生 pAN1492。使用 OAN1232 (GCTAGCTGTCGACACATGGTGCGTGATAACTTGCCC, SEQ ID NO: 204) 和 OAN1233 (GCTAGCTGGTACCAGGCCTGCTGCTACCTGCTCCAGAAGGC, SEQ ID NO: 205) 从人基因组 DNA 中扩增 ETRB 启动子，并经 *Sac*I/*Kpn*I 克隆入 pBluescript 中，产生 pAN1432。将 ETRB 启动子经 *Stu*I/*Eco*RI 从 pAN1432 中切出，并克隆入用 *Hind*III/Klenow/*Eco*RI 切割的 pAN1486 中，产生 pAN1489。使用 OAN1234 (GCTAGCTGTCGACATAAGCCAGTGACAAAAAGATACATAC,SEQ ID NO: 206) 和 OAN1235 (GCTAGCTGGTACCAGGCCTTATTTGATCTCTGTGGCTTCTTGAG, SEQ ID NO: 207) 从人基因组 DNA 中扩增 TLR4 启动子，并经 *Sal*I/*Kpn*I 克隆入 pBluescript 中，产生 pAN1433。将 TLR4 启动子用 *Stu*I/*Bam*HI 从 pAN1433 中切出，并克隆入 *Hind*III/Klenow/*Bgl*II 切割的 pAN1486 中，产生 pAN1491。使用 OAN1249 (CTAGCTGATATCAGCTTAGCGGTTTAC ATGACTTGAC, SEQ ID NO: 208) 和 OAN1250 (CTAGCTAAGCTTCACGCAGGA GAGGAAGGCCATG, SEQ ID NO: 209) 从 pAN1491 中扩增 TLR4 启动子，并经 *Eco*RV/*Hind*III 克隆入 pAN1486 中，产生 pAN1509。使用 OAN1236 (GCTAGCTGTCGACTTAAATTCCTATTTATTAACCTTTTTAGC, SEQ ID NO: 210) 和 OAN1237 (GCTAGCTGGTACCAGGCCTGTCACCACCCACAGTAAAGGTTC, SEQ ID NO: 211) 从人基因组 DNA 中扩增 FCER1A 启动子，并经 *Sac*I/*Kpn*I 克隆入 pBluescript 中，产生 pAN1434。将 FCER1A 启动子经 *Stu*I/*Eco*RI 从 pAN1434 中切出，并经 *Hind*III/Klenow/*Eco*RI 克隆入 pAN1486 中，产生 pAN1490。使用 OAN1261 (CTAGCTGAT ATCGCTAGCCATGCTCCTGAATATGTAT, SEQ ID NO: 212) 和 OAN1262 (CTAGCTAAGCTTGGCAGGAGCCCTCTTCTTCATGGACTCCTGG, SEQ ID NO: 213) 从 pAN1490 中扩增 FCER1A 启动子，并经 *Eco*RV/*Hind*III 克隆入 pAN1485 中，产生 pAN1515。

[0126]　诱饵质粒的克隆

对于每一诱饵质粒，使用侧翼为取自在 ETRA、ETRB、TLR4 或 FCER1A 启动子上游和下游的序列的 21 bp 的 18 bp 靶位点。包括 *Nco*I 位点用于限制性分析。以这样的方式设计寡核苷酸并退火，以产生允许用 *Hin*dIII/*Xho*I 切割并直接连接入 pAbAi (Clontech,) 中的 5'*Hin*dIII 和 3'*Xho*I 位点(表 5)。

[0127]　<u>表 5 :</u>用于将靶位点克隆入 pAbAi 载体中的寡核苷酸

靶位点	寡聚物名称	寡聚物序列5`-3`	诱饵质粒
ETRA			
-855	OAN1018 OAN1019	AGCTTGTGAACTGTCTTGGAAGTGGATCCTCCAGCCCCTGCTACATGGAGCAAAAACGAGCTGTCCCATGGC (SEQ ID NO: 214), 60 bp 插入片段 TCGAGCCATGGGACAGCTCGTTTTTGCTCCATGTAGCAGGGGCTGGAGGATCCACTTCCAAGACAGTTCACA (SEQ ID NO: 215), 60 bp 插入片段	pAN1083
-555	OAN1082 OAN1083	AGCTTAGGCAGTGGCCTTTGTCCCTCATCTCCTCTCCCACCCCCAATTTAGGATAAAGTATCTGCCCATGGC (SEQ ID NO: 216) TCGAGCCATGGGCAGATACTTTATCCTAAATTGGGGGTGGGAGAGGAGATGAGGGACAAAGGCCACTGCCTA (SEQ ID NO: 217)	pAN1160
-487	OAN1084 OAN1085	AGCTTAGACGTTGAGACCCACTTTCTGTAAGGTCGGCTTCTTCATTGTTTGAATTTCTTGAGGTTCCATGGC (SEQ ID NO: 218) TCGAGCCATGGAACCTCAAGAAATTCAAACAATGAAGAAGCCGACCTTACAGAAAGTGGGTCTCAACGTCTA (SEQ ID NO: 219)	pAN1161
-447	OAN1090 OAN1091	AGCTTATTGTTTGAATTTCTTGAGGTTTCACGGAGCCACGCGCTGGAACCTTCCATAGTCTCTCCCCATGGC (SEQ ID NO: 220) TCGAGCCATGGGGAGAGACTATGGAAGGTTCCAGCGCGTGGCTCCGTGAAACCTCAAGAAATTCAAACAATA (SEQ ID NO: 221)	pAN1164
-37	OAN1092 OAN1093	AGCTTAAAAAAGACTCCTGCCCTTCAGGGCCTGGAAGGGGGCGGCAGCTTTGTGCTTTTTAGTGGCCATGGC (SEQ ID NO: 222) TCGAGCCATGGCCACTAAAAAGCACAAAGCTGCCGCCCCCTTCCAGGCCCTGAAGGGCAGGAGTCTTTTTTA (SEQ ID NO: 223)	pAN1165
-306	OAN1024 OAN1025	AGCTTGCGTGCTCCCTCTTAAGTTTAGAGGCCGTTGAGGAGCCGAAGTGGACAGCAGTTTACTGGCCATGGC (SEQ ID NO: 224) TCGAGCCATGGCCAGTAAACTGCTGTCCACTTCGGCTCCTCAACGGCCTCTAAACTTAAGAGGGAGCACGCA (SEQ ID NO: 225)	pAN1086

-230	OAN1088 OAN1089	AGCTTGGCAGGGAAGACGGAGAAGAAACCACC CGTGGGCCCTGGCTCTGTGTCCAGTTGTTCCG TCCATGGC (SEQ ID NO: 226) TCGAGCCATGGACGGAACAACTGGACACAGAG CCAGGGCCCACGGGTGGTTTCTTCTCCGTCTT CCCTGCCA (SEQ ID NO: 227)	pAN1163
-103	OAN1022 OAN1023	AGCTTGTCTGTCAAACTCTACCCTCTCTCCTCC ACATCCCCCACCTTTTCTTTCAGGAAGGAAATC CATGGC (SEQ ID NO: 228) TCGAGCCATGGATTTCCTTCCTGAAAGAAAAGG TGGGGGATGTGGAGGAGAGAGGGTAGAGTTT GACAGACA (SEQ ID NO: 229)	pAN1085
+74	OAN1020 OAN1021	AGCTTAGTGGAAGGTCTGGAGCTTTGGGAGGA GACGGGGAGGACAGACTGGAGGCGTGTTCCT CCCCATGGC (SEQ ID NO: 230) TCGAGCCATGGGGAGGAACACGCCTCCAGTCT GTCCTCCCCGTCTCCTCCCAAAGCTCCAGACC TTCCACTA (SEQ ID NO: 231)	pAN1084
ETRB			
-1149	OAN1198 OAN1199	AGCTTGGACGAGGACTGCCCCCCTCCCTCGG GCAACTACTACTGATGCTGTCCAGGCATCGCC CACCATGGC (SEQ ID NO: 232) TCGAGCCATGGTGGGCGATGCCTGGACAGCAT CAGTAGTAGTTGCCCGAGGGAGGGGGGCAGT CCTCGTCCA (SEQ ID NO: 233)	pAN1383
-487	OAN1214 OAN1215	AGCTTCGAGTTCAATCGCGGGGTATAGAGGTT CCCCTGCGGGGCAAAATGCAGAGCTTGACACA ACCATGGC (SEQ ID NO: 234) TCGAGCCATGGTTGTGTCAAGCTCTGCATTTTG CCCCGCAGGGGAACCTCTATACCCCGCGATTG AACTCGA (SEQ ID NO: 235)	pAN1417
TLR4			
-276	OAN1186 OAN1187	AGCTTACCTGATTGTTTTCCTAAATTCACCAAG CCCAGGCAGAGGTCAGATGACTAATTGGGATA CCATGGC (SEQ ID NO: 236) TCGAGCCATGGTATCCCAATTAGTCATCTGACC TCTGCCTGGGCTTGGTGAATTTAGGAAAACAAT CAGGTA (SEQ ID NO: 237)	pAN1377
-55	OAN1188 OAN1189	AGCTTACTGCTTTGAATACACCAATTGCTGTGG GGCGGCTCGAGGAAGAGAAGACACCAGTGCC TCCATGGC (SEQ ID NO: 238) TCGAGCCATGGAGGCACTGGTGTCTTCTCTTC CTCGAGCCGCCCCACAGCAATTGGTGTATTCA AAGCAGTA (SEQ ID NO: 239)	pAN1378

+113	OAN1190 OAN1191	AGCTTGCTGGGACTCTGATCCCAGCCATGGCC TTCCTCTCCTGCGTGAGACCAGAAAGCTGGGA GCCATGGC (SEQ ID NO: 240) TCGAGCCATGGCTCCCAGCTTTCTGGTCTCAC GCAGGAGAGGAAGGCCATGGCTGGGATCAGA GTCCCAGCA (SEQ ID NO: 241)	pAN1379
FCER1A			
-147	OAN1192 OAN1193	AGCTTTAAGTGGGTAAATATTAAATTGCCCAGT TGGGCACCATCCTGAATATTATCTCTAAAGAAC CATGGC (SEQ ID NO: 242) TCGAGCCATGGTTCTTTAGAGATAATATTCAGG ATGGTGCCCAACTGGGCAATTTAATATTTACCC ACTTAA (SEQ ID NO: 243)	pAN1380
+17	OAN1194 OAN1195	AGCTTCCAGCACAGTAAGCACCAGGAGTCCAT GAAGAAGATGGCTCCTGCCATGGAATCCCCTA CCCATGGC (SEQ ID NO: 244) TCGAGCCATGGGTAGGGGATTCCATGGCAGGA GCCATCTTCTTCATGGACTCCTGGTGCTTACTG TGCTGGA (SEQ ID NO: 245)	pAN1381

[0128] *用于哺乳动物转染的人工转录因子的克隆*

对于生成DNA片段*Xba*I-*Eco*RV-NNNNNN-*Xho*I-NNNNNN-*Age*I-3xmyc-STOP-*Not*I-*Eco*RI，用Platinum *Pfx* DNA聚合酶、OAN1032 (AATCGCTCTAGAGATATCATATATCTCGAGATATATACCGGTGAGCAGAAACTCATCTCTG, SEQ ID NO: 246)和OAN1033 (GCGATTGAATTCGCGGCCGCTTACAGATCTTCCTCAGAGA, SEQ ID NO: 247)将3xmyc标签从pWS250中扩增，用*Xba*I/*Eco*RI切割，连接入用*Xba*I/*Eco*RI切割的pcDNA3(-)中，产生pAN1109。使用Platinum *Pfx* DNA聚合酶、OAN1034 (AATCGCGATATCATGGATGCTAAGTCCCTGA, SEQ ID NO: 248)和OAN1035 (GCGATTCTCGAGCCCCACTTTACGTTTCTTTT, SEQ ID NO: 249)从pAN1021中扩增KRAB-NLS。将PCR产物用*Eco*RV/*Xho*I切割并连接入用*Eco*RV/*Xho*I切割的pAN1109中，产生pAN1110。

[0129] 用Platinum *Pfx* DNA聚合酶、OAN1036 (AATCGCCTCGAGCCCGGGCCGGGTGAAAAGCCCTAT, SEQ ID NO: 250)、OAN1037 (GCGATTACCGGTCTGTGCTGATGAGCCCC, SEQ ID NO: 251)将ZFP-855A的DNA序列从pAN1021中扩增，用*Xho*I/*Age*I消化并克隆入用*Xho*I/*Age*I切割的pAN1110中，以产生pAN1111。类似地，用OAN1038 (AATCGCCTCGAGCCCGGGCCAGGCGAAAAGCCCTAC, SEQ ID NO: 252)和OAN1039 (GCGATTACCGGTCTGTGCTGAACTACCGCC, SEQ ID NO: 253)从pAN1022中扩增ZFP+74A，克隆入pAN1110中，并产生pAN1112。

[0130] 使用*Xho*I/*Age*I消化通过合适的6ZFP（通过酵母单杂交鉴定到的）例如通过ZFP-855C代替pAN1111的ZFP-855A，产生pAN1133。

[0131] 此外，通过在第一DNA合成步骤中退火OAN1096 (AATCGCGATATCATGGCGGCGGCGGTTCGGATGAACATCCAGATGCTGCTGGA, SEQ ID NO: 254)、OAN1097 (ATCCAGATGCTGCTGGAGGCGGCCGACTATCTGGAGCGGCGGGAGAGAGAAGCT, SEQ ID NO: 255)、OAN1098 (GGTATGGTAACATGGAGGCATAACCATGTTCAGCTTCTCTCTCCCGC, SEQ ID NO: 256)、OAN1099 (GCGATTCTCGAGCCCCACTTTACGTTTCTTTTTCGGGTATGGTAACATGGAGG, SEQ ID NO: 257)使用Platinum *Pfx* DNA聚合酶生成SID-NLS (SID对应于根据Beerli, R.R. 等，1998, *Proc Natl Acad Sci U S A* 95, 14628-14633的Mad mSin3相互作用结构域的氨基酸1-36)。将该PCR产物的等分试样作为模板与Platinum *Pfx* DNA聚合酶、OAN1096和OAN1099用于第二DNA合成步骤。将第二PCR产物用*Xho*I/*Eco*RV切割，并用于代替用*Xho*I/*Eco*RV切割的pAN1111中的KRAB-NLS。将所获的质粒pAN1208用于在*Xho*I/*Age*I处理后用任何来自Y1H筛选的6ZFP代替ZFP-855A。

