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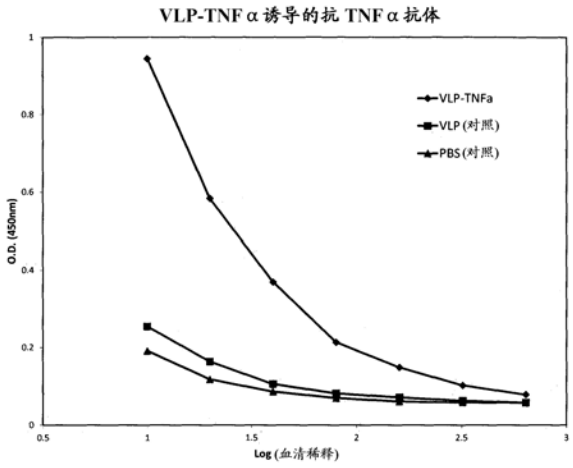
(54)发明名称

病毒样颗粒组合物

(57)摘要

本发明提供包含多肽和至少一种抗原的颗粒,和包含它们的组合物。



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1.包含病毒结构多肽和至少一种抗原的病毒样颗粒,其中所述病毒结构多肽衍生自基孔肯雅病毒(CHIKV)或委内瑞拉马脑炎病毒(VEEV),所述抗原与病毒结构多肽的被膜蛋白融合,融合的蛋白能够自我装配以形成病毒结构颗粒,其中所述抗原的N-末端残基和C-末端残基之间的空间距离为30 Å或更小,并且其中所述抗原并非源自所述病毒结构多肽所衍生自的病毒。

2.权利要求1的病毒样颗粒,其中所述病毒结构多肽衍生自基孔肯雅病毒(CHIKV)。

3.权利要求1的病毒样颗粒,其中所述病毒结构多肽包含衣壳和/或被膜蛋白E3、E2、6K和E1。

4.权利要求3的病毒样颗粒,其中将所述至少一种抗原插入到被膜蛋白。

5.权利要求4的病毒样颗粒,其中将所述至少一种抗原插入到被膜蛋白的E2。

6.权利要求1的病毒样颗粒,其中所述抗原是选自自身抗原和癌抗原的至少一种。

7.权利要求1的病毒样颗粒,其中所述抗原是衍生自TNF-α、CD20或CTLA4的多肽。

8.权利要求7的病毒样颗粒,其中所述多肽和所述至少一种抗原是

i) 衍生自基孔肯雅病毒(CHIKV)的多肽和TNF-α的多肽;

ii) 衍生自基孔肯雅病毒(CHIKV)的多肽和CD20的多肽;

iii) 衍生自委内瑞拉马脑炎病毒(VEEV)的多肽和TNF-α的多肽;或

iv) 衍生自委内瑞拉马脑炎病毒(VEEV)的多肽和CD20的多肽

v) 衍生自委内瑞拉马脑炎病毒(VEEV)的多肽和CTLA4的多肽。

9.权利要求1的病毒样颗粒,其中所述病毒结构多肽和所述至少一种抗原直接融合。

10.权利要求1的病毒样颗粒,其中所述至少一种抗原与所述病毒结构多肽融合,其中一个或两个接头插入在所述抗原的N-末端残基和所述病毒结构多肽之间和/或在所述抗原的C-末端残基和所述病毒结构多肽之间。

11.权利要求9的病毒样颗粒,其中所述至少一种抗原插入在SEQ ID No.1或2的残基519和520之间、SEQ ID No.1或2的残基530和531之间、SEQ ID No.1或2的残基531和532之间或SEQ ID No.1或2的残基532和533之间。

12.权利要求1的病毒样颗粒,其中所述融合蛋白是由SEQ ID No. 4、5、6、7或8所示的氨基酸序列组成的蛋白。

13.权利要求1的病毒样颗粒,其中所述融合蛋白衍生自以下蛋白质:所述蛋白质由与SEQ ID No. 4、5、6、7或8所示的氨基酸序列具有90%或更高的序列同一性的氨基酸序列组成。

14.权利要求1的病毒样颗粒,其中所述至少一种抗原以化学交联方式与所述多肽连接。

15.分离的核酸分子,包含编码权利要求1-14中任一项的病毒样颗粒的核苷酸序列。

16.分离的核酸分子,由SEQ ID No. 13、14、15、16或17所示的核苷酸序列组成。

17.分离的核酸分子,由与SEQ ID No. 13、14、15、16或17所示的核苷酸序列具有90%或更高的序列同一性的核苷酸序列组成。

18.包含权利要求15-17中任一项的核酸分子的载体,其中所述载体任选包含与所述核酸分子操作性连接的表达控制序列。

19.组合物,包含权利要求1-14中任一项的病毒样颗粒和/或权利要求15-17中任一项

的分离的核酸分子和/或权利要求18的载体。

20.药物组合物,包含:

(a) 权利要求1-14中任一项的病毒样颗粒和/或权利要求15-17中任一项的分离的核酸分子和/或权利要求18的载体;和

(b) 药学上可接受的载体。

21.疫苗组合物,包含权利要求1-14中任一项的病毒样颗粒。

22.DNA疫苗组合物,包含权利要求15-17中任一项的分离的核酸分子和/或权利要求18的载体。

23.产生抗体的方法,包括使权利要求1-14中任一项的病毒样颗粒和/或权利要求15-17中任一项的分离的核酸分子和/或权利要求18的载体与哺乳动物接触,其中所述方法用于非治疗目的。

24.权利要求23的方法,其中所述抗体是单克隆抗体。

25.权利要求20-22中任一项的组合物在制备免疫调节药物中的用途。

26.权利要求20-22中任一项的组合物在制备用于治疗自身免疫性疾病的药物中的用途。

27.权利要求20-22中任一项的组合物在制备用于在哺乳动物中诱导和/或增强针对抗原的免疫应答的药物中的用途。

28.权利要求20-22中任一项的组合物在制备用于治疗癌症的药物中的用途。

29.通过权利要求23或24的方法所获得的抗体在制备用于被动免疫的药物中的用途。

30.通过权利要求23或24的方法所获得的抗体在制备用于治疗癌症的药物中的用途。

31.权利要求25-30中任一项的用途,其中所述至少一种抗原是癌抗原。

32.权利要求25-30中任一项的用途,其中所述至少一种抗原是一种或多种癌抗原。

33.在巨噬细胞上呈递抗原的方法,包括使权利要求1-14中任一项的颗粒和/或权利要求15-17中任一项的分离的核酸分子和/或权利要求18的载体与哺乳动物细胞离体接触。

34.产生权利要求1-14中任一项的病毒样颗粒的方法,包括:制备包含编码所述颗粒的核苷酸序列的基因;培养已用所述基因转染的细胞,以表达所述颗粒;和回收所述颗粒。

病毒样颗粒组合物

[0001] 本申请是申请日为2013年2月15日,中国国家申请号为201380020165.9,发明名称为“病毒样颗粒组合物”的发明申请的分案申请。

[0002] 相关申请的交叉引用

本申请要求于2012年2月16日申请的美国临时专利申请号61/599,746的权益,其全部内容都通过引用结合到本文中。

技术背景

[0003] 本发明涉及包含多肽和至少一种抗原的颗粒,和包含它们的组合物。

[0004] 背景

病毒样颗粒(VLP)是多蛋白结构,其模拟真实的天然病毒的组织和构造但缺少病毒基因组,可能产生更安全和更便宜的疫苗候选物。一部分预防性的基于VLP的疫苗目前在全球范围内已商业化:葛兰素史克公司的Engerix® (乙肝病毒)和Cervarix® (人乳头瘤病毒),以及默克公司(Merck & Co., Inc.)的Recombivax HB® (乙肝病毒)和Gardasil® (人乳头瘤病毒)就是一些实例。其它基于VLP的疫苗候选物处于临床试验中或正在进行临床前评价,例如,流感病毒、细小病毒、Norwalk和各种嵌合VLP。许多其它的仍仅限于小规模基础研究,尽管它们在临床前试验中是成功的。关于大规模VLP生产,在工艺控制、监测和优化的背景下讨论。因此鉴定和讨论了主要的上下游技术挑战。对于治疗性或预防性的疫苗接种,伴随最新的临床试验结果和近来基于嵌合VLP技术的进展,暂时呈现出成功的基于VLP的疫苗的突起。(Expert Rev. Vaccines 9(10), 1149-1176, 2010)。