[0132] 此外，根据Gommans, W.M. 等，2007, *Mol Carcinog* 46, 391-401按N-末端NLS，随后为6ZFP、GGSGGS (SEQ ID NO: 9) 接头序列、人KRAB的氨基酸11-55和C-末端3xmyc标签将蛋白结构域的次序重排列。首先，DNA片段*Age*I-*Eco*RI-NNNNNN-*Bam*HI-3xmyc-STOP-*Not*I-*Hin*dIII用pAN1133作为模板、Platinum *Pfx* DNA聚合酶、OAN1100 (GCGATTACCGGTGAATTCATATATGGATCCGAGCAGAAACTCATCTCT, SEQ ID NO: 258)、OAN1101 (GCGATTAAGCTTGCGGCCGCTTACAGATCTTCCTCAGAGA, SEQ ID NO: 259)通过PCR生成，用*Age*I/*Hin*dIII切割，连接入用*Age*I/*Hin*dIII切割的pAN1109中，产生pAN1183。其次，*Eco*RV-ATG-NLS-*Xho*I-*Xma*I-ZFP-855C-*Age*I-GGSGGS接头-*EcoRI*用pAN1133作为模板、Platinum *Pfx* DNA聚合酶、OAN1104 (GCGATTGATATC ATGCCGAAAAAGAAACGTAAAG, SEQ ID NO: 260)、OAN1105 (GCGATTGAATTCGCTGCCGCCGCTGCCGCCACCGGTATGAGTCCTCT, SEQ ID NO: 261)通过PCR产生，并使用*Eco*RI/*Eco*RV克隆插入到pAN1183中，产生pAN1184。第三，将人KRAB的氨基酸11-55用Platinum *Pfx* DNA聚合酶、OAN1106 (GCGATTGAATTCC GCACACTGGTTACCT, SEQ ID NO: 262)、OAN1107 (GCGATTGGATCCATAGCC CAGGCTAACC, SEQ ID NO: 263)从pAN1133中扩增，用*Eco*RI/*Bam*HI切割，并连接入用*Eco*RI/*Bam*HI切割的pAN1184中。将最终的质粒pAN1185通过用*Xho*I/*Age*I切割用于用任何来自Y1H筛选的6ZFP代替ZFP-855C。

[0133] 对于激活ATF的克隆，通过用*Eco*RI/*Bam*HI切割并插入退火的OAN1253 (SEQ ID NO: 264)、OAN1254 (SEQ ID NO: 265)、OAN1255 (SEQ ID NO: 266)和OAN1256 (SEQ ID NO: 267)中，将C-末端KRAB结构域用VP64编码序列代替。

[0134] <u>改良的酵母单杂交(Y1H)筛选</u>

酵母菌株和培养基

酿酒酵母(*Saccharomyces cerevisiae*)Y1H Gold购自Clontech，YPD培养基和YPD琼脂购自Carl Roth。合成缺陷型(SD)培养基含有20 g/l葡萄糖、6.8 g/l $Na_2HPO_4 \cdot 2H_2O$、9.7

g/l $NaH_2PO_4 \cdot 2H_2O$（均来自 Carl Roth）、1.4 g/l 酵母合成缺陷型培养基添加物、6.7 g/l 酵母氮源基础、0.1 g/l L-色氨酸、0.1 g/l L-亮氨酸、0.05 g/l L-腺嘌呤、0.05 g/l L-组氨酸、0.05 g/l 尿嘧啶（均来自 Sigma-Aldrich）。SD-U 培养基含有除了尿嘧啶之外的所有组分，制备不含 L-亮氨酸的 SD-L。SD 琼脂板不含有磷酸钠，但含有 16 g/l Bacto 琼脂 (BD)。金担子素 A (AbA) 购自 Clontech。

[0135] *诱饵酵母菌株的制备*

在 20 μl 的总体积中用 *Bst*BI 将约 5 μg 的每种诱饵质粒线性化，并将一半的反应混合物直接用于酿酒酵母 Y1H Gold 的热激转化。在转化前一天将酵母细胞用于接种 5 ml YPD 培养基，并在滚瓶机(roller)上在 RT 下生长过夜。将一毫升该预培养物用新鲜 YPD 培养基 1:20 稀释，并在 30℃，225 rpm 下孵育 2-3 小时。对于每一转化反应，通过离心收获 1 OD_{600}，将酵母细胞用 1 ml 无菌水洗涤一次并用 1 ml TE/LiAc (10 mM Tris/HCl, pH 7.5, 1 mM EDTA, 100 mM 醋酸锂）洗涤一次。最后，将酵母细胞重悬于 50 μl TE/LiAc 中，并与 50 μg 单链鲑鱼精 DNA (Sigma-Aldrich)、10 ul 的 *Bst*BI 线性化的诱饵质粒（见上文）和 300 μl PEG/TE/LiAc (10 mM Tris/HCl, pH 7.5, 1 mM EDTA, 100 mM醋酸锂，50% (w/v) PEG 3350) 混合。将细胞和 DNA 在滚瓶机上在 RT 下孵育 20 分钟，随后置于 42℃水浴中 15 分钟。最后，通过离心收集酵母细胞，重悬于 100 μl 无菌水中，并涂布在 SD-U 琼脂板上。在 30℃下孵育 3 天后，选择来自每一转化反应的生长在 SD-U 上的 8 个克隆，以分析它们对金担子素 A (AbA) 的敏感性。预培养物在滚瓶机上在 RT 下生长过夜。对于每一培养物，测量 OD_{600}，并用无菌水调整为 OD_{600}=0.3。从该第一稀释中，用无菌水制备五个额外的 1/10 稀释步骤。对于每一克隆，将每一稀释步骤的 5 μl 点在含有 SD-U、SD-U 100 ng/ml AbA、SD-U 150 ng/ml AbA 和 SD-U 200 ng/ml AbA 的琼脂板上。在 30℃下孵育 3 天后，选择在 SD-U 上生长良好并对 AbA 最敏感的三个克隆用于进一步分析。通过 Matchmaker Insert Check PCR Mix 1 (Clontech) 按照制造商说明书验证诱饵质粒稳定整合入酵母基因组中。将三个克隆中的一个用于随后的 Y1H 筛选。

[0136] *用六聚锌指蛋白文库转化诱饵酵母菌株*

将 50 μl 的酵母诱饵菌株预培养物稀释至 100 ml YPD 培养基中，并在 30℃和 225 rpm 下孵育直到 OD_{600}=1.6-2.0（大约 20 小时）。通过在水平转子 (5 分钟，1500×*g*, 4℃）中离心收集细胞。根据 Benatuil L. 等，2010, *Protein Eng Des Sel* 23, 155-159 完成电感受态细胞的制备。对于每一转化反应，将 400 μl 电感受态诱饵酵母细胞与 1 μg 编码 6ZFP 文库的猎物质粒混合并在冰上孵育 3 分钟。将细胞 -DNA 悬浮液转移至预冷的 2 mm 电穿孔杯中。电穿孔 (EasyjecT Plus 电穿孔仪，2.5 kV 和 25 μF) 后，将酵母细胞转移至 8 ml 的 YPD:1 M 山梨醇 1:1 的混合物中，并在 30℃和 225 rpm 下孵育 90 分钟。通过离心收集细胞，并在 1 ml 的 SD-L 培养基中重悬。将 50 μl 的等分试样涂布在含有 1000-4000 ng/ml AbA 的 10 cm SD-L 琼脂板上。此外，将 50 μl 的细胞悬浮液用于制备 1/100 和 1/1000 稀释，并将 50 μl 未稀释的和稀释的细胞铺板至 SD-L 上。所有平板在 30℃下孵育 3 天。从具有稀释的转化子的平板上计算获得的克隆的总数。尽管用未稀释细胞的 SD-L 平板表明所有转化子的生长，但如果猎物 6ZFP 成功结合到它的诱饵靶位点上，则含有 AbA 的 SD-L 平板仅产生菌落形成。

[0137] *阳性相互作用的验证和编码 6ZFP 的猎物质粒的回收*

对于最初分析，从含有最高 AbA 浓度的 SD-L 平板上挑出四十个形状良好的菌落，并将酵母细胞在含有 3000-4000 ng/ml AbA 的 SD-L 上重新划线两次，以获得单菌落。对于每一克隆，将一个菌落用于接种 5 ml SD-L 培养基，并将细胞在 RT 下生长过夜。第二天，用无菌水调节 OD_{600}=0.3，制备五个额外的 1/10 稀释，并将每一稀释步骤的 5 μl 点在 SD-L、SD-L 1000 ng/ml AbA、SD-L 1500 ng/ml AbA、SD-L 2000 ng/ml AbA、SD-L 3000 ng/ml AbA 和 SD-L 4000 ng/ml AbA 的两块平板上。按照它们在高 AbA 浓度上生长的能力将克隆分级。从最佳生长的克隆中，将 5 ml 初始 SD-L 预培养物用于离心下细胞，并将它们在 100 μl 水或剩余培养基中重悬。加入 50 U 溶细胞酶 (Sigma-Aldrich, L2524) 后，将细胞在水平振荡器中在 30℃和 300 rpm 下孵育 1 小时。将生成的球芽用来自 NucleoSpin Plasmid 试剂盒的 250 μl A1 缓冲液稀释，加入一匙尖（one spatula tip）玻璃珠 (Sigma-Aldrich, G8772)，并将管通过涡旋剧烈混合 20 秒。允许玻璃珠沉降，并将 250 μl 上清液转移至新管中，并用于继续进行标准 NucleoSpin Plasmid 试剂盒方案。用 50 μl 洗脱缓冲液洗脱后，通过热激转化或电穿孔将 5 μl 质粒 DNA 转化入大肠杆菌 DH5α 中。 从含氨苄青霉素的 LB 平板上挑取两个单独的菌落，分离质粒并将文库插入片段测序。将获得结果分析对于每一靶位点的 6ZFP 之间的共有序列。

[0138] <u>细胞培养和转染</u>

HeLa 细胞在 5% CO_2 和 37℃下生长在添加有 4.5 g/l 葡萄糖、10% 热失活胎牛血清、2 mM L- 谷氨酰胺和 1 mM 丙酮酸钠 (均来自 Sigma-Aldrich) 的 Dulbecco's Modified Eagle's Medium (DMEM) 中。对于萤光素酶报道基因测定，将 7000 HeLa 细胞 / 孔接种入 96 孔板中。第二天，使用 Effectene Transfection Reagent (Qiagen) 按照制造商说明书进行共转染。编码人工转录因子和编码萤光素酶的质粒中量制备物（midi preparations）以比例 3 :1 使用。转染后 6 小时和 24 小时，每孔用 100 μl 新鲜的 DMEM 更换培养基。U937 (Sigma) 和 KU812F 细胞 (Sigma) 生长在添加有 10% FBS、2 mM 谷氨酰胺和 1 mM 丙酮酸钠的 RMPI-1640 培养基中。使用 Cell Line Nucleofector 试剂盒 C (Amaxa) 或 Cell Line Nucleofector 试剂盒 T (Amaxa) 按照制造商说明书通过核转染来转染 U937 和 KU812F 细胞。RBL-2H3 细胞 (DSMZ) 生长在添加有 2 mM 谷氨酰胺和 1 mM 丙酮酸盐的 70% MEM/20% RMPI-1640/10% 热失活 FBS 中。使用 Cell line nucleofector 试剂盒 T (Amaxa) 核转染 RBL-2H3 细胞。

[0139] 按照供应商建议使用平滑肌细胞生长培养基 2 来生长初级人子宫平滑肌细胞 (hUtSMCs, PromoCell)。

[0140] <u>组合的萤光素酶 /SEAP 启动子活性测定</u>

用人工转录因子表达构建体和携带有在 ETRA、ETRB、TLR4 或 FCER1 启动子控制下的分泌型 Gaussia 萤光素酶和在组成型 CMV 启动子控制下的分泌型碱性磷酸酶 (Secrete-Pair Dual Luminescence Assay, GeneCopeia, Rockville, MD) 的质粒共转染 HeLa 或 RBL-2H3 细胞。转染后两天，收集细胞培养物上清液，并使用 Secrete-Pair Dual Luminescence 测定 (GeneCopoeia) 或 SEAP 报道基因测定 (Roche) 测量萤光素酶活性和 SEAP 活性。将用 YFP-N1 (Clontech) 代替人工转录因子表达构建体的共转染用作对照。将萤光素酶活性对 SEAP 活性归一化，并表示为对照的百分比。

[0141] <u>人子宫平滑肌细胞 (hUtSMC) 网格收缩测定</u>

将 250 μl 的无菌牛胶原 (3.1 mg/ml; #5005-B Nutacon) 与 30 μl 10xPBS 和 22.5 μl

0.1 N NaOH 混合以达到 pH 7.4。将在 200 μl 的 SMC 培养基 2 中的 25000 hUtSMC 加入以中和胶原，温柔混合，转移至 24 孔组织培养板上，并允许在 37℃、5% CO_2 下聚合 45 分钟。聚合后，加入 500 μl 的 SMC 生长培养基 2。对于用人工转录因子处理，将 1 μM A074V 或作为对照的合适量的缓冲液在聚合后立即加入和在 24 和 48 小时后再次加入。聚合后 72 小时，通过轻柔摇晃或用匙帮助将网格从管壁上脱离下，并加入 100 nM 的 ET-1 或缓冲液对照。扫描网格并使用 ImageJ 软件通过图像分析测定网格面积。

[0142] IL-6 检测

按照制造商推荐 (Amaxa) 用 TLR4 特异性人工转录因子或对照载体的表达质粒核转染 $1x10^6$ U937 细胞。将来自每一核转染的 $1.25x10^5$ 个细胞转移至 12 孔板中，并在用不同 LPS 浓度刺激 8 小时前，用 100 nM 佛波醇 -12- 肉豆蔻酸酯 -13- 乙酸酯 (PMA; Sigma) 刺激 48 小时。使用 IL-6 ELISA (Orgenium) 按照制造商推荐在细胞培养物上清液中分析 IL-6 的浓度。

[0143] IgE 结合能力的流式细胞术测定

为了测定 IgE 与 KU812F 细胞的结合，将 $1*10^6$ 个细胞在 2 ml 的 FACS 缓冲液 (1x PBS, 2% FBS) 中洗涤一次，随后重悬于 0.5 ml FACS 缓冲液中。将 $2*10^5$ 个细胞与 10 μg/ml 的人 IgE (abcam) 孵育 30 分钟，用 500 μl FACS 缓冲液洗涤一次，随后加入 FITC 标记的小鼠抗人 IgE (5 μg/ml, abcam) 30 分钟。将样品在 500 μl FACS 缓冲液中洗涤一次，并重悬于 700 μl FACS 缓冲液中。通过流式细胞术 (Cyan ADP, Beckman Coulter) 分析样品。使用未染色的细胞和仅用 FITC 标记的小鼠抗人 IgE 处理的细胞作为对照。

[0144] 使用 MTS 测定的细胞增殖的测定

将 7000 个 HeLa 细胞或 hUtSMC 接种于 96 孔板的 100 μl 培养基中，并分别用特异性的人工转录因子或合适的缓冲液对照处理 48 或 72 小时。为了测定细胞增殖，按照制造商推荐使用 CellTiter 96 Aqueous Non-Radioactive Cell Proliferation Assay (Promega)。将一式三份完成的实验独立重复至少三次。

[0145] 人工转录因子蛋白的产生

将用给定的人工转录因子的表达质粒转化的大肠杆菌 BL21(DE3) 生长在添加有 100 μM $ZnCl_2$ 的 1L LB 培养基中，直至达到 0.8-1 的 OD_{600}，并用 1 mM IPTG 诱导两小时。通过离心收集细菌，通过超声处理制备细菌裂解物，并纯化包涵体。为此目的，通过离心 (5000g, 4℃，15 分钟) 收集包涵体，并在 20 ml 的结合缓冲液 (50 mM HEPES, 500 mM NaCl, 10 mM 咪唑；pH 7.5) 中洗涤三次。将纯化的包涵体在冰上于 30 ml 结合缓冲液 A (50 mM HEPES, 500 mM NaCl, 10 mM 咪唑，6M GuHCl; pH 7.5) 中溶解一小时。将溶解的包涵体在 4℃和 13'000 g 下离心 40 分钟，并通过 0.45 μm PVDF 滤器过滤。使用 His-Trap 柱在 Äktaprime FPLC (GeHealthcare) 上用结合缓冲液 A 和洗脱缓冲液 B(50 mM HEPES, 500 mM NaCl, 500 mM 咪唑，6M GuHCl; pH 7.5) 纯化 His 标签化的人工转录因子。将含有纯化的人工转录因子的级分合并，并在 4℃下透析过夜，在人工转录因子含有 SID 结构域的情况下，对缓冲液 S (50 mM Tris-HCl, 500 mM NaCl, 200 mM 精氨酸，100 μM $ZnCl_2$, 5 mM GSH, 0.5 mM GSSG, 50% 甘油；pH 7.5) 透析，或者对于含有 KRAB 结构域的人工转录因子，则对缓冲液 K (50 mM Tris-HCl, 300 mM NaCl, 500 mM 精氨酸，100 μM $ZnCl_2$, 5 mM GSH, 0.5 mM GSSG, 50% 甘油；pH 8.5) 透析。透析后，将蛋白样品在 4℃下以 14'000 rpm 离心 30 分钟，并使用 0.22 μm Millex-GV

针头式滤器(filter tips)(Millipore)无菌过滤。

[0146] 统计学分析

使用SPSS(IBM)利用Student's t检验(其中为合适的(Excel, Microsoft Cooperation)或通用的线性单变量模型)完成统计学分析。显示的所有实验为三次独立实验的平均值,并带有代表SEM的误差棒。

序列表

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Flammer, Josef
Neutzner, Albert
Huxley, Alice

<120> 内皮素受体 A 表达的调节

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<150> EP11184706.7
<151> 2011-10-11

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<210> 10
<211> 255
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 10

Met Ala Ala Ala Val Arg Met Asn Ile Gln Met Leu Leu Glu Ala Ala
1 5 10 15

Asp Tyr Leu Glu Arg Arg Glu Arg Glu Ala Glu His Gly Tyr Ala Ser
20 25 30

Met Leu Pro Tyr Pro Lys Lys Lys Arg Lys Val Gly Leu Glu Pro Gly
35 40 45

Pro Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser
50 55 60

Asp Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys
65 70 75 80

Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn
85 90 95

Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys
100 105 110

Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu Val Arg His
115 120 125

Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly
130 135 140

Lys Ser Phe Ser Asp Pro Gly Asn Leu Val Arg His Gln Arg Thr His
145 150 155 160

Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser
165 170 175

Gln Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr Gly Glu Lys
180 185 190

Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Arg Ala His
195 200 205

Leu Glu Arg His Gln Arg Thr His Thr Gly Gly Ser Ser Ala Gln Thr
210 215 220

Gly Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Glu Gln Lys Leu Ile
225 230 235 240

Ser Glu Glu Asp Leu Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu
245 250 255

<210> 11
<211> 246
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 11

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

1 5 10 15

Asp Tyr Leu Glu Arg Arg Glu Arg Glu Ala Glu His Gly Tyr Ala Ser
20 25 30

Met Leu Pro Tyr Pro Lys Lys Lys Arg Lys Val Gly Leu Glu Pro Gly
35 40 45

Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser
50 55 60

Asp Glu Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr
65 70 75 80

Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu Val
85 90 95

Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu
100 105 110

Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu Val Arg His Gln Arg
115 120 125

Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser
130 135 140

Phe Ser Asp Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr Gly
145 150 155 160

Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Arg
165 170 175

Ala His Leu Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr
180 185 190

Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu Val
195 200 205

Arg His Gln Arg Thr His Thr Gly Glu Gln Lys Leu Ile Ser Glu Glu
210 215 220

Asp Leu Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Glu Gln Lys Leu
225 230 235 240

Ile Ser Glu Glu Asp Leu
245

<210> 12
<211> 246
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 12

Met Ala Ala Ala Val Arg Met Asn Ile Gln Met Leu Leu Glu Ala Ala
1 5 10 15

Asp Tyr Leu Glu Arg Arg Glu Arg Glu Ala Glu His Gly Tyr Ala Ser

20 25 30

Met Leu Pro Tyr Pro Lys Lys Lys Arg Lys Val Gly Leu Glu Pro Gly
35 40 45

Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser
50 55 60

Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr
65 70 75 80

Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asp Leu Val
85 90 95

Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu
100 105 110

Cys Gly Lys Ser Phe Ser Asp Pro Gly Asn Leu Val Arg His Gln Arg
115 120 125

Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser
130 135 140

Phe Ser Gln Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr Gly
145 150 155 160

Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro
165 170 175

Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr
180 185 190

Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu Val
195 200 205

Arg His Gln Arg Thr His Thr Gly Glu Gln Lys Leu Ile Ser Glu Glu
210 215 220

Asp Leu Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Glu Gln Lys Leu
225 230 235 240

Ile Ser Glu Glu Asp Leu
245

<210> 13
<211> 246
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 13

Met Ala Ala Ala Val Arg Met Asn Ile Gln Met Leu Leu Glu Ala Ala
1 5 10 15

Asp Tyr Leu Glu Arg Arg Glu Arg Glu Ala Glu His Gly Tyr Ala Ser
20 25 30

Met Leu Pro Tyr Pro Lys Lys Lys Arg Lys Val Gly Leu Glu Pro Gly

35 40 45

Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser
50 55 60

Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr
65 70 75 80

Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu Val
85 90 95

Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu
100 105 110

Cys Gly Lys Ser Phe Ser Thr Ser Gly His Leu Val Arg His Gln Arg
115 120 125

Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser
130 135 140

Phe Ser Asp Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr Gly
145 150 155 160

Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser
165 170 175

Ser Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr
180 185 190

Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Glu Leu Val
195 200 205

Arg His Gln Arg Thr His Thr Gly Glu Gln Lys Leu Ile Ser Glu Glu
210 215 220

Asp Leu Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Glu Gln Lys Leu
225 230 235 240

Ile Ser Glu Glu Asp Leu
245

<210> 14
<211> 279
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 14

Met His His His His His His Gly Tyr Gly Arg Lys Lys Arg Arg Gln
1 5 10 15

Arg Arg Arg Gly Tyr Pro Tyr Asp Val Pro Asp Tyr Ala Pro Trp Asp
20 25 30

Ile Met Ala Ala Ala Val Arg Met Asn Ile Gln Met Leu Leu Glu Ala
35 40 45

Ala Asp Tyr Leu Glu Arg Arg Glu Arg Glu Ala Glu His Gly Tyr Ala

50 55 60

Ser Met Leu Pro Tyr Pro Lys Lys Lys Arg Lys Val Gly Leu Glu Pro
65 70 75 80

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
85 90 95

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
100 105 110

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu
115 120 125

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
130 135 140

Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly His Leu Val Arg His Gln
145 150 155 160

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
165 170 175

Ser Phe Ser Asp Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr
180 185 190

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
195 200 205

Ser Ser Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
210 215 220

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Glu Leu
225 230 235 240

Val Arg His Gln Arg Thr His Thr Gly Glu Gln Lys Leu Ile Ser Glu
245 250 255

Glu Asp Leu Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Glu Gln Lys
260 265 270

Leu Ile Ser Glu Glu Asp Leu
275

<210> 15
<211> 276
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 15

Met Pro Lys Lys Lys Arg Lys Val Gly Leu Glu Pro Gly Glu Lys Pro
1 5 10 15

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn Leu
20 25 30

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro

35 40 45

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asp Leu Val Arg His Gln
50 55 60

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
65 70 75 80

Ser Phe Ser Asp Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr
85 90 95

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
100 105 110

Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
115 120 125

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
130 135 140

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
145 150 155 160

Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu Val Arg His Gln
165 170 175

Arg Thr His Thr Gly Gly Gly Ser Gly Gly Ser Glu Phe Gly Arg Ala
180 185 190

Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu
195 200 205

Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe
210 215 220

Asp Leu Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp
225 230 235 240

Met Leu Ile Asn Gly Ser Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu
245 250 255

Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Glu Gln Lys Leu Ile Ser
260 265 270

Glu Glu Asp Leu
275

<210> 16
<211> 276
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 16

Met Pro Lys Lys Lys Arg Lys Val Gly Leu Glu Pro Gly Glu Lys Pro
1 5 10 15

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

20 25 30

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
35 40 45

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu Val Arg His Gln
50 55 60

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
65 70 75 80

Ser Phe Ser Thr Ser Gly His Leu Val Arg His Gln Arg Thr His Thr
85 90 95

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
100 105 110

Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
115 120 125

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
130 135 140

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
145 150 155 160

Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Glu Leu Val Arg His Gln
165 170 175

Arg Thr His Thr Gly Gly Gly Ser Gly Gly Ser Glu Phe Gly Arg Ala
180 185 190

Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu
195 200 205

Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe
210 215 220

Asp Leu Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu Asp
225 230 235 240

Met Leu Ile Asn Gly Ser Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu
245 250 255

Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Glu Gln Lys Leu Ile Ser
260 265 270

Glu Glu Asp Leu
275

<210> 17
<211> 309
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 17

Met His His His His His His Gly Tyr Gly Arg Lys Lys Arg Arg Gln

1 5 10 15

Arg Arg Arg Gly Tyr Pro Tyr Asp Val Pro Asp Tyr Ala Pro Trp Asp
20 25 30

Ile Met Pro Lys Lys Lys Arg Lys Val Gly Leu Glu Pro Gly Glu Lys
35 40 45

Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn
50 55 60

Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys
65 70 75 80

Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu Val Arg His
85 90 95

Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly
100 105 110

Lys Ser Phe Ser Thr Ser Gly His Leu Val Arg His Gln Arg Thr His
115 120 125

Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser
130 135 140

Asp Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys
145 150 155 160

Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser
165 170 175

Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys
180 185 190

Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Glu Leu Val Arg His
195 200 205

Gln Arg Thr His Thr Gly Gly Gly Ser Gly Gly Ser Glu Phe Gly Arg
210 215 220

Ala Asp Ala Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala
225 230 235 240

Leu Asp Asp Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu Asp Asp
245 250 255

Phe Asp Leu Asp Met Leu Gly Ser Asp Ala Leu Asp Asp Phe Asp Leu
260 265 270

Asp Met Leu Ile Asn Gly Ser Glu Gln Lys Leu Ile Ser Glu Glu Asp
275 280 285

Leu Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Glu Gln Lys Leu Ile
290 295 300

Ser Glu Glu Asp Leu
305

<210> 18
<211> 246
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 18

Met Ala Ala Ala Val Arg Met Asn Ile Gln Met Leu Leu Glu Ala Ala
1 5 10 15

Asp Tyr Leu Glu Arg Arg Glu Arg Glu Ala Glu His Gly Tyr Ala Ser
20 25 30

Met Leu Pro Tyr Pro Lys Lys Lys Arg Lys Val Gly Leu Glu Pro Gly
35 40 45

Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Thr
50 55 60

Gly Ala Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr
65 70 75 80

Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Lys Asn Ser Leu Thr
85 90 95

Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu
100 105 110

Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu Thr Glu His Gln Arg
115 120 125

Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser
130 135 140

Phe Ser Arg Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr Gly
145 150 155 160

Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser
165 170 175

Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr
180 185 190

Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu Thr
195 200 205

Glu His Gln Arg Thr His Thr Gly Glu Gln Lys Leu Ile Ser Glu Glu
210 215 220

Asp Leu Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Glu Gln Lys Leu
225 230 235 240

Ile Ser Glu Glu Asp Leu
245

<210> 19
<211> 218
<212> PRT

<213> 人工序列

<220>
<223> 合成构建体

<400> 19

Met Ala Ala Ala Val Arg Met Asn Ile Gln Met Leu Leu Glu Ala Ala
1 5 10 15

Asp Tyr Leu Glu Arg Arg Glu Arg Glu Ala Glu His Gly Tyr Ala Ser
20 25 30

Met Leu Pro Tyr Pro Lys Lys Lys Arg Lys Val Gly Leu Glu Pro Gly
35 40 45

Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser
50 55 60

Gly His Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr
65 70 75 80

Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu Thr
85 90 95

Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu
100 105 110

Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu Thr Glu His Gln Arg
115 120 125

Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser
130 135 140

Phe Ser Arg Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly
145 150 155 160

Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser
165 170 175

Asp Lys Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Gln Lys Leu
180 185 190

Ile Ser Glu Glu Asp Leu Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu
195 200 205

Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu
210 215

<210> 20
<211> 266
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 20

Met Pro Lys Lys Lys Arg Lys Val Gly Leu Glu Pro Gly Glu Lys Pro
1 5 10 15

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

20 25 30

Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
35 40 45

Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly His Leu Thr Glu His Gln
50 55 60

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
65 70 75 80

Ser Phe Ser Thr Ser Gly Asn Leu Thr Glu His Gln Arg Thr His Thr
85 90 95

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
100 105 110

Ser Gly Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
115 120 125

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn Leu
130 135 140

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
145 150 155 160

Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu Val Arg His Gln
165 170 175

Arg Thr His Thr Gly Gly Gly Ser Gly Gly Ser Glu Phe Arg Thr Leu
180 185 190

Val Thr Phe Lys Asp Val Phe Val Asp Phe Thr Arg Glu Glu Trp Lys
195 200 205

Leu Leu Asp Thr Ala Gln Gln Ile Val Tyr Arg Asn Val Met Leu Glu
210 215 220

Asn Tyr Lys Asn Leu Val Ser Leu Gly Tyr Gly Ser Glu Gln Lys Leu
225 230 235 240

Ile Ser Glu Glu Asp Leu Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu
245 250 255

Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu
260 265

<210> 21
<211> 266
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 21

Met Pro Lys Lys Lys Arg Lys Val Gly Leu Glu Pro Gly Glu Lys Pro
1 5 10 15

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu

20 25 30

Ala Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
35 40 45

Glu Cys Gly Lys Ser Phe Ser Arg Ala Asp Asn Leu Thr Glu His Gln
50 55 60

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
65 70 75 80

Ser Phe Ser Ser Arg Arg Thr Cys Arg Ala His Gln Arg Thr His Thr
85 90 95

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
100 105 110

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
115 120 125

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Asn Leu
130 135 140

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
145 150 155 160

Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Ser Leu Val Arg His Gln
165 170 175