[0005] 自从基孔肯雅病毒(CHIKV)于2004年自肯尼亚再度出现以来,这种甲病毒已经感染了非洲、欧洲和亚洲的几百万人。由于缺乏疫苗或抗病毒治疗,该疾病的严重性和该流行性病毒的传播带来了严重的公共健康威胁。据报道针对流行性基孔肯雅病毒的VLP疫苗保护非人类灵长类动物免于感染(Nat Med. 2010 March;16(3): 334-338)。美国专利公布号2012/0003266公开了包含一种或多种基孔肯雅病毒结构多肽的病毒样颗粒(VLP),其可用于配制针对基孔肯雅的疫苗或抗原组合物,其诱导针对感染或其至少一种症状的免疫力。WO2012/106356公开了修饰的甲病毒或黄病毒病毒样颗粒(VLP)和用于增强修饰的VLP的生产的方法,用于预防或治疗甲病毒和黄病毒-介导的疾病。(这些引用的参考文献通过引用结合到本文中)。

[0006] 发明概述

在第一方面,本发明提供能够自我装配的颗粒,其包含多肽和至少一种抗原,其中所述多肽包含至少一个第一附着位点和所述至少一种抗原包含至少一个第二附着位点,和其中所述多肽和所述抗原通过所述至少一个第一和所述至少一个第二附着位点而连接。

[0007] 在第二方面,本发明提供核酸分子,其包含编码在本发明第一方面中提供的颗粒的核苷酸序列。

[0008] 在第三方面,本发明提供组合物,其包含在本发明第一方面中提供的颗粒和/或在本发明第二方面中提供的核酸分子。

[0009] 在第四方面，本发明提供产生抗体的方法，包括使在本发明第一方面中提供的颗粒和/或在本发明第二方面中提供的核酸分子与哺乳动物接触。

[0010] 在第五方面，本发明提供免疫调节的方法，治疗自身免疫性疾病的方法，在哺乳动物中诱导和/或增强针对抗原的免疫应答的方法，和治疗癌症的方法，包括将在本发明第三方面中提供的组合物给予哺乳动物。

[0011] 在第六方面，本发明提供被动免疫的方法，包括将在本发明第四方面中提供的抗体给予哺乳动物。

[0012] 在第七方面，本发明提供在巨噬细胞上呈递抗原的方法，包括使在本发明第一方面中提供的颗粒和/或在本发明第二方面中提供的核酸分子与哺乳动物接触。

[0013] 在第八方面，本发明提供用于产生在本发明第一方面中提供的颗粒的方法，包括：制备包含编码所述颗粒的核苷酸序列的基因；培养已用所述基因转染的细胞，以表达所述颗粒；和回收所述颗粒。

[0014] 附图简述

图1显示待插入到委内瑞拉马脑炎病毒(VEEV)结构多肽中的TNFα序列的修饰。

[0015] 图2显示蛋白质印迹结果，表明TNFα缀合的VLP已表达。

[0016] 图3显示VLP_CHI 512载体。

[0017] 图4显示VLP_CHI 532载体。

[0018] 图5显示VLP_CHI 520载体。

[0019] 图6显示VLP_VEEV VLP 518载体。

[0020] 图7显示VLP_VEEV VLP 519载体。

[0021] 图8显示VLP_VEEV VLP 538载体。

[0022] 图9显示由TNFα衍生的肽-缀合的病毒样颗粒所诱导的抗TNFα抗体的检测。

[0023] 图10显示由CD20衍生的肽-缀合的病毒样颗粒所诱导的抗人CD20抗体的检测。

[0024] 图11显示由CD20衍生的肽-缀合的病毒样颗粒所诱导的抗小鼠CD20抗体的检测。

[0025] 发明详述

(1)包含多肽和至少一种抗原的颗粒

在第一方面，本发明提供能够自我装配的颗粒，其包含多肽和至少一种抗原，其中所述多肽包含至少一个第一附着位点和所述至少一种抗原包含至少一个第二附着位点，和其中所述多肽和所述抗原通过所述至少一个第一和所述至少一个第二附着位点而连接。

[0026] 如本文所用，“能够自我装配的颗粒”是指由至少一种自发装配的组分构成的颗粒。所述组分可以是多肽或非肽化合物。在一个实施方案中，“能够自我装配的颗粒”可以是包含至少一种多肽或由其组成的颗粒。所述至少一种多肽由一种或多种类型的肽组成。在一个实施方案中，所述颗粒的直径为至少10nm，例如至少20nm，优选地至少50nm。在一个实施方案中，所述颗粒的分子量为100 kDa至100,000kDa，优选400kDa 至30,000kDa。

[0027] 用于本发明的多肽并未被限定，只要它自发装配。所述多肽可以是病毒结构多肽。因此，本发明提供的颗粒可以是病毒样颗粒。

[0028] 病毒结构多肽可以是天然存在的病毒多肽或其修饰的多肽。在一个实施方案中，所述修饰的多肽与包括衣壳和被膜蛋白在内的天然存在的病毒结构多肽具有至少70%、75%、80%、85%、90%、95%或98%氨基酸序列同一性。在一个实施方案中，所述修饰的多肽是突

变体，其中至多10%的氨基酸被缺失、置换和/或添加到包括衣壳和被膜蛋白在内的天然存在的病毒结构多肽。

[0029] 在一个实施方案中，用于本发明的病毒结构多肽包含衣壳和/或被膜蛋白或其片段或由其组成。例如，被膜蛋白包含选自E3、E2、6K和E1的至少一种。用于本发明的病毒结构多肽可衍生自甲病毒或黄病毒。因此，本发明提供的颗粒可以是衍生自甲病毒或黄病毒的病毒样颗粒。

[0030] 甲病毒和黄病毒的实例包括但不限于奥拉病毒(Aura virus)、Babanki病毒、Barmah Forest病毒(BFV)、Bebaru病毒、Cabassou病毒、基孔肯雅病毒(CHIKV)、东方马脑炎病毒(EEEV)、埃拉特病毒(Eilat virus)、沼泽地病毒(Everglades virus)、摩根堡病毒(Fort Morgan virus)、盖塔病毒(Getah virus)、高地J病毒(Highlands J virus)、Kyzylagach病毒、马雅罗病毒(Mayaro virus)、Me Tri病毒、米德尔堡病毒(Middelburg virus)、Mosso das Pedras病毒、Mucambo病毒、恩杜姆病毒(Ndumu virus)、奥绒绒病毒(O'nyong-nyong virus)、Pixuna病毒、Rio Negro病毒、罗斯河病毒(Ross river virus，RRV)、鲑鱼胰腺病病毒(Salmon pancreas disease virus)、Semliki Forest病毒、辛德比斯病毒(Sindbis virus)、南方象海豹病毒(Southern elephant seal virus)、Tonate病毒、Trocara病毒、Una病毒、委内瑞拉马脑炎病毒(VEEV)、西方马脑炎病毒(WEEV)、Whataroa病毒、西尼罗病毒、登革热病毒、蜱传脑炎病毒和黄热病病毒。

[0031] 本文所用的术语“抗原”是指如果被MHC分子呈递，能够被抗体或T细胞受体(TCR)结合的分子。术语“抗原”，如本文使用，也包括T细胞表位。在存在于除红细胞外的机体所有细胞上的MHC I类的情况下，或在存在于免疫细胞和尤其是抗原呈递细胞上的MHC II类的情况下，T细胞表位被T细胞受体识别。这样的识别事件导致T细胞活化和随后的效应器机制，例如T细胞的增殖、细胞因子的分泌、穿孔素的分泌等。抗原还能被免疫系统识别和/或能够诱导体液免疫应答和/或细胞免疫应答，导致B-和/或T-淋巴细胞的活化。然而，至少在某些情况下，这可能需要抗原含有或者连接于TH细胞表位，并且包含于佐剂中。一种抗原可能包含一种或多种表位(B和T表位)。上面提到的特异性反应指抗原优选地通常以高选择性方式与其相应的抗体或TCR反应，而不与可能由其它抗原诱导的许多其它抗体或TCR反应。本文所用的抗原也可以是几种不同抗原的混合物。抗原，如本文所用，包括但不限于变应原、自体抗原、半抗原、癌抗原(即肿瘤抗原)和感染性疾病抗原以及有机小分子例如滥用的药物(例如烟碱)及其片段和衍生物。此外，用于本发明的抗原可以是肽、蛋白质、结构域、碳水化合物、生物碱、脂质或小分子例如甾体激素及其片段和衍生物、自身抗体和细胞因子本身。