Arg Thr His Thr Gly Gly Gly Ser Gly Gly Ser Glu Phe Arg Thr Leu
180 185 190

Val Thr Phe Lys Asp Val Phe Val Asp Phe Thr Arg Glu Glu Trp Lys
195 200 205

Leu Leu Asp Thr Ala Gln Gln Ile Val Tyr Arg Asn Val Met Leu Glu
210 215 220

Asn Tyr Lys Asn Leu Val Ser Leu Gly Tyr Gly Ser Glu Gln Lys Leu
225 230 235 240

Ile Ser Glu Glu Asp Leu Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu
245 250 255

Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu
260 265

<210> 22
<211> 299
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 22

Met His His His His His His Gly Tyr Gly Arg Lys Lys Arg Arg Gln
1 5 10 15

Arg Arg Arg Gly Tyr Pro Tyr Asp Val Pro Asp Tyr Ala Pro Trp Asp

20 25 30

Ile Met Pro Lys Lys Lys Arg Lys Val Gly Leu Glu Pro Gly Glu Lys
35 40 45

Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Arg Ala His
50 55 60

Leu Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys
65 70 75 80

Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly His Leu Thr Glu His
85 90 95

Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly
100 105 110

Lys Ser Phe Ser Thr Ser Gly Asn Leu Thr Glu His Gln Arg Thr His
115 120 125

Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser
130 135 140

Thr Ser Gly Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys
145 150 155 160

Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn
165 170 175

Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys
180 185 190

Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu Val Arg His
195 200 205

Gln Arg Thr His Thr Gly Gly Gly Ser Gly Gly Ser Glu Phe Arg Thr
210 215 220

Leu Val Thr Phe Lys Asp Val Phe Val Asp Phe Thr Arg Glu Glu Trp
225 230 235 240

Lys Leu Leu Asp Thr Ala Gln Gln Ile Val Tyr Arg Asn Val Met Leu
245 250 255

Glu Asn Tyr Lys Asn Leu Val Ser Leu Gly Tyr Gly Ser Glu Gln Lys
260 265 270

Leu Ile Ser Glu Glu Asp Leu Glu Gln Lys Leu Ile Ser Glu Glu Asp
275 280 285

Leu Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu
290 295

<210> 23
<211> 308
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 23

Met Asp Ala Lys Ser Leu Thr Ala Trp Ser Arg Thr Leu Val Thr Phe
1 5 10 15

Lys Asp Val Phe Val Asp Phe Thr Arg Glu Glu Trp Lys Leu Leu Asp
20 25 30

Thr Ala Gln Gln Ile Val Tyr Arg Asn Val Met Leu Glu Asn Tyr Lys
35 40 45

Asn Leu Val Ser Leu Gly Tyr Gln Leu Thr Lys Pro Asp Val Ile Leu
50 55 60

Arg Leu Glu Lys Gly Glu Glu Pro Trp Leu Val Glu Arg Glu Ile His
65 70 75 80

Gln Glu Thr His Pro Asp Ser Glu Thr Ala Phe Glu Ile Lys Ser Ser
85 90 95

Val Ser Pro Lys Lys Lys Arg Lys Val Gly Leu Glu Pro Gly Glu Lys
100 105 110

Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His
115 120 125

Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys
130 135 140

Pro Glu Cys Gly Lys Ser Phe Ser Arg Asn Asp Ala Leu Thr Glu His
145 150 155 160

Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly
165 170 175

Lys Ser Phe Ser Gln Ser Gly Asn Leu Thr Glu His Gln Arg Thr His
180 185 190

Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser
195 200 205

Thr Ser Gly Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys
210 215 220

Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly His
225 230 235 240

Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys
245 250 255

Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His
260 265 270

Gln Arg Thr His Thr Gly Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu
275 280 285

Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Glu Gln Lys Leu Ile Ser
290 295 300

Glu Glu Asp Leu
305

<210> 24
<211> 341
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 24

Met His His His His His His Gly Tyr Gly Arg Lys Lys Arg Arg Gln
1 5 10 15

Arg Arg Arg Gly Tyr Pro Tyr Asp Val Pro Asp Tyr Ala Pro Trp Asp
20 25 30

Ile Met Asp Ala Lys Ser Leu Thr Ala Trp Ser Arg Thr Leu Val Thr
35 40 45

Phe Lys Asp Val Phe Val Asp Phe Thr Arg Glu Glu Trp Lys Leu Leu
50 55 60

Asp Thr Ala Gln Gln Ile Val Tyr Arg Asn Val Met Leu Glu Asn Tyr
65 70 75 80

Lys Asn Leu Val Ser Leu Gly Tyr Gln Leu Thr Lys Pro Asp Val Ile
85 90 95

Leu Arg Leu Glu Lys Gly Glu Glu Pro Trp Leu Val Glu Arg Glu Ile
100 105 110

His Gln Glu Thr His Pro Asp Ser Glu Thr Ala Phe Glu Ile Lys Ser
115 120 125

Ser Val Ser Pro Lys Lys Lys Arg Lys Val Gly Leu Glu Pro Gly Glu
130 135 140

Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly
145 150 155 160

His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys
165 170 175

Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Asn Asp Ala Leu Thr Glu
180 185 190

His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys
195 200 205

Gly Lys Ser Phe Ser Gln Ser Gly Asn Leu Thr Glu His Gln Arg Thr
210 215 220

His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe
225 230 235 240

Ser Thr Ser Gly Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu
245 250 255

Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly
260 265 270

His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys
275 280 285

Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu Val Arg
290 295 300

His Gln Arg Thr His Thr Gly Glu Gln Lys Leu Ile Ser Glu Glu Asp
305 310 315 320

Leu Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Glu Gln Lys Leu Ile
325 330 335

Ser Glu Glu Asp Leu
340

<210> 25
<211> 6950
<212> DNA
<213> 智人

<400> 25
gtgtctatga atttaactat tctaggtacc tcatctaagt gggataataa aatatctatc 60

tttcctttta tgtctggctt atttcactta acataatatc ttaaacgttc atccatgtgg 120

tagcatatat cattcttttt taaagctgaa taatgttctg tgttatgtac atgtatttat 180

atacatatac atacatgtat ataccacatt ttgtttatcc attcttccac tgatggatat 240 ttggattgtt tccatctttt ggctagtttt cacctttttgg cttttctgaa taatgctgct 300

atgaatatgg gtgtacaaat atctgtttga gactctgctt tcaattattt aggtaagtac 360

caaaaagtag aattgctgga tcatagggta attttatgtt taattttttgg agggctgcca 420

tgctgttttc cacaactgct acactatatt ttacattcag actggcaatg cacaagggtt 480

ccaatttctc aacattcttg ccaacacttg ttctttgctg tttttgcttt tgttttacta 540

taatggctat cctaataggt gtgaaggaag aatttttagt aactagtcct acaccacagt 600

gagatcagct gtctcaatag gtgggtcatg atgaatgtgt tctagcaaag actggacaga 660

ttgacatatt cagatatgca ggtgatgcac tgtccaagtg tgtctggcca cagagtgaat 720

aagggctgaa atccagcaca tgtttcacgg gccaagatgt gaactgcctc ttttgggagg 780

aagcagtaag tttttctttc ccgaaaatat tgtcagcttg ccaagccaca tgcccaaagg 840

gtcacctttt tttaatataa acaatggcac ttataaaagc tattagttat tctggttggc 900

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<400> 27
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<213> 智人

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<213> 智人

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<212> DNA
<213> 智人

<400> 30
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<210> 31
<211> 168
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<400> 31

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
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Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
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Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Arg Ala His Leu
35 40 45

Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Glu Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Gly Asp Leu Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 32
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 32

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Ser Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Arg Ala His Leu
35 40 45

Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly His Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Gly Asp Leu Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

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<220>
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Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Ser Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro

50 55 60

Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly Ala Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Gly Asp Leu Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 34
<211> 168
<212> PRT
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<220>
<223> 合成构建体

<400> 34

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Ser Gly Asp Leu Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly Asp Leu
35 40 45

Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly Asp Leu Arg Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly His Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Ser Leu

145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 35
<211> 168
<212> PRT
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<220>
<223> 合成构建体

<400> 35

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly His Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Arg Ala His Leu Glu Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Asp Pro Gly Ala Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 36
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<400> 36

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Ser Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly His Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Gly Asp Leu Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
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Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
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<210> 37

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<400> 37

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Ser Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Arg Ala His Leu
35 40 45

Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu Ala Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Asp Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Ser Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
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<210> 38
<211> 15
<212> DNA
<213> 智人

<400> 38
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<210> 39
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<400> 39

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Ser Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Arg Ala His Leu Glu Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Glu Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly His Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 40
<211> 168

<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 40

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Arg Ala His Leu
35 40 45

Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Asp Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu
145 150 155 160

Ala Arg His Gln Arg Thr His Thr
165

<210> 41
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 41

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Ser Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly Asp Leu
35 40 45

Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Ser Gly Asp Leu Arg Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu
145 150 155 160

Ala Arg His Gln Arg Thr His Thr
165

<210> 42
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 42

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg

1 5 10 15

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Glu Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu
145 150 155 160

Ala Arg His Gln Arg Thr His Thr
165

<210> 43
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 43

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
1 5 10 15

Pro Gly Ala Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Arg Ala His Leu
35 40 45

Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr

100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 44
<211> 15
<212> DNA
<213> 智人

<400> 44
aaggtcggct tcttc 15

<210> 45
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 45

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr

1 5 10 15

Ser Gly Asn Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Ser Gly Asp Leu Arg Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
115 120 125

Ser Gly Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 46
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 46

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Thr Gly Ala Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Ser Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu Ala Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Ser Ser Asn Leu Val Arg His Gln Arg Thr His Thr

100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Ser Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 47
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 47

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Ser
1 5 10 15

Arg Arg Thr Cys Arg Ala His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu Ala Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Ser Ser Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Ser Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Ser Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 48
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 48

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Ser
1 5 10 15

Lys Lys His Leu Ala Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asp Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Asn Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Ser Ser Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
115 120 125

Ser Gly Glu Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 49
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 49

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Thr Gly Ala Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu
35 40 45

Ala Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu Ala Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Ser Ser Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Ser Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Ser Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 50
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 50

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Ser Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Asp Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Ser Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 51
<211> 15
<212> DNA
<213> 智人

<400> 51
cggagccacg cgctg 15

<210> 52
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 52

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Ser Gly Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Asn Asp Ala Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asp Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Gly His Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
145 150 155 160

Thr Glu His Gln Arg Thr His Thr
165

<210> 53
<211> 18
<212> DNA
<213> 智人

<400> 53
cggctcctca acggcctc 18

<210> 54
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 54

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Lys Asn Ser Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Ser Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
115 120 125

Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 55
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 55

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Arg Ala His Leu Glu Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Ser Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 56
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 56

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Asn Ser Thr Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Arg Ala His Leu Glu Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Ser Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu
145 150 155 160

Ala Arg His Gln Arg Thr His Thr
165

<210> 57
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 57

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Ser His Ser Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Arg Ala His Leu Glu Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Ser Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu
145 150 155 160

Ala Arg His Gln Arg Thr His Thr
165

<210> 58
<211> 18
<212> DNA
<213> 智人

<400> 58
ccacccgtgg gccctggc 18

<210> 59
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 59

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly His Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Asp Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Thr Gly Ala Leu
145 150 155 160

Thr Glu His Gln Arg Thr His Thr
165

<210> 60
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 60

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Glu Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Asp Pro Gly His Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ala Asp Asn Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Lys Asn Ser Leu
145 150 155 160

Thr Glu His Gln Arg Thr His Thr
165

<210> 61
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 61

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Asn Asp Thr Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro

50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Arg Ala His Leu Glu Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Ser Gly Asp Leu Arg Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
115 120 125

Thr Gly Ala Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
145 150 155 160

Thr Glu His Gln Arg Thr His Thr
165

<210> 62
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 62

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Glu Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Asp Pro Gly His Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Asn Asp Thr Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Ser Arg Arg Thr Cys

145 150 155 160

Arg Ala His Gln Arg Thr His Thr
165

<210> 63
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 63

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly His Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Ser Arg Arg Thr Cys
145 150 155 160

Arg Ala His Gln Arg Thr His Thr
165

<210> 64
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 64

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly His Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Ser Ser Ser Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Ser Arg Arg Thr Cys
145 150 155 160

Arg Ala His Gln Arg Thr His Thr
165

<210> 65
<211> 18

<212> DNA
<213> 智人

<400> 65
ctcctccaca tcccccac 18

<210> 66
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 66

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Ser Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly Ala Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Glu Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Ser Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 67
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 67

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
1 5 10 15

Pro Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Gly Asp Leu Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 68

<211> 168

<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 68

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
1 5 10 15

Cys Arg Asp Leu Ala Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly His Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 69
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 69

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Asp Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
115 120 125

Ser Gly Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly Ala Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 70
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 70

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr

1 5 10 15

Ser Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu
145 150 155 160

Ala Arg His Gln Arg Thr His Thr
165

<210> 71
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 71

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu
35 40 45

Ala Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr

100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 72
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 72

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Ser Gly Glu Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asp Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 73
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 73

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1   5   10   15

Ser Ser Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
            20   25   30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu
        35   40   45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
    50   55   60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asp Leu Val Arg His Gln
65   70   75   80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
                85   90   95

Ser Phe Ser Thr Ser Gly Glu Leu Val Arg His Gln Arg Thr His Thr
            100   105   110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
        115   120   125

Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
    130   135   140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asp Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 74
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 74

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
1 5 10 15

Pro Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu
35 40 45

Ala Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Ser Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 75
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 75

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
1 5 10 15

Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asp Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
115 120 125

Pro Gly Ala Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu
145 150 155 160

Ala Arg His Gln Arg Thr His Thr
165

<210> 76
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 76

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
1 5 10 15

Pro Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asp Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly Ala Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 77
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 77

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Asp Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro

50 55 60

Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
115 120 125

Ser Gly Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu
145 150 155 160

Ala Arg His Gln Arg Thr His Thr
165

<210> 78
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 78

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Asp Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Ser Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu

145 150 155 160

Ala Arg His Gln Arg Thr His Thr
165

<210> 79
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 79

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asp Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly Ala Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 80
<211> 140
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 80

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
1 5 10 15

Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
115 120 125

Pro Gly Ala Leu Val Arg His Gln Arg Thr His Thr
130 135 140

<210> 81
<211> 18
<212> DNA
<213> 智人

<400> 81
ggcctggaag ggggcggc 18

<210> 82

<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 82

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Ser Gly Glu Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Glu Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 83
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 83

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Ser Gly Asp Leu Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly Asp Leu
35 40 45

Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 84
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 84

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
1 5 10 15

Pro Gly Ala Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Asp Cys Arg Asp Leu Ala Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 85
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 85

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Ser Ser Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu Ala Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ala Asp Asn Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 86
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 86

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Ser Gly Asp Leu Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly Asp Leu

35 40 45

Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Asn Asp Ala Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 87
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 87

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Asn Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Asp Pro Gly His Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
115 120 125

Thr Gly Ala Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro

130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu
145 150 155 160

Ala Arg His Gln Arg Thr His Thr
165

<210> 88
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 88

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Ser Gly Asp Leu Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly Asp Leu
35 40 45

Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly Asp Leu Arg Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Ser
115 120 125

Lys Lys His Leu Ala Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 89
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 89

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Glu Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Ser Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Asp Cys Arg Asp Leu Ala Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 90
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 90

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Asn Asp Ala Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu
145 150 155 160

Ala Arg His Gln Arg Thr His Thr
165

<210> 91
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 91

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
1 5 10 15

Cys Arg Asp Leu Ala Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Asp Cys Arg Asp Leu Ala Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 92
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 92

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Ser Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly His Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 93
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 93

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Ser Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Glu Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly Asp Leu Arg Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys

85 90 95

Ser Phe Ser Arg Ser Asp Asp Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly Ala Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 94
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 94

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
1 5 10 15

Pro Gly Ala Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly Asp Leu
35 40 45

Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asp Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Asn Asp Ala Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu
145 150 155 160

Ala Arg His Gln Arg Thr His Thr
165

<210> 95

<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 95

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Ser Gly Asp Leu Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly Asp Leu
35 40 45

Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Arg Ala His Leu
145 150 155 160

Glu Arg His Gln Arg Thr His Thr
165

<210> 96
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<213> 智人

<400> 96
ggaggagacg gggaggac 18

<210> 97
<211> 168
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<220>
<223> 合成构建体

<400> 97

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
1 5 10 15

Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Asp Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Arg Ala His Leu
145 150 155 160

Glu Arg His Gln Arg Thr His Thr
165

<210> 98

<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 98

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Ser Ser Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Asp Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 99
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 99

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly Ala Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Asp Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 100
<211> 168
<212> PRT
<213> 人工序列

<220>
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<400> 100

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Ser Gly Asp Leu Arg Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Glu Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 101
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 101

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Glu Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Asp Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 102
<211> 164
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 102

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Ile
1 5 10 15

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
20 25 30

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn Leu Val Arg His Gln

35 40 45

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
50 55 60

Ser Phe Ser Asp Pro Gly His Leu Val Arg His Gln Arg Thr His Thr
65 70 75 80

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
85 90 95

Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
100 105 110

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
115 120 125

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
130 135 140

Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu Val Arg His Gln
145 150 155 160

Arg Thr His Thr

<210> 103
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 103

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly His Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly Asn Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Ser Gly Asp Leu Arg Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
115 120 125

Pro Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro

130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu
145 150 155 160

Ala Arg His Gln Arg Thr His Thr
165

<210> 104
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 104

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly Asn Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly His Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu
145 150 155 160

Ala Arg His Gln Arg Thr His Thr
165

<210> 105
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 105

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly Ala Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asp Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 106
<211> 168
<212> PRT
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<220>
<223> 合成构建体

<400> 106

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu Ala Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 107
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 107

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
1 5 10 15

Pro Gly Ala Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu Ala Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Asp Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 108
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 108

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1   5   10   15

Ser Gly Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
            20   25   30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly Asn Leu
        35   40   45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
    50   55   60

Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu Val Arg His Gln
65   70   75   80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
                85   90   95

Ser Phe Ser Arg Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr
            100   105   110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
        115   120   125

Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
    130   135   140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu
145 150 155 160

Ala Arg His Gln Arg Thr His Thr
165

<210> 109
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 109

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
1 5 10 15

Pro Gly Ala Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys

85 90 95

Ser Phe Ser Thr Ser Gly Glu Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
115 120 125

Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 110
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Ser Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly Ala Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Asp Pro Gly His Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Arg Ala His Leu
145 150 155 160

Glu Arg His Gln Arg Thr His Thr
165

<210> 111

<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 111

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Asp Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
115 120 125

Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Ser Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 112
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 112

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly Asn Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Glu Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Ser Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Arg Ala His Leu
145 150 155 160

Glu Arg His Gln Arg Thr His Thr
165

<210> 113
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 113

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
1 5 10 15

Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Asp Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
115 120 125

Ser Gly Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 114
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 114

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asp Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly Asn Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
115 120 125

Pro Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 115
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 115

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
1 5 10 15

Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu

35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly His Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Asp Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Glu Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Ser Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 116
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 116

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Ser Ser Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly His Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
115 120 125

Pro Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro

130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 117
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 117

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu Ala Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
115 120 125

Pro Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly Ala Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 118
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 118

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly His Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Asp Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Ser Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Glu Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 119
<211> 18
<212> DNA
<213> 智人

<400> 119
ctcgggcaac tactactg 18

<210> 120
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 120

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Asn Asp Ala Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Ser Arg Arg Thr Cys
35 40 45

Arg Ala His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Asn Ser Thr Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Ser Lys Lys His Leu Ala Glu His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
145 150 155 160

Thr Glu His Gln Arg Thr His Thr
165

<210> 121
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 121

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Asn Asp Ala Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Lys Asn Ser Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
145 150 155 160

Thr Glu His Gln Arg Thr His Thr
165

<210> 122
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 122

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Ser
1 5 10 15

Arg Arg Thr Cys Arg Ala His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Asn Asp Ala Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
145 150 155 160

Thr Glu His Gln Arg Thr His Thr
165

<210> 123
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 123

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Ser
1 5 10 15

Lys Lys His Leu Ala Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
145 150 155 160

Thr Glu His Gln Arg Thr His Thr
165

<210> 124
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 124

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1   5   10   15

Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
            20   25   30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Ser Arg Arg Thr Cys
        35   40   45

Arg Ala His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
    50   55   60

Glu Cys Gly Lys Ser Phe Ser Thr Lys Asn Ser Leu Thr Glu His Gln
65   70   75   80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
                85   90   95

Ser Phe Ser Thr Lys Asn Ser Leu Thr Glu His Gln Arg Thr His Thr
            100   105   110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
        115   120   125

Cys Arg Asp Leu Ala Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
    130   135   140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Ser Lys Lys His Leu
145 150 155 160

Ala Glu His Gln Arg Thr His Thr
165

<210> 125
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 125

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Lys Asn Ser Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Ser Arg Arg Thr Cys Arg Ala His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys

85 90 95

Ser Phe Ser Arg Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
145 150 155 160

Thr Glu His Gln Arg Thr His Thr
165

<210> 126
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 126

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Thr Gly Ala Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Thr Lys Asn Ser Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Ser Lys Lys His Leu Ala Glu His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
145 150 155 160

Thr Glu His Gln Arg Thr His Thr
165

<210> 127

<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 127

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Asn Asp Ala Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Thr Gly Ala Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Thr Gly Ala Leu Thr Glu His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
115 120 125

Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
145 150 155 160

Thr Glu His Gln Arg Thr His Thr
165

<210> 128
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 128

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Lys Asn Ser Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Ser Arg Arg Thr Cys
35 40 45

Arg Ala His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
145 150 155 160

Thr Glu His Gln Arg Thr His Thr
165

<210> 129
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 129

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Ser Gly Asn Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser His Thr Gly His Leu
35 40 45

Leu Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
145 150 155 160

Thr Glu His Gln Arg Thr His Thr
165

<210> 130
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 130

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Asn Asp Ala Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
145 150 155 160

Thr Glu His Gln Arg Thr His Thr
165

<210> 131
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 131

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Thr Gly Ala Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Ser Arg Arg Thr Cys

35 40 45

Arg Ala His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
145 150 155 160

Thr Glu His Gln Arg Thr His Thr
165

<210> 132
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 132

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Lys Asn Ser Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Ser Arg Arg Thr Cys
35 40 45

Arg Ala His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

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

130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
145 150 155 160

Thr Glu His Gln Arg Thr His Thr
165

<210> 133
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 133

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Thr Gly Ala Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Lys Asn Ser Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
145 150 155 160

Thr Glu His Gln Arg Thr His Thr
165

<210> 134
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 134

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Ser
1 5 10 15

Lys Lys His Leu Ala Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Lys Asn Ser Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
115 120 125

Pro Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Lys Asn Ser Leu
145 150 155 160

Thr Glu His Gln Arg Thr His Thr
165

<210> 135
<211> 140
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 135

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Ser Gly His Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr
130 135 140

<210> 136
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 136

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Thr Gly Ala Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Asn Asp Ala Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Ser Arg Arg Thr Cys Arg Ala His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Ser Arg Arg Thr Cys Arg Ala His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Ser Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Lys Asn Ser Leu
145 150 155 160

Thr Glu His Gln Arg Thr His Thr
165

<210> 137
<211> 18
<212> DNA
<213> 智人

<400> 137
gaggttcccc tgcggggc 18

<210> 138
<211> 168
<212> PRT
<213> 人工序列

<220>

<223> 合成构建体

<400> 138

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Asn Asp Ala Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Ser Arg Arg Thr Cys Arg Ala His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
115 120 125

Ser Gly Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 139
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 139

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
1 5 10 15

Pro Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Asn Asp Ala Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Ser Lys Lys His Leu Ala Glu His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
115 120 125

Ser Gly Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 140
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 140

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Ser Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro

20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Thr Lys Asn Ser Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Ser Arg Arg Thr Cys Arg Ala His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
115 120 125

Ser Gly Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 141
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 141

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Thr Thr Gly Ala Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Ser Arg Arg Thr Cys Arg Ala His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr

115 120 125

Ser Gly Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 142
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 142

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Ser Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Asn Asp Ala Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Ser Arg Arg Thr Cys Arg Ala His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Ser Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 143
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 143

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Asn Asp Ala Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Ser Arg Arg Thr Cys Arg Ala His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Ser Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 144
<211> 18
<212> DNA
<213> 智人

<400> 144
caccaagccc aggcagag 18

<210> 145
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 145

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ala Asp Asn Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Gly Asn Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Lys Asn Ser Leu
145 150 155 160

Thr Glu His Gln Arg Thr His Thr
165

<210> 146
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 146

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly Asp Leu
35 40 45

Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ala Asp Asn Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Ser Ser Ser Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
115 120 125

Lys Asn Ser Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ala Asp Asn Leu
145 150 155 160

Thr Glu His Gln Arg Thr His Thr
165

<210> 147
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 147

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ala Asp Asn Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Ser Ser Ser Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Gly Asn Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Thr Gly Ala Leu
145 150 155 160

Thr Glu His Gln Arg Thr His Thr
165

<210> 148
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 148

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly Asp Leu
35 40 45

Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Asn Asp Ala Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Ser Ser Ser Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Gly Asn Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Asn Asp Ala Leu
145 150 155 160

Thr Glu His Gln Arg Thr His Thr
165

<210> 149
<211> 168
<212> PRT

<213> 人工序列

<220>
<223> 合成构建体

<400> 149

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly Asp Leu
35 40 45

Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ala Asp Asn Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
115 120 125

Lys Asn Ser Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Ser Arg Arg Thr Cys
145 150 155 160

Arg Ala His Gln Arg Thr His Thr
165

<210> 150
<211> 168
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<220>
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<400> 150

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly Asp Leu
35 40 45

Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ala Asp Asn Leu Thr Glu His Gln

65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Ser Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Gly Asn Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly Asn Leu
145 150 155 160

Thr Glu His Gln Arg Thr His Thr
165

<210> 151
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 151

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly Asp Leu
35 40 45

Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ala Asp Asn Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Ser Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
115 120 125

Lys Asn Ser Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Ser Arg Arg Thr Cys
145 150 155 160

Arg Ala His Gln Arg Thr His Thr

165

<210> 152
<211> 168
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<220>
<223> 合成构建体

<400> 152

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly Asp Leu
35 40 45

Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ala Asp Asn Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Ser Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Gly Asn Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Ser Arg Arg Thr Cys
145 150 155 160

Arg Ala His Gln Arg Thr His Thr
165

<210> 153
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 153

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Asn Asp Ala Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Glu Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Gly Asn Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Ser Arg Arg Thr Cys
145 150 155 160

Arg Ala His Gln Arg Thr His Thr
165

<210> 154
<211> 18
<212> DNA
<213> 智人

<400> 154

gctgtggggc ggctcgag 18

<210> 155
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 155

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
1 5 10 15

Pro Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Thr Gly Ala Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Ser Arg Arg Thr Cys Arg Ala His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Ser Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 156
<211> 168
<212> PRT
<213> 人工序列

<220>
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<400> 156

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly His Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Ser Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 157
<211> 168
<212> PRT
<213> 人工序列

<220>

<223> 合成构建体

<400> 157

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
1 5 10 15

Pro Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Thr Gly Ala Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Ser Lys Lys His Leu Ala Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Glu Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
115 120 125

Cys Arg Asp Leu Ala Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 158
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 158

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Glu Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Ser Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 159
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<223> 合成构建体

<400> 159

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
1 5 10 15

Cys Arg Asp Leu Ala Arg His Gln Arg Thr His Thr Gly Glu Lys Pro

20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ala Asp Asn Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Ser Arg Arg Thr Cys Arg Ala His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Ser Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Ser Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 160
<211> 168
<212> PRT
<213> 人工序列

<220>
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<400> 160

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
1 5 10 15

Pro Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Lys Asn Ser Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Thr Ser His Ser Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Ser Ser Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg

115 120 125

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu
145 150 155 160

Ala Arg His Gln Arg Thr His Thr
165

<210> 161
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 161

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Asp Cys Arg Asp Leu Ala Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Gly Asp Leu Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu
145 150 155 160

Ala Arg His Gln Arg Thr His Thr
165

<210> 162
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 162

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Ser Ser Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Asn Asp Ala Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Thr Ser His Ser Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 163
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 163

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
1 5 10 15

Pro Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Thr Thr Gly Ala Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Ser Gly Asp Leu Arg Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Glu Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 164
<211> 168
<212> PRT
<213> 人工序列

<220>
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<400> 164

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
1 5 10 15

Cys Arg Asp Leu Ala Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Asn Ser Thr Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Ser Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 165
<211> 18
<212> DNA

<213> 智人

<400> 165
atggccttcc tctcctgc 18

<210> 166
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 166

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Asn Ser Thr Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Gly Asp Leu Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu
145 150 155 160

Ala Arg His Gln Arg Thr His Thr
165

<210> 167
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 167

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Ser
1 5 10 15

Lys Lys His Leu Ala Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Ser Gly Asp Leu Arg Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 168
<211> 168
<212> PRT

<213> 人工序列

<220>
<223> 合成构建体

<400> 168

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Arg Ala His Leu
35 40 45

Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
115 120 125

Pro Gly Ala Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu
145 150 155 160

Ala Arg His Gln Arg Thr His Thr
165

<210> 169
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 169

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Ser
1 5 10 15

Lys Lys His Leu Ala Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu Val Arg His Gln

65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Ser Ser Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 170
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 170

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Ser
1 5 10 15

Lys Lys His Leu Ala Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Arg Ala His Leu Glu Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
115 120 125

Pro Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly Asp Leu
145 150 155 160

Arg Arg His Gln Arg Thr His Thr

165

<210> 171
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 171

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Ser Gly Asn Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly Asp Leu Arg Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
115 120 125

Pro Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly Asp Leu
145 150 155 160