[0032] 细胞因子的实例包括但不限于：白介素(IL)，包括超过30个种类，例如IL-1α、IL-1β、IL-2、-3、-4、-5、-6、-7、-8、-9、-10、-11至-37；干扰素(IFN)，例如IFN-α、IFN-β和IFN-γ；肿瘤坏死因子(TNF)，例如TNF-α和TNF-β；转化生长因子(TGF)，例如TGF-α和TGF-β；集落刺激因子(CSF)，例如粒细胞-集落刺激因子(G-CSF)、粒细胞-巨噬细胞-集落刺激因子(GM-CSF)、巨噬细胞-集落刺激因子(M-CSF)、红细胞生成素(EPO)、干细胞因子(SCF)和单核细胞趋化和活化因子(MCAF)；生长因子(GF)例如表皮生长因子(EGF)、成纤维细胞生长因子(FGF)、胰岛素样生长因子(IGF)、神经生长因子(NGF)、脑衍生的神经营养因子(BDNF)、血小板衍生的生长因子(PDGF)、血管内皮生长因子(VEGF)、肝细胞生长因子(HGF)、角质细胞生

长因子(KGF)、血小板生成素(TPO)、和骨形态发生蛋白(BMP);和其它多肽因子,包括LIF、kit配体(KL)、MPO (髓过氧化物酶)和CRP (C-反应蛋白);COX (环加氧酶),例如COX-1、COX-2和COX-3;NOS (一氧化氮合酶)例如NOS-1、NOS-2和NOS-3;等等。

[0033] 细胞因子还包括趋化因子,其是诱导趋化性的细胞因子。有两个主要类型的趋化因子,CXC和CC。CXC趋化因子,例如嗜中性粒细胞-活化蛋白-2 (NAP-2)和黑素瘤生长刺激活性蛋白(MGSA),主要对于嗜中性粒细胞和T淋巴细胞是趋化性的,而CC趋化因子,例如RANTES、巨噬细胞炎性蛋白(MIP)包括MIP-1α和MIP-1β、角质细胞-衍生的趋化因子(KC)、单核细胞趋化蛋白(MCP-1、MCP-2、MCP-3、MCP-4和MCP-5)和嗜酸性粒细胞趋化因子(-1和-2),对于其它细胞类型中的巨噬细胞、T淋巴细胞、嗜酸性粒细胞、嗜中性粒细胞、树突细胞和嗜碱性粒细胞是趋化性的。还存在趋化因子淋巴细胞趋化蛋白-1、淋巴细胞趋化蛋白-2 (两者都是C趋化因子)和fractalkine (一种CX3C趋化因子),这些未落入主要趋化因子亚家族的任何一类中。

[0034] 本文所用的术语“抗原决定簇”是指被B或T-淋巴细胞特异性识别的抗原部分。B-淋巴细胞经由抗体产生而响应外源抗原决定簇,而T淋巴细胞是细胞免疫的介质。因此,抗原决定簇或表位是由抗体识别的抗原部分,或者是在MHC的情况下由T细胞受体识别的抗原部分。抗原决定簇含有一个或多个表位。

[0035] 本文所用的术语“抗体”是指能够结合表位或抗原决定簇的分子。该术语意指包括完整抗体及其抗原结合片段,包括单链抗体。这样的抗体包括人抗原结合抗体片段和包括但不限于Fab、Fab'和F(ab')2、Fd、单链Fvs (scFv)、单链抗体、二硫键连接的Fvs (sdFv)和包含VL或VH结构域的片段。抗体可以来自任何动物来源,包括鸟类和哺乳动物。优选地,抗体是哺乳动物抗体,所述哺乳动物例如人、鼠、兔、山羊、豚鼠、骆驼、马等,或是其它合适的动物(例如鸡)。如本文所用,“人”抗体包括具有人免疫球蛋白的氨基酸序列的抗体,并包括分离自人免疫球蛋白文库或一种或多种人免疫球蛋白的转基因动物(其不表达内源免疫球蛋白)的抗体,例如描述于美国专利号5,939,598,其公开内容通过引用全部结合到本文中。

[0036] 抗原可以是并非源自病毒(例如基孔肯雅病毒、委内瑞拉马脑炎病毒)的一种物质(例如蛋白)。

[0037] 在一个实施方案中,用于本发明的抗原是表1所列举的至少一个靶标或源自它们的多肽。

表 1

靶标	用途
GD2	成神经细胞瘤
CA-125（模拟）	卵巢癌
CD41（整联蛋白 α-IIb）	血小板凝集抑制剂
TNF-α	类风湿性关节炎等
EpCAM	前列腺癌和乳腺癌
TNF-α	脓毒症
CD20	淋巴瘤
VEGFR2	癌症
IL-6	类风湿性关节炎
CD52	CLL, CTCL
CEA	结肠直肠癌
TAG-72	非小细胞肺癌
HLA-DR	血癌
CEA	胃肠癌
L-选择素（CD62L）	严重损伤病人
IL-6 受体	类风湿性关节炎
Rh 因子	新生儿溶血症
β 淀粉样蛋白	阿尔茨海默病
CD25（IL-2 受体的 α 链）	防止器官移植排斥
磷酯酰丝氨酸	癌症，病毒感染
CD22	非霍奇金淋巴瘤
BAFF	非霍奇金淋巴瘤等
CD125	哮喘
CCL11（嗜酸性粒细胞趋化因子-1）	严重过敏病症
CEA-相关抗原	类性损伤和转移
VEGF-A	转移性癌症
纤维蛋白 II，β 链	血栓栓塞
CD44 v6	鳞状细胞癌
CD19	癌症
CD30 (TNFRSF8)	血癌
IL-12, IL-23	银屑病，类风湿性关节炎，类性肠病，多发性硬化
IL-1	类风湿性关节炎
黏蛋白 CanAg	结肠直肠癌等
前列腺癌细胞	前列腺癌
EpCAM, CD3	卵巢癌，恶性腹水，胃癌
TAG-72	肿瘤检测
CD4	防止器官移植排斥，治疗自身免疫病
TNF-α	克罗恩病
EGFR	转移性结肠直肠癌和头颈癌
EpCAM	卵巢癌和其它实体癌
IGF-1 受体	实体癌
CD4	类风湿性关节炎
MUC1	胰腺癌
TRAIL-R2	癌症
甲型流感血凝素	感染性疾病/甲型流感
CD40	血癌
CD25（IL-2 受体的 α 链）	防止器官移植排斥
RANKL	骨质疏松症，骨转移等
B-淋巴瘤细胞	淋巴瘤
GD3 神经节苷酯	恶性黑素瘤
C5	阵发性睡眠性血红蛋白尿症
内毒素	革兰氏阴性菌所致的脓毒症
EpCAM	结肠直肠癌
LFA-1 (CD11a)	银屑病（阻断 T 细胞迁移）
Hsp90	侵袭性念珠菌感染
SLAMF7	多发性骨髓瘤
CD22	癌症，SLE
ITGB2 (CD18)	心脏病发作，中风，创伤性休克
HER2/neu, CD3	乳腺癌等
整联蛋白 αvβ3	黑素瘤，前列腺癌，卵巢癌等
乙肝表面抗原	乙肝
CD15	霍尔类
叶酸受体 1	卵巢癌

表 1 (续)