Arg Arg His Gln Arg Thr His Thr
165

<210> 172
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 172

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Asn Asp Ala Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Pro Gly His Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Arg Ala His Leu Glu Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Arg Ser Asp Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
115 120 125

Pro Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Ser Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 173
<211> 168
<212> PRT
<213> 人工序列

<220>

<223> 合成构建体

<400> 173

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Ser
1 5 10 15

Arg Arg Thr Cys Arg Ala His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asn Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly His Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
115 120 125

Ser Gly Asp Leu Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu
145 150 155 160

Ala Arg His Gln Arg Thr His Thr
165

<210> 174
<211> 18
<212> DNA
<213> 智人

<400> 174
gcccagttgg gcaccatc 18

<210> 175
<211> 168
<212> PRT
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<220>
<223> 合成构建体

<400> 175

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
1 5 10 15

Pro Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Asn Asp Ala Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly Asn Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Ser Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
115 120 125

Ser Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 176
<211> 168
<212> PRT
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<220>

<223> 合成构建体

<400> 176

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Ser Ser Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Asn Asp Ala Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly Asn Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Ser Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
115 120 125

Ser Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 177
<211> 168
<212> PRT
<213> 人工序列

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<400> 177

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Ser Ser Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Asn Asp Ala Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly His Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Ser Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
115 120 125

Ser Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 178
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 178

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Ser Gly Ser Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro

20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Asn Asp Ala Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly His Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Ser Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
115 120 125

Ser Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 179
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 179

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Ser Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Asn Asp Ala Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly His Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Ser Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln

115 120 125

Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 180
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 180

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Ser Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Asn Asp Ala Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly Asn Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Ser Ser Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
115 120 125

Ser Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 181
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 181

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Arg Ala His Leu Glu Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Asn Asp Ala Leu
35 40 45

Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly His Leu Thr Glu His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Ser Ser Ser Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
115 120 125

Ser Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 182
<211> 18
<212> DNA
<213> 智人

<400> 182
gtccatgaag aagatggc 18

<210> 183
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 183

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Ser Gly His Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Ser Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu Ala Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 184
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 184

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
1 5 10 15

Ser Gly Glu Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Asp Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 185
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 185

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Glu Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu Ala Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 186
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 186

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
1 5 10 15

Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu Ala Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 187
<211> 168
<212> PRT

<213> 人工序列

<220>
<223> 合成构建体

<400> 187

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
1 5 10 15

Ser Asp Asp Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr Ser Gly Asn Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu Val Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Gln Ser Ser Ser Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Thr
115 120 125

Thr Gly Ala Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 188
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 188

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
1 5 10 15

Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu Ala Arg His Gln

65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 189
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 189

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Ser Gly Asp Leu Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu Ala Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ala Asp Asn Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr

165

<210> 190
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 190

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Asp
1 5 10 15

Pro Gly Asn Leu Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Asn Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Asp Cys Arg Asp Leu Ala Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln Ser Ser Ser Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 191
<211> 168
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 191

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Gln
1 5 10 15

Ser Gly Asp Leu Arg Arg His Gln Arg Thr His Thr Gly Glu Lys Pro
20 25 30

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Glu Leu
35 40 45

Val Arg His Gln Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro
50 55 60

Glu Cys Gly Lys Ser Phe Ser Gln Ser Gly Asp Leu Arg Arg His Gln
65 70 75 80

Arg Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys
85 90 95

Ser Phe Ser Thr Ser Gly Asn Leu Val Arg His Gln Arg Thr His Thr
100 105 110

Gly Glu Lys Pro Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg
115 120 125

Ser Asp Lys Leu Thr Glu His Gln Arg Thr His Thr Gly Glu Lys Pro
130 135 140

Tyr Lys Cys Pro Glu Cys Gly Lys Ser Phe Ser Arg Ser Asp Lys Leu
145 150 155 160

Val Arg His Gln Arg Thr His Thr
165

<210> 192
<211> 12
<212> PRT
<213> 人工序列

<220>

<223> 合成构建体

<400> 192

Pro Val Arg Arg Pro Arg Arg Arg Arg Arg Arg Lys
1 5 10

<210> 193
<211> 12
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 193

Thr His Arg Leu Pro Arg Arg Arg Arg Arg Arg Lys
1 5 10

<210> 194
<211> 9
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 194

Arg Arg Arg Arg Arg Arg Arg Arg Arg
1 5

<210> 195
<211> 9
<212> PRT

<213> Influenza A virus

<400> 195

Tyr Pro Tyr Asp Val Pro Asp Tyr Ala
1 5

<210> 196
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 196

Pro Lys Lys Lys Arg Lys Val
1 5

<210> 197
<211> 7
<212> PRT
<213> 人工序列

<220>
<223> 合成构建体

<400> 197

Tyr Lys Asp Asp Asp Asp Lys
1 5

<210> 198
<211> 57
<212> DNA

<213> 人工序列

<220>
<223> 合成构建体

<400> 198
tcgacaggcc caggcggccc tcgaggatat catgatgact agtggccagg ccggccc 57

<210> 199
<211> 57
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 199
aattgggccg gcctggccac tagtcatcat gatatcctcg agggccgcct gggcctg 57

<210> 200
<211> 23
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 200
cgccgcatgc attcatgcag gcc 23

<210> 201
<211> 17
<212> DNA
<213> 人工序列

<220>

<223> 合成构建体

<400> 201
tgcatgaatg catgcgg 17

<210> 202
<211> 37
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 202
aatcgcgagc tccttaagaa actggcagct tccactt 37

<210> 203
<211> 31
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 203
aatcgcctcg agctgccggg tccgcgcggc g 31

<210> 204
<211> 36
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 204

gctagctgtc gacacatggt gcgtgataac ttgccc 36

<210> 205
<211> 41
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 205
gctagctggt accaggcctg ctgctacctg ctccagaagg c 41

<210> 206
<211> 40
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 206
gctagctgtc gacataagcc agtgacaaaa agatacatac 40

<210> 207
<211> 44
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 207
gctagctggt accaggcctt atttgatctc tgtggcttct tgag 44

<210> 208
<211> 37
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 208
ctagctgata tcagcttagc ggtttacatg acttgac 37

<210> 209
<211> 34
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 209
ctagctaagc ttcacgcagg agaggaaggc catg 34

<210> 210
<211> 42
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 210
gctagctgtc gacttaaatt cctatttatt aacctttta gc 42

<210> 211
<211> 42
<212> DNA

<213> 人工序列

<220>
<223> 合成构建体

<400> 211
gctagctggt accaggcctg tcaccaccca cagtaaaggt tc 42

<210> 212
<211> 37
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 212
ctagctgata tcgctagcca tgctcctgaa tatgtat 37

<210> 213
<211> 43
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 213
ctagctaagc ttggcaggag ccctcttctt catggactcc tgg 43

<210> 214
<211> 72
<212> DNA
<213> 人工序列

<220>

<223> 合成构建体

<400> 214
agcttgtgaa ctgtcttgga agtggatcct ccagcccctg ctacatggag caaaaacgag 60

ctgtcccatg gc 72

<210> 215
<211> 72
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 215
tcgagccatg ggacagctcg tttttgctcc atgtagcagg ggctggagga tccacttcca 60

agacagttca ca 72

<210> 216
<211> 72
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 216
agcttaggca gtggcctttg tccctcatct cctctcccac ccccaattta ggataaagta 60

tctgcccatg gc 72

<210> 217
<211> 72
<212> DNA

<213> 人工序列

<220>
<223> 合成构建体

<400> 217
tcgagccatg ggcagatact ttatcctaaa ttgggggtgg gagaggagat gagggacaaa 60

ggccactgcc ta 72

<210> 218
<211> 72
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 218
agcttagacg ttgagaccca ctttctgtaa ggtcggcttc ttcattgttt gaatttcttg 60

aggttccatg gc 72

<210> 219
<211> 72
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 219
tcgagccatg gaacctcaag aaattcaaac aatgaagaag ccgaccttac agaaagtggg 60

tctcaacgtc ta 72

<210> 220
<211> 72
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 220
agcttattgt ttgaatttct tgaggtttca cggagccacg cgctggaacc ttccatagtc 60

tctccccatg gc 72

<210> 221
<211> 72
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 221
tcgagccatg gggagagact atggaaggtt ccagcgcgtg gctccgtgaa acctcaagaa 60

attcaaacaa ta 72

<210> 222
<211> 72
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 222
agcttaaaaa agactcctgc ccttcagggc ctggaagggg gcggcagctt tgtgcttttt 60

agtggccatg gc 72

<210> 223
<211> 72
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 223
tcgagccatg gccactaaaa agcacaaagc tgccgccccc ttccaggccc tgaagggcag 60

gagtcttttt ta 72

<210> 224
<211> 72
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 224
agcttgcgtg ctccctctta agtttagagg ccgttgagga gccgaagtgg acagcagttt 60

actggccatg gc 72

<210> 225
<211> 72
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 225
tcgagccatg gccagtaaac tgctgtccac ttcggctcct caacggcctc taaacttaag 60

agggagcacg ca 72

<210> 226
<211> 72
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 226
agcttggcag ggaagacgga gaagaaacca cccgtgggcc ctggctctgt gtccagttgt 60

tccgtccatg gc 72

<210> 227
<211> 72
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 227
tcgagccatg gacggaacaa ctggacacag agccagggcc cacgggtggt ttcttctccg 60

tcttccctgc ca 72

<210> 228
<211> 72
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 228
agcttgtctg tcaaactcta ccctctctcc tccacatccc ccaccttttc tttcaggaag 60

gaaatccatg gc 72

<210> 229
<211> 72
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 229
tcgagccatg gatttccttc ctgaaagaaa aggtggggga tgtggaggag agagggtaga 60

gtttgacaga ca 72

<210> 230
<211> 72
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 230
agcttagtgg aaggtctgga gctttgggag gagacgggga ggacagactg gaggcgtgtt 60

cctccccatg gc 72

<210> 231
<211> 72

<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 231
tcgagccatg gggaggaaca cgcctccagt ctgtcctccc cgtctcctcc caaagctcca 60

gaccttccac ta 72

<210> 232
<211> 72
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 232
agcttggacg aggactgccc ccctccctcg ggcaactact actgatgctg tccaggcatc 60

gcccaccatg gc 72

<210> 233
<211> 72
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 233
tcgagccatg gtgggcgatg cctggacagc atcagtagta gttgcccgag ggagggggc 60

agtcctcgtc ca 72

<210> 234
<211> 72
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 234
agcttcgagt tcaatcgcgg ggtatagagg ttcccctgcg gggcaaaatg cagagcttga 60

cacaaccatg gc 72

<210> 235
<211> 72
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 235
tcgagccatg gttgtgtcaa gctctgcatt ttgccccgca ggggaacctc tataccccgc 60

gattgaactc ga 72

<210> 236
<211> 72
<212> DNA
<213> 人工序列

<220>
<223> 合成构建体

<400> 236
agcttacctg attgttttcc taaattcacc aagcccaggc agaggtcaga tgactaattg 60

ggataccatg gc 72

<210> 237
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tcgatgactt tgacctggat atgttgggaa 90

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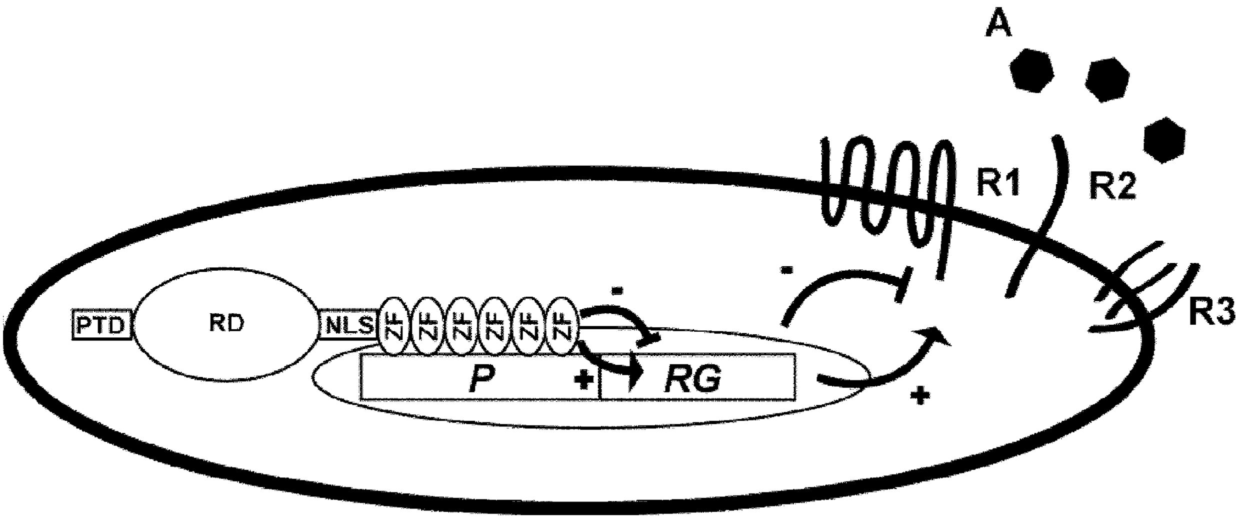

图 1

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-1028 CTTAAGAAACTGGCAGCTTCCACTTTCTGTCTCTGGGGACATTCACTCTTGGATCCCCGC

 -968 CACCATGCTGTGAGGAAGCCCAAACCACAAGTCTCCACAAGTCTTTGTGGAGAGACGCAC
                                                         TS-855
 -908 GTGGAGAAAAACTAACACTCAACACCAAGCAAGTGAACTGTCTTGGAAGTGGATCCTCCA

 -848 GCCCCTGCTACATGGAGCAAAAACGAGCTGTCCCAGACAGGCTCTGCCCAAACTGCAGAC

 -788 TGATAAGCAGAGTAAATGAGTGTTGTTATTTTAAGCCACTACGTTTTATAGTAATTTGTT

 -728 TAGCTGCAGCAGATAGCCGGAACAGCATGGGATATAACATGACCAGTGCTCCAACCTCAC

 -668 ACTTCTACCATGTGCTGACTCTAGCAGTGCACTGAAGGACTCCAAGGCAGGCCTTCCCTG
                                                         TS-555
 -608 AGGAGACCCCAGTTTTTACTCACATGTCACAGGCAGTGGCCTTTGTCCCTCATCTCCTCT

 -548 CCCACCCCCAATTTAGGATAAAGTATCTGCCGTGATAAAGACGTTGAGACCCACTTTCTG
       TS-487                                   TS-447
 -488 TAAGGTCGGCTTCTTCATTGTTTGAATTTCTTGAGGTTTCACGGAGCCACGCGCTGGAAC

 -428 CTTCCATAGTCTCTCCTGAGGCTCCTTCTTTGCCCTGGGCTGGAGGTCTGTAGCCGTGGG

 -368 ATGCTGGCTACAAGGGACAAGATAGAAGCAAACCACCTGATCCAGTAAACTGCTGTCCAC
        TS-306
 -308 TTCGGCTCCTCAACGGCCTCTAAGCTTAAGAGGGAGCACGCAAGCCAAGCAAAGGCGGCA
                    TS-230
 -248 GGGAAGACGGAGAAGAAACCACCCGTGGGCCCTGGCTCTGTGTCCAGTTGTTCCGTCACA

 -188 GATCAAATCTGCCTGCACTAAGAGGATGGGTTCCTCTGCAAGGCCTTTCGGAATTCTGAG
                          TS-103
 -128 TCTTGTCTGTCAAACTCTACCCTCTCTCCTCCACATCCCCCACCTTTTCTTTCAGGAAGG
                                 TS-37
  -68 AAATAGTTAAAAAAGACTCCTGCCCTTCAGGGCCTGGAAGGGGGCGGCAGCTTTGTGCTT
           +1
   -8 TTTAGTGGCCGCGTCCCAGGATAGCTGGAAGGTTAGGACGCTCTTGCGGTCCCAGAGTGG
                     TS+74
  +53 AGTGGAAGGTCTGGAGCTTTGGGAGGAGACGGGGAGGACAGACTGGAGGCGTGTTCCTCC

 +113 GGAGTTTTCTTTTTCGTGCGAGCCCTCGCGCGCGCGTACAGTCATCCCGCTGGTCTGACG

 +173 ATTGTGGAGAGGCGGTGGAGAGGCTTCATCCACCCCACCCGGTCGTCGCCGGGGATTGGG

 +233 GTCCCAGCGAGACCTCCCCGGGAGAAGCAGTGCCCAGGAAGTTTTCTGAAGCCGGGGAAG

 +293 CTGTGCAGCCGAAGCCGCCGCCGCGCCGGAGCCCGGGACACCGGCCACCCTCCGCGCCAC

 +353 CCACCCTCGCCGGCTCCGGCTTCCTCTGGCCCAGGCGCCGCGCGGACCCGGCAG
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图 2

-480　CCTTGAGTTCAGACTGGAAGCCTCTAGAATTGTGAGAAAATGAATGTCTGTTGTTTAAGC

-420　CACCCAGTCTGTGGTATTTCCTTATGGCAGCCCCAGCAAACTAATACAAATAGTGTTTCC

-360　ACAGCTGAAACAAAATTGGAAAATCACCGTCATCCTAGAGAGTTACAAGGGCTATTTTAA

TS-276

-300　TAGAACCTGATTGTTTTCCTAAATTCACCAAGCCCAGGCAGAGGTCAGATGACTAATTGG

-240　GATAAAAGCCAACTAGCTTCCTCTTGCTGTTTCTTTAGCCACTGGTCTGCAGGCGTTTTC

-181　TTCTTCTAACTTCCTCTCCTGTGACAAAAGAGATAACTATTAGAGAAACAAAAGTCCAGA

-121　ATGCTAAGGTTGCCGCTTTCACTTCCTCTCACCCTTTAGCCCAGAACTGCTTTGAATACA

TS-55

-61　CCAATTGCTGTGGGGCGGCTCGAGGAAGAGAAGACACCAGTGCCTCAGAAACTGCTCGGT

+**1**

-1　C**A**GACGGTGATAGCGAGCCACGCATTCACAGGGCCACTGCTGCTCACAGAAGCAGTGAGG

TS+113

+60　ATGATGCCAGG**ATGATGTCTGCCTCGCGCCTGGCTGGGACTCTGATCCCAGCCATGGCCT**

+120　**TCCTCTCCTGCGTGAGACCAGAAAGCTGGGAGCCCTGCGTGGAG**

图 3

TS-147

-168　TAAGTGGGTAAATATTAAATTGCCCAGTTGGGCACCATCCTGAATATTATCTCTAAAGAA

-108　AGAAGCAAAACCAGGCACAGCTGATGGGTTAACCAGATATGATACAGAAAACATTTCCTT

+**1**

-48　CTGCTTTTTGGTTTTAAGCCTATATTTGAAGCCTTAGATCTCTCCAGC**A**CAGTAAGCACC

TS+17

+13　AGGAGTCCATGAAGAAG**ATGGCTCCTGCCATGGAATCCCC**

图 4

TS-1149

-1177 TGTCCCCGGACGAGGACTGCCCCCCTCCCTCGGGCAACTACTACTGATGCTGTCCAGGCA

-1117 TCGCCCAAGGGGAAAGGTTGCAGCGGGGTCGGAAGGCGCGGGAGGAGTCTGGCGGTGATT

-1057 GATGGGAAGGGATGAATGAATAAAAGTACTTGTCTGATGGCAGCAGAGACCCCGAGCAAA

-997 CGGTGGAGGCTACACTGTCTGGCATTCTCGCAGCGTTTCGTCAGAGCCGGACCCGCCTGC

-937 AGCTCAAGGGAGGCGTGCTCCTCTCCCAGAGCAGGCTGGAACCCAGCTGGGTTCCGCCTC

-877 CCGGGAAGGTGGTCTCCATTCGTCGCTCTGCATCTGGTTTGTCAGATCCGAGAGGTAAAC

-817 ATTCGGGCTTGGTGTTGAATTAAAATCATTGATTGAACCTTATTCTGGGGCTTCGGTTTG

-757 GCTTACTAGTTTGGGATTTTAAAAAAATAAAAATTAAGCCTATAGAGAGGGCAAATTAAA

-697 ATTAGGTTGGGTAAAGGAAGGAGCGCGAGTGTTTGAAGCCGTTTGGAGGGAACAGCGGTT

-637 TCCAAGTTCCTGCTGACTTGAGAAGTCTCTGCGGGTTTCCGAATCTCCGGCGCACTCCTG

-577 GGCGCGCTGCGGGAGCTGTAGCTCAGCCAGCCAGGGAGTAGCGGCTTTCATCCGCCGGGA

TS-487

-517 GGAGTCTTTCGAGTTCAATCGCGGGGTATAGAGGTTCCCCTGCGGGGCAAAATGCAGAGC

-457 TTGACACAAGCCCTTGGCCTCTAGGTGCCTTAATTCCGCGGTTCCCACGCACGCTTAACT

-397 AAGACGTGTCTGTATTCCTCCCGTTACGTGAAAGAGTTCGGAGCTTTGCCTGGGACCCCC

-337 ATCATTCCCTCCCTGGCACACCCCTTCCAGAACGCCCCGCCCCACTGCATATTATTTACC

-277 CCTCCTGGCCACGCGGGGGAAGAAAAACAGCTGAGAGGGCATCAGGAAGGAGTTTCGACC

-217 CGCGCTGGCGAGTCATGAGCGCCAAGTTTCCCACTGGCGCGCAAACTTGAGTTACTTTTG

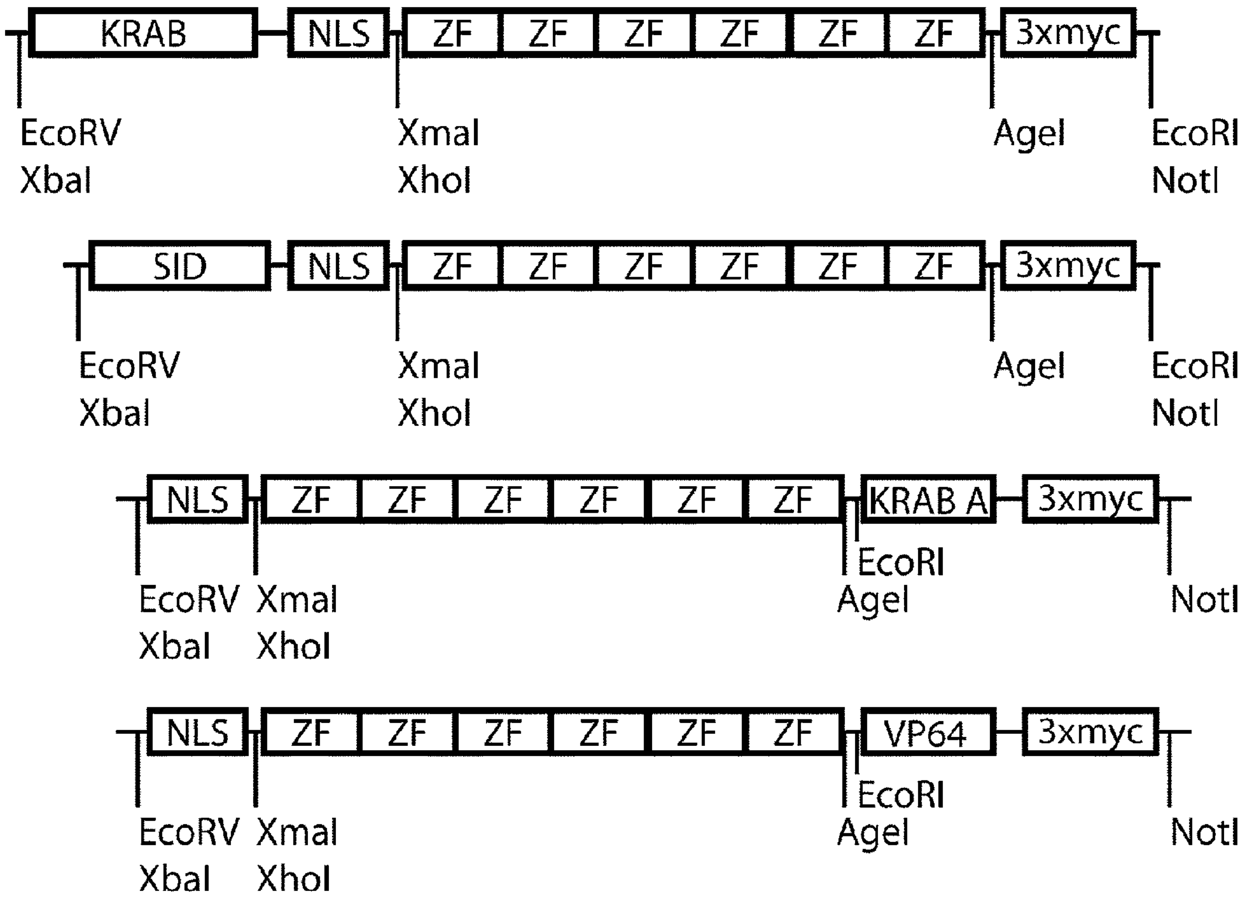
-157 AGCGTGGATACTGGCGAAGAGGCTGCGGGCGGTATTAGCGTTTGCAGCGACTTGGCTCGG

-97 GCAGCTGACCCAAGTGTCCTGTCTTCCTTCCTCTGCTTGTCTCTAGGCTCTGAAACTGCG

+**1**

-37 GAGCGGCCACCGGACGCCTTCTGGAGCAGGTAGCAGC**ATG**

图 5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NLS
ZF ZF ZF ZF ZF ZF
3xmyc
EcoRV
XbaI
XmaI
XhoI
AgeI
EcoRI
NotI
NLS
ZF ZF ZF ZF ZF ZF
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NLS
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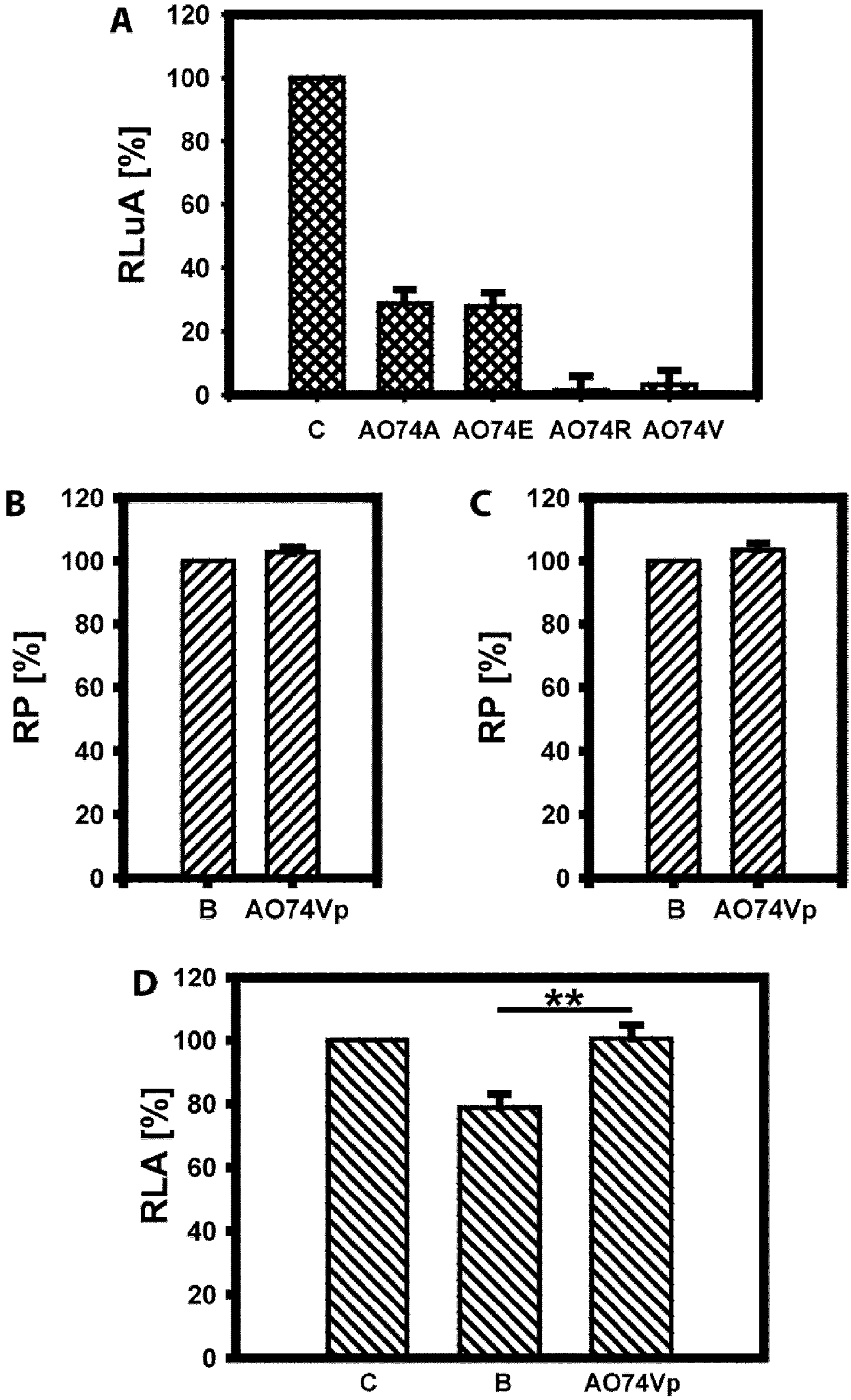
XhoI
AgeI
NotI

图 6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40
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RLA [%]
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**
C
B
AO74Vp