靶标	用途
呼吸道合胞病毒	呼吸道合胞病毒感染
IL-22	类风湿性关节炎、银屑病
1GF-1 受体	肾上腺皮质癌、非小细胞肺癌等
IFN-γ	克罗恩病等
狂犬病病毒糖蛋白	狂犬病（预防）
TGF-β	特发性肺纤维化、局灶性节段性肾小球硬化、癌症
CD80	B 细胞淋巴瘤
β 淀粉样蛋白	阿尔茨海默病
CD147 (basigin)	移植物抗宿主病
CD33	急性骨髓性白血病
碳酸酐酶 9 (CA-IX)	透明细胞肾细胞癌
GPNMB	黑素瘤、乳腺癌
TNF-α	类风湿性关节炎、银屑病性关节炎、强直性脊柱炎
CD23（IgE 受体）	过敏性哮喘
CD4	HIV 感染
CD20	非霍奇金淋巴瘤
CA-125	卵巢癌
心肌球蛋白	心脏造影
TNF-α	类风湿性关节炎、强直性脊柱炎、银屑病性关节炎、银屑病、克罗恩病、溃疡性结肠炎
CD51	实体瘤（前列腺癌、黑素瘤）
CD25（IL-2 受体的α链）	移植物抗宿主病
CD22	癌症
CD152	黑素瘤
CD30 (TNFRSF8)	霍奇金淋巴瘤
CD4	慢性哮喘
CEA	结肠直肠癌
IL-13	哮喘
NCA-90（粒细胞抗原）	诊断试剂
TGFβ2	青光眼术后的疤痕减少
TRAIL-R2	癌症
乙肝表面抗原	乙肝
CD33	癌症
CD56	癌症
CD40	多发性骨髓瘤、非霍奇金淋巴瘤、霍奇金淋巴瘤
CD23（IgE 受体）	慢性淋巴细胞性白血病
TRAIL-R1	癌症
EGFR	结肠直肠癌、肺癌和胃癌
IL-5	哮喘和白细胞疾病
TGFβ1	系统性硬皮病
CD74	多发性骨髓瘤和其它血液恶性肿瘤
GD3 神经节苷脂	小细胞肺癌
呼吸道合胞病毒	呼吸道合胞病毒（预防）
CD3	防止器官移植排斥
C242 抗原	结肠直肠癌
5T4	非小细胞肺癌、肾细胞癌
整联蛋白α4	多发性硬化、克罗恩病
内毒素	脓毒症
EGFR	非小细胞肺癌
EGFR	鳞状细胞癌、头颈癌、鼻咽癌、胶质瘤
CD20	类风湿性关节炎、红斑狼疮等
LFA-1 (CD11a)	防止器官移植排斥、免疫性疾病
CD20	慢性淋巴细胞性白血病等
PDGF-R α	癌症
IgE Fc 区	过敏性哮喘
EpCAM	癌症
CA-125	卵巢癌
CD3	糖尿病 1 型
脂磷壁酸	脓毒症（葡萄球菌）
呼吸道合胞病毒	呼吸道合胞病毒（预防）
EGFR	结肠直肠癌

表 1 (续)

靶标	用途
呼吸道合胞病毒	呼吸道合胞病毒（预防）
EGFR	结肠直肠癌
铜绿假单胞菌	铜绿假单胞菌感染
IL-4	哮喘
MUC1	癌症
HER2/neu	癌症
C5	心脏手术副作用的减少
腺癌抗原	腺癌
CD4	克罗恩病、多发性硬化
波形蛋白	脑癌
CCR5	HIV 感染
狂犬病毒糖蛋白	狂犬病（预防）
VEGFR2	实体瘤
VEGF-A	黄斑变性（湿式）
炭疽毒素，保护性抗原	炭疽（预防和治疗）
巨细胞病毒糖蛋白 B	巨细胞病毒感染
IL-5	气道、皮肤和胃肠道类癌
HGF	实体瘤
CD20	淋巴瘤、白血病、某些自身免病症
IGF-1 受体	癌症
IFN-α	系统性红斑狼疮
CD11, CD18	出血性休克等
CD154 (CD40L)	风湿病
TAG-72	癌症
巨细胞病毒	巨细胞病毒感染
FAP	癌症
IFN-α	SLE、皮肌炎、多肌炎
CD2	银屑病、移植物抗宿主病（预防）
β淀粉样蛋白	阿尔茨海默病
鞘氨醇-1-磷酸	脉络膜和视网膜新血管形成
肌肉生长抑素	肌肉萎缩
NCA-90（粒细胞抗原）	骨髓炎
甲胎蛋白	癌症
整联蛋白αIIbβ3	经皮冠状动脉介入
IgE	过敏性反应
NGF	疼痛
CD19	癌症
凝聚因子 A	金黄色葡萄球菌感染
生腱蛋白 C	癌症
CD3	糖尿病 1 型
CD28	慢性淋巴细胞性白血病、类风湿性关节炎
CTLA-4	癌症
TRAIL-R2	癌症
IL-13	霍奇金淋巴瘤
IL-6 受体	类风湿性关节炎
CD154 (CD40L)	类风湿性关节炎、狼疮性肾炎
CD20	滤泡性淋巴瘤
HER2/neu	乳腺癌
CTLA-4	癌症
EpCAM	癌症
乙肝病毒	慢性乙肝
大肠杆菌	大肠杆菌所致的腹泻
IL-12, IL-23	多发性硬化、银屑病、银屑病性关节炎
整联蛋白α4β7	克罗恩病、溃疡性结肠炎
CD20	非霍奇金淋巴瘤
AOC3 (VAP-1)	炎症
CD3	克罗恩病、溃疡性结肠炎
整联蛋白α5β1	实体瘤
肿瘤抗原CTAA16.88	结肠直肠癌
EGFR	头颈部的鳞状细胞癌
CD4	类风湿性关节炎、银屑病、T 细胞淋巴瘤
CD5	系统性红斑狼疮、移植物抗宿主病

[0038] 在一个实施方案中，用于本发明的抗原是选自CTLA-4、PD-1、TIM-3、BTLA、VISTA、LAG-3、CD28、OX40、GITR、CD137、CD27和HVEM的至少一种蛋白或源自它们的多肽。CTLA-4、PD-1、TIM-3、BTLA、VISTA和LAG-3是T细胞刺激的抑制性受体，以及CD28、OX40、GITR、CD137、CD27和HVEM是T细胞刺激的活化受体(参见Mellman等人，Nature 480，480-489 (2011))。

[0039] 用于本发明的抗原可以是衍生自天然存在的蛋白的修饰的多肽。所述修饰的多肽

可以是天然存在的蛋白的片段。在一个实施方案中，所述修饰的多肽与衍生自天然存在的蛋白的多肽具有至少70%、75%、80%、85%、90%、95%或98%氨基酸序列同一性。在一个实施方案中，所述衍生的修饰的多肽是突变体，其中基于衍生自天然存在的蛋白的多肽，至多10%的氨基酸被缺失、置换和/或添加。

[0040] 在本发明提供的颗粒中，多肽和抗原可通过存在于所述多肽中的至少一个第一附着位点和存在于所述抗原中的至少一个第二附着位点而连接。

[0041] 如本文所用，“第一附着位点”和“第二附着位点”各自是指超过一种物质彼此连接的位点。

[0042] 在一个实施方案中，所述多肽和所述抗原直接融合。或者，可将一个或两个接头插入在所述抗原的N-末端残基和所述多肽之间和/或在所述抗原的C-末端残基和所述多肽之间。

[0043] 所述抗原或所述多肽可以被截短和用短接头代替。在某些实施方案中，所述抗原或所述多肽包括一个或多个肽接头。典型地，接头由2-25个氨基酸组成。通常长度为2-15个氨基酸，尽管在某些情况下，可以是仅一个，例如单一的甘氨酸残基。

[0044] 在一个实施方案中，其中编码多肽的多核苷酸与编码抗原的多核苷酸经基因融合的核酸分子，在宿主细胞中表达，使得第一附着位点和第二附着位点通过肽键连接。在这种情况下，所述多肽和所述抗原通过肽键连接。对于该实施方案，可自原始多肽或抗原，遗传修饰第一附着位点和/或第二附着位点。例如，自所述多肽修饰第一附着位点，使得通过包括SG、GS、SGG、GGS和SGSG在内的接头肽，将所述多肽与所述抗原缀合。

[0045] 当所述多肽与所述抗原化学缀合时，第一附着位点和第二附着位点可通过化学交联接头(其是一种化合物)而连接。

[0046] 交联接头的实例包括但不限于SMPH、Sulfo-MBS、Sulfo-EMCS、Sulfo-GMBS、Sulfo-SIAB、Sulfo-SMPB、Sulfo-SMCC、SVSB、SIA和其它交联接头，得自Pierce Chemical Company。

[0047] 在一个实施方案中，本发明提供的颗粒包含与抗原连接的多肽，其中当在抗原或含有所述抗原的天然存在的蛋白或源自其的修饰的蛋白的晶体中测定距离时，所述抗原的N-末端残基和C-末端残基之间的空间距离为30Å或更小。

[0048] 用于本发明的抗原可以由本领域技术人员设计。例如，用于本发明的抗原可以是天然存在的蛋白或其片段。或者，本发明使用的抗原可以是自天然存在的蛋白或其片段修饰的蛋白。本领域技术人员可以设计抗原，使得当在抗原或含有所述抗原的天然存在的蛋白或源自其的修饰的蛋白的晶体中测定距离时，抗原的N-末端残基和C-末端残基之间的空间距离为30Å或更小。例如，可以使用免费软件，包括PyMOL (例如PyMOL v0.99: http://www.pymol.org)，设计用于本发明提供的颗粒的抗原。在一个实施方案中，抗原的N-末端残基和C-末端残基之间的空间距离为30Å (埃)或更小、20Å或更小、或10Å或更小(例如5Å至15Å、5 Å至12 Å 、5 Å至11 Å 、5 Å至10 Å 、5 Å至8 Å 、8 Å至15 Å 、8 Å至13 Å 、8 Å至12 Å 、8 Å至11 Å 、9 Å至12 Å 、9 Å至11 Å 、9 Å至10 Å或10 Å至11 Å)。

[0049] 基孔肯雅病毒样颗粒或委内瑞拉马脑炎病毒样颗粒

在一个实施方案中，本发明提供基孔肯雅病毒样颗粒或委内瑞拉马脑炎病毒样颗

粒,其包含基孔肯雅或委内瑞拉马脑炎病毒结构多肽和至少一种抗原,其中所述基孔肯雅病毒结构多肽或所述委内瑞拉马脑炎病毒结构多肽包含至少一个第一附着位点和所述至少一种抗原包含至少一个第二附着位点,和其中所述基孔肯雅或委内瑞拉马脑炎病毒结构多肽和所述至少一种抗原通过所述至少一个第一和所述至少一个第二附着位点而连接。

[0050] 在一个实施方案中,当在抗原或含有所述抗原的天然存在的蛋白或源自其的修饰的蛋白的晶体中测定距离时,抗原的N-末端残基和C-末端残基之间的空间距离可以是30 Å或更小; 25 Å或更小; 20 Å或更小; 15 Å或更小; 14 Å或更小; 13 Å或更小; 12 Å或更小; 11 Å或更小; 10 Å或更小; 9 Å或更小;或8 Å或更小(例如5 Å至15 Å 、5 Å至12 Å 、5 Å至11 Å 、5 Å至10 Å 、5 Å至8 Å 、8 Å至15 Å 、8 Å至13 Å 、8 Å至12 Å、8 Å至11 Å、9 Å至12 Å 、9 Å至11 Å 、9 Å至11 Å或10 Å至11 Å)。

[0051] 在一个实施方案中,所述抗原通过化学交联方式或作为以遗传工程方式产生的融合蛋白而与基孔肯雅或委内瑞拉马脑炎病毒结构多肽连接。

[0052] 用于本发明的基孔肯雅或委内瑞拉马脑炎病毒结构多肽可包含基孔肯雅或委内瑞拉马脑炎病毒被膜蛋白和/或衣壳。

[0053] 基孔肯雅病毒的实例包括但不限于37997和LR2006 OPY-1毒株。

[0054] 委内瑞拉马脑炎病毒的实例包括但不限于TC-83。

[0055] 用于本发明的基孔肯雅或委内瑞拉马脑炎病毒结构多肽可以是天然存在的病毒结构多肽或其修饰的多肽。所述修饰的多肽可以是天然存在的病毒结构多肽的片段。在一个实施方案中,所述修饰的多肽与天然存在的病毒衣壳和/或被膜蛋白具有至少70%、75%、80%、85%、90%、95%或98%的氨基酸序列同一性。在一个实施方案中,所述修饰的多肽是突变体,其中基于天然存在的病毒衣壳和/或被膜蛋白,至多10%的氨基酸被缺失、置换和/或添加。例如,可将K64A或K64N突变引入本发明所用的委内瑞拉马脑炎病毒结构多肽的衣壳中。

[0056] 基孔肯雅或委内瑞拉马脑炎病毒被膜蛋白可包含选自E3、E2、6K和E1的至少一种。

[0057] 基孔肯雅病毒结构多肽的实例包括但不限于基孔肯雅病毒株37997的E3-E2-6K-E1、基孔肯雅病毒株37997的衣壳-E3-E2-6K-E1、基孔肯雅病毒株LR2006 OPY-1的E3-E2-6K-E1和基孔肯雅病毒LR2006 OPY-1的衣壳-E3-E2-6K-E1。

[0058] 委内瑞拉马脑炎病毒结构多肽的实例包括但不限于委内瑞拉马脑炎病毒株TC-83的E3-E2-6K-E1和委内瑞拉马脑炎病毒株TC-83的衣壳-E3-E2-6K-E1。

[0059] 示例性的基孔肯雅病毒结构多肽序列以Genbank登录号ABX40006.1提供,其描述如下(SEQ ID No.:1):

mefiptqtfynrryqprpwtprptiqvirprprpqrqagqlaqlisavnkltmravpqq
kprrnrknkkqkqkqqapqnntnqkkqppkkkpaqkkkkpgrrermcmkiendcifevk
hegkvtgyaclvgdkvmkpahvkgtidnadlaklafkrsskydlecaqipvhmksdask
fthekpegyynwhhgavqysggrftiptgagkpgdsgrpifdnkgrvvaivlgganega
rtalsvvtwnkdivtkitpegaeewslaipvmcllanttfpcsqppctpccyekepeet
lrmlednvmrpgyyqllqasltcsphrqrrstkdnfnvykatrpylahcpdcgeghsch
spvalerirneatdgtlkiqvslqigiktddshdwtklrymdnhmpadaeraglfvrts
apctitgtmghfilarcpkgetltvgftdsrkishscthpfhhdppvigrekfhsrpqh
gkelpcstyvqstaatteeievhmppdtpdrtlmsqqsgnvkitvngqtvrykcncggs
neglttdkvinnckvdqchaavtnhkkwqynsplvprnaelgdrkgkihipfplanvt
crvpkarnptvtygknqvimllypdhptllsyrnmgeepnyqeewvmhkkevvltvpte
glevtwgnnepykywpqlstngtahghpheiilyyyelyptmtvvvvsvatfillsmvg
maagmcmcarrrcitpyeltpgatvpfllsliccirtakaatyqeaaiylwneqqplfw
lqaliplaalivlcnclrllpcccktlaflavmsvgahtvsayehvtvipntvgvpykt
lvnrpgyspmvlemellsvtleptlsldyitceyktvipspyvkccgtaeckdknlpdy
sckvftgvypfmwggaycfcdaentqlseahveksescktefasayrahtasasaklrv
lyqgnnitvtayangdhavtvkdakfivgpmssawtpfdnkivvykgdvynmdyppfga
grpgqfgdiqsrtpeskdvyantqlvlqrpavgtvhvpysqapsgfkywlkergaslqh
tapfgcqiatnpvravncavgnmpisidipeaaftrvvdapsltdmscevpacthssdf
ggvaiikyaaskkgkcavhsmtnavtireaeievegnsqlqisfstalasaefrvqvcs
tqvhcaaechppkdhivnypashttlgvqdisatamswvqkitggvglvvavaaliliv
vlcvsfsrh