图 7

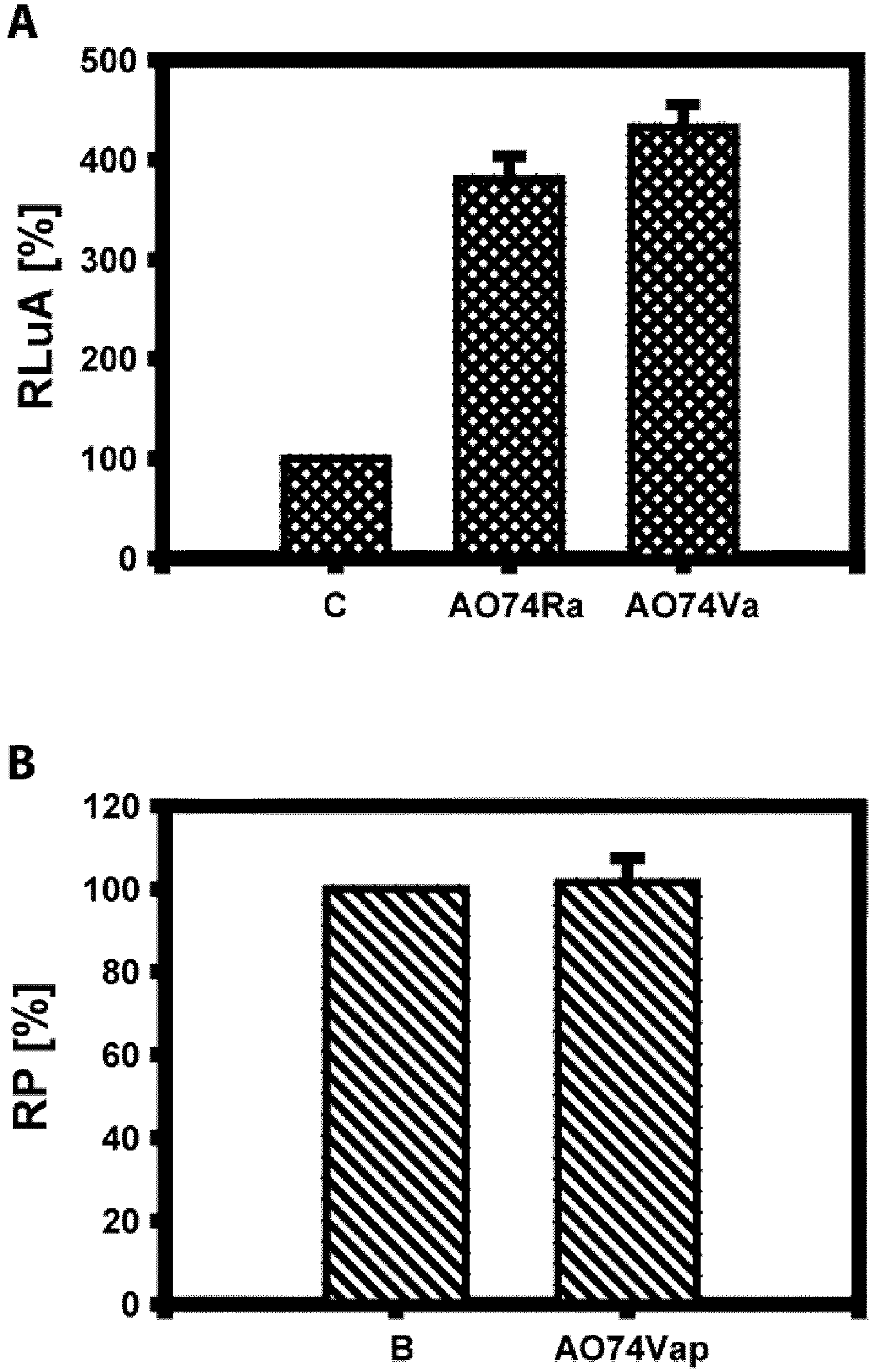
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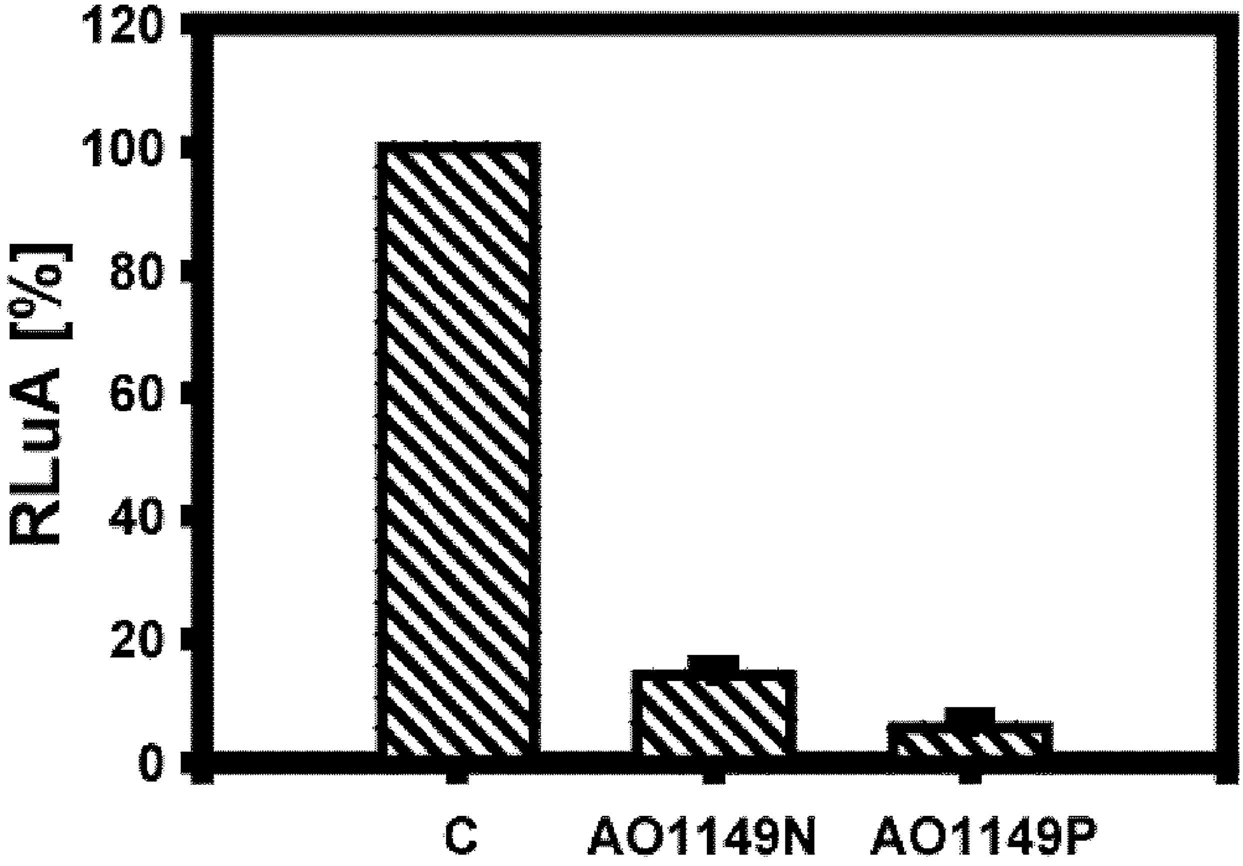
图 8



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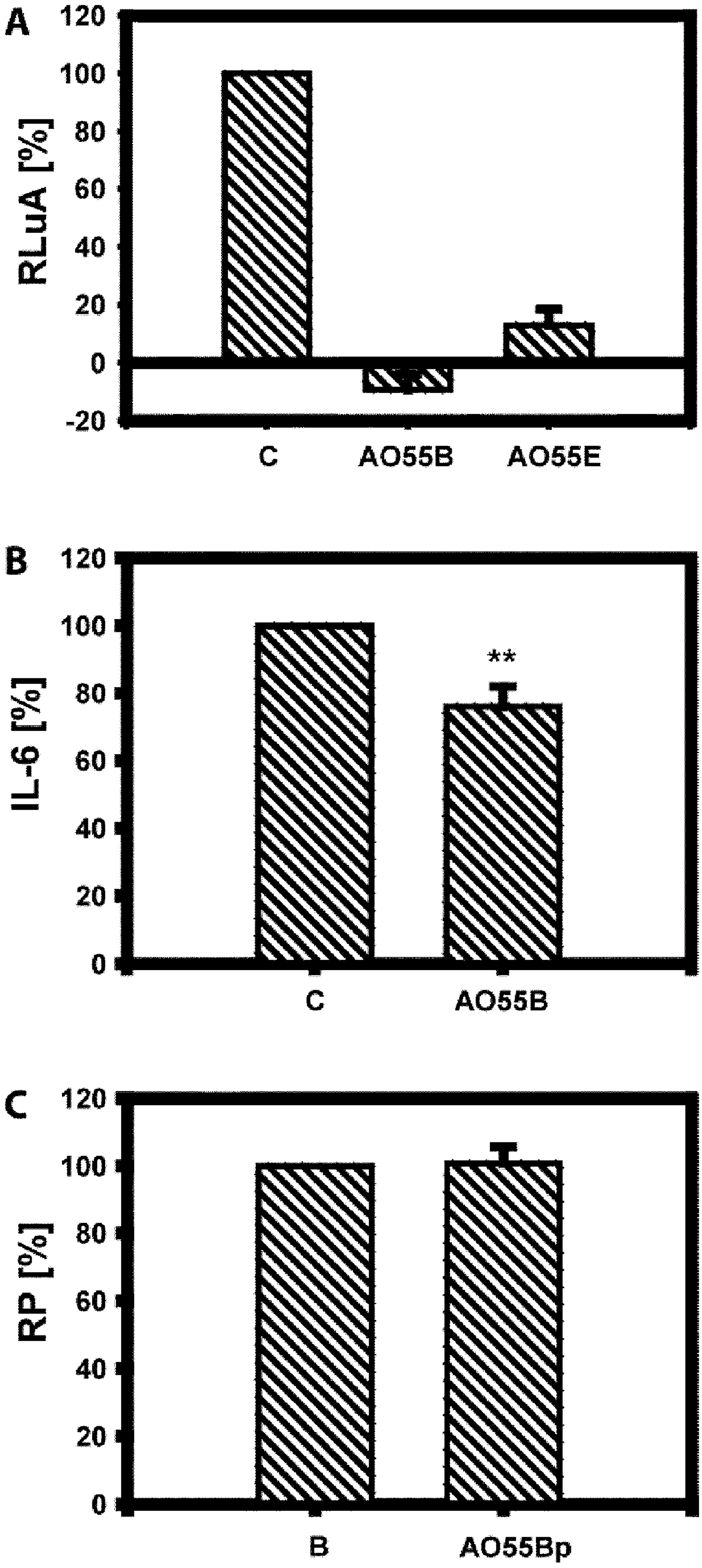
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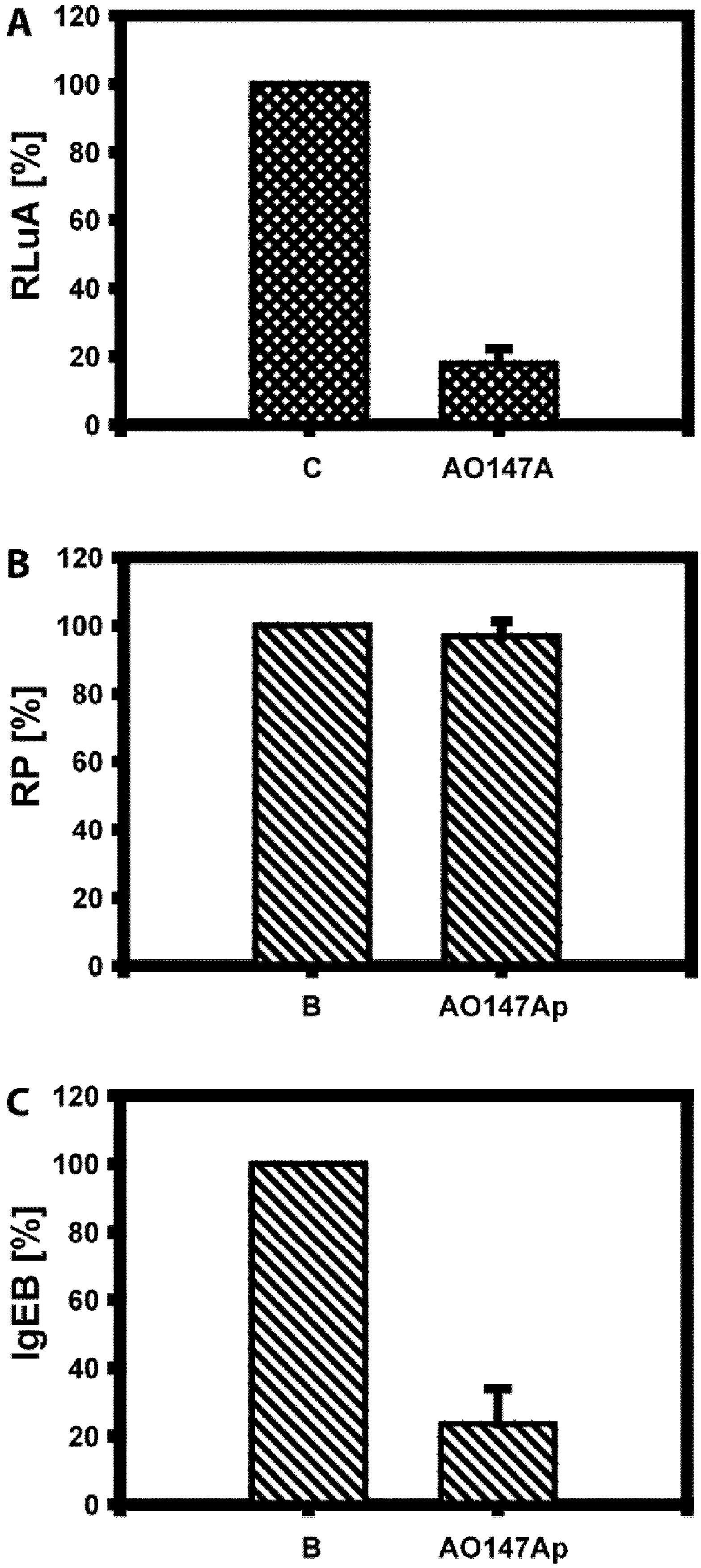
图 10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RP [%]
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AO147Ap
C
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100
80
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40
20
0
IgEB [%]
B
AO147Ap

图 11

New Process for the Preparation of Crystal Modifications for Use in the Preparation of Esomeprazole Sodium Salt

The present invention relates to a new process for the preparation of crystal modifications for use in the preparation of esomeprazole sodium salt. Further, the present invention also relates to the use of the new crystal modifications for the treatment of gastrointestinal disorders, pharmaceutical compositions containing them as well as the crystal modifications, as such.