另一示例性的基孔肯雅病毒结构多肽序列以Genbank登录号ABX40011.1提供,其描述如下(SEQ ID No.:2):

mefiptqtfynrryqprpwaprptiqvirprprpqrqagqlaqlisavnkltmravpqq
kprrnrknkkqrqkkqapqndpkqkkqppqkkpaqkkkkpgrrermcmkiendcifevk

hegkvmgyaclvgdkvmkpahvkgtidnadlaklafkrsskydlecaqipvhmksdask
fthekpegyynwhhgavqysggrftiptgagkpgdsgrpifdnkgrvvaivlgganega
rtalsvvtwnkdivtkitpegaeewslalpvlcllanttfpcsqppctpccyekepest
lrmlednvmrpgyyqllkasltcsphrqrrstkdnfnvykatrpylahcpdcgeghsch
spialerirneatdgtlkiqvslqigiktddshdwtklrymdshtpadaeragllvrts
apctitgtmghfilarcpkgetltvgftdsrkishtcthpfhheppvigrerfhsrpqh
gkelpcstyvqstaataeeievhmppdtpdrtlmtqqsgnvkitvngqtvrykcncggs
neglttdkvinnckidqchaavtnhknwqynsplvprnaelgdrkgkihipfplanvt
crvpkarnptvtygknqvtmllypdhptllsyrnmgqepnyheewvthkkevtltvpte
glevtwgnnepykywpqmstngtahghpheiilyyyelyptmtvvivsvasfvllsmvg
tavgmcvcarrrcitpyeltpgatvpfllsllccvrttkaatyyeaaaylwneqqplfw
lqaliplaalivlcnclkllpcccktlaflavmsigahtvsayehvtvipntvgvpykt
lvnrpgyspmvlemelqsvtleptlsldyitceyktvipspyvkccgtaeckdkslpdy
sckvftgvypfmwggaycfcdaentqlseahveksescktefasayrahtasasaklrv
lyqgnnitvaayangdhavtvkdakfvvgpmssawtpfdnkivvykgdvynmdyppfga
grpgqfgdiqsrtpeskdvyantqlvlqrpaagtvhvpysqapsgfkywlkergaslqh
tapfgcqiatnpvravncavgnipisidipdaaftrvvdapsvtdmscevpacthssdf
ggvaiikytaskkgkcavhsmtnavtireadvevegnsqlqisfstalasaefrvqvcs
tqvhcaaachppkdhivnypashttlgvqdisttamswvqkitggvglivavaaliliv
vlcvsfsrh.

示例性的委内瑞拉马脑炎病毒结构多肽描述如下(SEQ ID No.:3):

mfpfqpmypmqpmpyrnpfaaprrpwfprtdpflamqvqeltrsmanltfkqrrdappe
gpsaakpkkeasqkqkgggqgkkknqgkkkaktgppnpkaqngnkkktnkkpgkrqrm
vmklesdktfpimlegkingyacvvggklfrpmhvegkidndvlaalktkkaskydley
advpqnmradtfkythekpqgyyswhhgavqyengrftvpkgvgakgdsgrpildnqgr
vvaivlggvnegsrtalsvvmwnekgvtvkytpenceqwslvttmcllanvtfpcaqpp
icydrkpaetlamlsvnvdnpgydelleaavkcpgrkrrsteelfneykltrpymarci
rcavgschspiaieavksdghdgyvrlqtssqygldssgnlkgrtmrydmhgtikeipl
hqvslytsrpchivdghgyfllarcpagdsitmefkkdsvrhscsvpyevkfnpvgrel
ythppehgveqacqvyahdaqnrgayvemhlpgsevdsslvslsgssvtvtppdgtsal
vececggtkisetinktkqfsqctkkeqcrayrlqndkwvynsdklpkaagatlkgklh
vpflladgkctvplapepmitfgfrsvslklhpknptylitrqladephythelisepa
vrnftvtekgwefvwgnhppkrfwaqetapgnphglphevithyyhrypmstilglsic
aaiatvsvaastwlfcrsrvacltpyrltpnaripfclavlccartaraettwesldhl
wnnnqqmfwiqlliplaalivvtrllrcvccvvpflvmagaagagayehattmpsqagi
syntivnragyaplpisitptkikliptvnleyvtchyktgmdspaikccgsqectpty
rpdeqckvftgvypfmwggaycfcdtentqvskayvmksddcladhaeaykahtasvqa
flnitvgehsivttvyvngetpvnfngvkitagplstawtpfdrkivqyageiynydfp
eygagqpgafgdiqsrtvsssdlyantnlvlqrpkagaihvpytqapsgfeqwkkdkap
slkftapfgceiytnpiraencavgsiplafdipdalftrvsetptlsaaectlnecvy
ssdfggiatvkysasksgkcavhvpsgtatlkeaavelteqgsatihfstanihpefrl
qictsyvtckgdchppkdhivthpqyhaqtftaavsktawtwltsllggsaviiiiglv
lativamyvltnqkhn.

在一个实施方案中,第一附着位点包含氨基,优选赖氨酸残基的氨基。在一个实施方案中,第二附着位点包含巯基,优选半胱氨酸的巯基。

[0060] 在一个实施方案中,使用化学交联接头,实现通过第一附着位点或第二附着位点的超过两种物质(例如抗原和基孔肯雅或委内瑞拉马脑炎病毒结构多肽)的缀合。交联接头的实例包括但不限于SMPH、Sulfo-MBS、Sulfo-EMCS、Sulfo-GMBS、Sulfo-SIAB、Sulfo-SMPB、Sulfo-SMCC、SVSB、SIA和其它交联接头,可得自Pierce Chemical Company。

[0061] 依照本发明,可以提供基孔肯雅或委内瑞拉马脑炎病毒样颗粒,其包括基孔肯雅或委内瑞拉马脑炎病毒结构多肽和抗原,其中所述基孔肯雅或委内瑞拉马脑炎病毒结构多肽和所述抗原表达为融合蛋白。

[0062] 在一个实施方案中,所述抗原可以与基孔肯雅或委内瑞拉马脑炎病毒结构多肽的任何位点融合。例如,所述抗原可以直接或间接连接到基孔肯雅或委内瑞拉马脑炎病毒结构多肽(例如衣壳、E3、E2、6K或E1)的N-或C-末端,或所述抗原可以插入到基孔肯雅或委内瑞拉马脑炎病毒结构蛋白(例如衣壳、E3、E2、6K或E1)中。

[0063] 在一个实施方案中,将至少一种抗原插入到基孔肯雅或委内瑞拉马脑炎病毒结构蛋白的E2中。例如,对于基孔肯雅病毒结构蛋白,将至少一种抗原插入到SEQ ID No.1或2的残基519和520之间(即SEQ ID No.1或2的519-位置的G和520-位置的Q之间);SEQ ID No.1或2的残基530和531之间(即SEQ ID No.1或2的530-位置的G和531-位置的S之间);SEQ ID No.1或2的残基531和532之间(即SEQ ID No.1或2的531-位置的S和532-位置的N之间);SEQ ID No.1或2的残基529和530之间(即SEQ ID No.1或2的529-位置的G和530-位置的G之间);或SEQ ID No.1或2的残基510和511之间(即SEQ ID No.1或2的510-位置的S和511-位置的G之间);或SEQ ID No.1或2的残基511和512之间(即SEQ ID No.1或2的511-位置的G和512-位置的N之间);或SEQ ID No.1或2的残基509和510之间(即SEQ ID No.1或2的509-位置的Q和510-位置的S之间)。

[0064] 例如,对于委内瑞拉马脑炎病毒结构蛋白,将至少一种抗原插入SEQ ID No.3的残基517和518之间(即SEQ ID No.3的517-位置的G和518-位置的S之间);SEQ ID No.3的残基

518和519之间(即SEQ ID No.3的518-位置的S和519-位置的S之间);SEQ ID No.3的残基519和520之间(即SEQ ID No.3的519-位置的S和520-位置的V之间);SEQ ID No.3的残基515和516之间(即SEQ ID No.3的515-位置的L和516-位置的S之间);SEQ ID No.3的残基516和517之间(即SEQ ID No.3的516-位置的S和517-位置的G之间);SEQ ID No.3的残基536和537之间(即SEQ ID No.3的536-位置的C和537-位置的G之间);SEQ ID No.3的残基537和538之间(即SEQ ID No.3的537-位置的G和538-位置的G之间);SEQ ID No.3的残基538和539之间(即SEQ ID No.3的538-位置的G和539-位置的T之间)。

[0065] 可使用本领域常规技术表达融合蛋白。各种表达系统可用于表达融合蛋白。例如,融合蛋白可以在293细胞、Sf9细胞或大肠杆菌中表达。

[0066] 在一个实施方案中,抗原是并非衍生自基孔肯雅或委内瑞拉马脑炎病毒的一种物质(例如蛋白)。抗原可以是选自自身抗原和癌抗原的至少一种。例如,抗原是衍生自TNF-α、CD20或CTLA4的多肽。因此,用于本发明的所述多肽和所述抗原的组合的实例包括但不限于

i) 衍生自基孔肯雅病毒(CHIKV)的多肽和衍生自TNF-α的多肽;

ii) 衍生自基孔肯雅病毒(CHIKV)的多肽和衍生自CD20的多肽;

iii) 衍生自委内瑞拉马脑炎病毒(VEEV)的多肽和衍生自TNF-α的多肽;或

iv) 衍生自委内瑞拉马脑炎病毒(VEEV)的多肽和衍生自CD20的多肽;

v) 衍生自委内瑞拉马脑炎病毒(VEEV)的多肽和衍生自CTLA4的多肽。

[0067] 衍生自基孔肯雅病毒(CHIKV)或委内瑞拉马脑炎病毒(VEEV)的多肽可以是天然存在的病毒多肽或其修饰的多肽。另外,衍生自TNF-α、CD20或CTLA4的多肽可以是天然存在的多肽或天然存在的多肽的修饰的多肽或天然存在的多肽或修饰的肽的片段。所述修饰的多肽可以是天然存在的病毒结构多肽的片段。

[0068] 在一个实施方案中,衍生自TNF-α、CD20或CTLA4的修饰的多肽与天然存在的多肽具有至少70%、75%、80%、85%、90%、95%或98%氨基酸序列同一性。在一个实施方案中,衍生自TNF-α、CD20或CTLA4的修饰的肽是突变体,其中基于衍生自TNF-α、CD20或CTLA4的天然存在的多肽,至多10%的氨基酸被缺失、置换和/或添加。

[0069] 当衍生自病毒的多肽与衍生自抗原的多肽缀合时,可以使用包括SG、GS、SGG、GGS SGSG和TRGGS在内的接头肽。衍生自病毒的多肽(以下称为"PFV")与衍生自抗原的多肽(以下称为"PFA")缀合的实例包括但不限于:PFV-SG-PFA-GS-PFV;PFV-SG-PFA-GGS-PFV;PFV-SSG-PFA-GS-PFV;PFV-SGG-PFA-GGS-PFV;PFV-SGSG-PFA-GS-PFV;和PFA-SGG-PFA-TRGGS-PFV。

[0070] 在一个实施方案中,本发明提供病毒样颗粒,包含:

i) 衍生自基孔肯雅病毒(CHIKV)的多肽和衍生自TNF-α的多肽的融合蛋白,其由SEQ ID No.4所示的氨基酸序列组成;

ii) 衍生自基孔肯雅病毒(CHIKV)的多肽和衍生自CD20的多肽的融合蛋白,其由SEQ ID No.5所示的氨基酸序列组成;

iii) 衍生自委内瑞拉马脑炎病毒(VEEV)的多肽和衍生自TNF-α的多肽的融合蛋白,其由SEQ ID No.6所示的氨基酸序列组成;或

iv) 衍生自委内瑞拉马脑炎病毒(VEEV)的多肽和衍生自CD20的多肽的融合蛋白,其由SEQ ID No.7所示的氨基酸序列组成;

v) 衍生自委内瑞拉马脑炎病毒(VEEV)的多肽和衍生自CTLA4的多肽的融合蛋白，其由SEQ ID No.8所示的氨基酸序列组成。

[0071] 在一个实施方案中，本发明提供包含融合蛋白的病毒样颗粒，所述融合蛋白是自具有SEQ ID No.4-8的任一个所示的氨基酸序列的融合蛋白修饰而来。所述修饰的融合蛋白与具有SEQ ID No.4-8的任一个所示的氨基酸序列的融合蛋白可具有至少70%、75%、80%、85%、90%、95%或98%氨基酸序列同一性。而且，所述修饰的融合蛋白可以是突变体，其中基于具有SEQ ID No.4-8的任一个所示的氨基酸序列的融合蛋白，至多10%的氨基酸被缺失、置换和/或添加。

[0072] (2)核苷酸、载体、宿主细胞

在第二方面，本发明提供包含核苷酸序列的核酸分子，所述核苷酸序列编码在本发明第一方面中提供的颗粒。

[0073] 在一个实施方案中，本发明提供包含核苷酸序列的核酸分子，所述核苷酸序列编码基孔肯雅或委内瑞拉马脑炎病毒样颗粒，如上所述。

[0074] 编码基孔肯雅或委内瑞拉马脑炎病毒样颗粒的核苷酸序列的实例包括但不限于：编码基孔肯雅病毒株37997的E3-E2-6K-E1的核苷酸序列，编码基孔肯雅病毒株37997的衣壳-E3-E2-6K-E1的核苷酸序列，编码基孔肯雅病毒株LR2006 OPY-1的E3-E2-6K-E1的核苷酸序列，编码基孔肯雅病毒LR2006 OPY-1的衣壳-E3-E2-6K-E1的核苷酸序列，编码委内瑞拉马脑炎病毒株TC-83的E3-E2-6K-E1的核苷酸序列和编码委内瑞拉马脑炎病毒TC-83的衣壳-E3-E2-6K-E1的核苷酸序列。

[0075] 对于基孔肯雅病毒，编码E3-E2-6K-E1的示例性的核苷酸序列描述如下(SEQ ID No.:9)：

Atgagcctcgccctcccggtcttgtgcctgttggcaaacactacattcccctgctctcagccgccttgcacaccctgctgctacgaaaaggaaccgg
aaagcaccttgcgcatgcttgaggacaacgtgatgagacccggatactaccagctactaaaagcatcgctgacttgctctccccaccgccaaagac
gcagtactaaggacaattttaatgtctataaagccacaagaccatatctagctcattgtcctgactgcggagaagggcattcgtgccacagccctatc
gcattggagcgcatcagaaatgaagcaacggacggaacgctgaaaatccaggtctctttgcagatcgggataaagacagatgacagccacgattg
gaccaagctgcgctatatggatagccatacgccagcggacgcggagcgagccggattgcttgtaaggacttcagcaccgtgcacgatcaccggg
accatgggacactttattctcgcccgatgcccgaaaggagagacgctgacagtgggatttacggacagcagaaagatcagccacacatgcacaca
cccgttccatcatgaaccacctgtgataggtagggagaggttccactctcgaccacaacatggtaaagagttaccttgcagcacgtacgtgcagag
caccgctgccactgctgaggagatagaggtgcatatgccccagatactcctgaccgcacgctgatgacgcagcagtctggcaacgtgaagatca
cagttaatgggcagacggtgcggtacaagtgcaactgcggtggctcaaacgagggactgacaaccacagacaaagtgatcaataactgcaaaatt
gatcagtgccatgctgcagtcactaatcacaagaattggcaatacaactccccttagtcccgcgcaacgctgaactcggggaccgtaaaggaaag

atccacatcccattcccattggcaaacgtgacttgcagagtgccaaaagcaagaaaccctacagtaacttacggaaaaaaccaagtcaccatgctg
ctgtatcctgaccatccgacactcttgtcttaccgtaacatgggacaggaaccaaattaccacgaggagtgggtgacacacaagaaggaggttacct
tgaccgtgcctactgagggtctggaggtcacttggggcaacaacgaaccatacaagtactggccgcagatgtctacgaacggtactgctcatggtc
acccacatgagataatcttgtactattatgagctgaccccactatgactgtagtcattgtgtcggtggcctcgttcgtgcttctgtcgatggtgggcaca
gcagtgggaatgtgtgtgtgcgcacggcgcagatgcattacaccatatgaattaacaccaggagccactgttcccttcctgctcagcctgctatgctg
cgtcagaacgaccaaggcggccacatattacgaggctgcggcatatctatggaacgaacagcagcccctgttctggttgcaggctcttatcccgct
ggccgccttgatcgtcctgtgcaactgtctgaaactcttgccatgctgctgtaagaccctggctttttagccgtaatgagcatcggtgcccacactgtg
agcgcgtacgaacacgtaacagtgatcccgaacacggtgggagtaccgtataagactcttgtcaacagaccgggttacagccccatggtgttgga
gatggagctacaatcagtcaccttggaaccaacactgtcacttgactacatcacgtgcgagtacaaaactgtcatccccctcccgtacgtgaagtgct
gtggtacagcagagtgcaaggacaagagcctaccagactacagctgcaaggtctttactggagtctacccatttatgtggggcggcgcctactgctt
ttgcgacgccgaaaatacgcaattgagcgaggcacatgtagagaaatctgaatcttgcaaaacagagtttgcatcggcctacagagcccacaccg
catcggcgtcggcgaagctccgcgtcctttaccaaggaaacaacattaccgtagctgcctacgctaacggtgaccatgccgtcacagtaaaggac
gccaagtttgtcgtgggcccaatgtcctccgcctggacacctttgacaacaaaatcgtggtgtacaaaggcgacgtctacaacatggactacccac
cttttggcgcaggaagaccaggacaatttggtgacattcaaagtcgtacaccggaaagtaaagacgtttatgccaacactcagttggtactacagag
gccagcagcaggcacggtacatgtaccatactctcaggcaccatctggcttcaagtattggctgaaggaacgaggagcatcgctacagcacacgg
caccgttcggttgccagattgcgacaaacccggtaagagctgtaaattgcgctgtggggaacataccaatttccatcgacataccggatgcggcctt
tactagggttgtcgatgcaccctctgtaacggacatgtcatgcgaagtaccagcctgcactcactcctccgactttgggggcgtcgccatcatcaaat
acacagctagcaagaaaggtaaatgtgcagtacattcgatgaccaacgccgttaccattcgagaagccgacgtagaagtagaggggaactccca
gctgcaaatatccttctcaacagccctggcaagcgccgagtttcgcgtgcaagtgtgctccacacaagtacactgcgcagccgcatgccaccctcc
aaaggaccacatagtcaattacccagcatcacacaccaccccttggggtccaggatatatccacaacggcaatgtcttgggtgcagaagattacggg
aggagtaggattaattgttgctgttgctgccttaattttaattgtggtgctatgcgtgtcgtttagcaggcac

。

[0076] 对于基孔肯雅病毒,编码E3-E2-6K-E1的另一示例性的核苷酸序列描述如下(SEQ ID No.:10):

Atgagtcttgccatcccagttatgtgcctgttggcaaacaccacgttcccctgctcccagccccctt gcacgccctgctgctacgaaaaggaaccgg
aggaaaccctacgcatgcttgaggacaacgtcatgagacctgggtactatcagctgctacaagcatccttaacatgttctccccaccgccagcgac
gcagcaccaaggacaacttcaatgtctataaagccacaagaccatacttagctcactgtcccgactgtggagaagggcactcgtgccatagtcccg
tagcactagaacgcatcagaaatgaagcgacagacgggacgctgaaaatccaggtctccttgcaaatcggaataaagacggatgacagccacga
ttggaccaagctgcgttatatggacaaccacatgccagcagacgcagagagggcggggctatttgtaagaacatcagcaccgtgtacgattactgg

aacaatgggacacttcatcctggcccgatgtccaaaaggggaaactctgacggtgggattcactgacagtaggaagattagtcactcatgtacgca
cccatttcaccacgaccctcctgtgataggtcgggaaaaattccattcccgaccgcagcacggtaaagagctaccttgcagcacgtacgtgcagag
caccgccgcaactaccgaggagatagaggtacacatgcccccagacacccctgatcgcacattaatgtcacaacagtccggcaacgtaaagatc
acagtcaatggccagacggtgcggtacaagtgtaattgcggtggctcaaatgaaggactaacaactacagacaaagtgattaataactgcaaggtt
gatcaatgtcatgccgcggtcaccaatcacaaaaagtggcagtataactcccctctggtcccgcgtaatgctgaacttggggaccgaaaaggaaaa
attcacatcccgtttccgctggcaaatgtaacatgcagggtgcctaaagcaaggaaccccaccgtgacgtacgggaaaaaccaagtcatcatgcta
ctgtatcctgaccacccaacactcctgtcctaccggaatatgggagaagaaccaaactatcaagaagagtgggtgatgcataagaaggaagtcgtg
ctaaccgtgccgactgaagggctcgaggtcacgtggggcaacaacgagccgtataagtattggccgcagttatctacaaacggtacagcccatgg
ccacccgcatgagataattctgtattattatgagctgtaccccactatgactgtagtagttgtgtcagtggccacgttcatactcctgtcgatggtgggta
tggcagcggggatgtgcatgtgtgcacgacgcagatgcatcacaccgtatgaactgacaccaggagctaccgtcccttcctgcttagcctaatatg
ctgcatcagaacagctaaagcggccacataccaagaggctgcgatatacctgtggaacgagcagcaacctttgttttggctacaagcccttattccg
ctggcagccctgattgttctatgcaactgtctgagactcttaccatgctgctgtaaaacgttggctttttagccgtaatgagcgtcggtgcccacactgt
gagcgcgtacgaacacgtaacagtgatcccgaacacggtgggagtaccgtataagactctagtcaatagacctggctacagccccatggtattgg
agatggaactactgtcagtcactttggagccaacactatcgcttgattacatcacgtgcgagtacaaaaccgtcatcccgtctccgtacgtgaagtgct
gcggtacagcagagtgcaaggacaaaaacctacctgactacagctgtaaggtcttcaccggcgtctacccatttatgtggggcggcgcctactgctt
ctgcgacgctgaaaacacgcagttgagcgaagcacacgtggagaagtccgaatcatgcaaaacagaatttgcatcagcatacagggctcataccg
catctgcatcagctaagctccgcgtcctttaccaaggaaataacatcactgtaactgcctatgcaaacggcgaccatgccgtcacagttaaggacgc
caaattcattgtggggccaatgtcttcagcctggacacctttcgacaacaaaattgtggtgtacaaaggtgacgtctataacatggactacccgccctt
tggcgcaggaagaccaggacaatttggcgatatccaaagtcgcacacctgagagtaaagacgtctatgctaatacacaactggtactgcagagac
cggctgtgggtacggtacacgtgccatactctcaggcaccatctggctttaagtattggctaaaagaacgcggggcgtcgctgcagcacacagcac
catttggctgccaaatagcaacaaacccggtaagagcggtgaactgcgccgtagggaacatgcccatctccatcgacataccggaagcggccttc
actagggtcgtcgacgcgcccctctttaacggacatgtcgtgcgaggtaccagcctgcacccattcctcagactttgggggcgtcgccattattaaata
tgcagccagcaagaaaggcaagtgtgcggtgcattcgatgactaacgccgtcactattcgggaagctgagatagaagttgaagggaattctcagct
gcaaatctctttctcgacggccttagccagcgccgaattccgcgtacaagtctgttctacacaagtacactgtgcagccgagtgccacccccccgaag
gaccacatagtcaactacccggcgtcacataccacccctcggggtccaggacatctccgctacggcgatgtcatgggtgcagaagatcacgggag
gtgtgggactggttgttgctgttgccgcactgattctaatcgtggtgctatgcgtgtcgttcagcaggcac

。

[0077] 对于基孔肯雅病毒,编码衣壳-E3-E2-6K-E1的示例性的核苷酸序列描述如下(SEQ

ID No.:11)：

atggagttcatcccgacgcaaactttctataacagaaggtaccaaccccgaccctgggc
cccacgccctacaattcaagtaattagacctagaccacgtccacagaggcaggctgggc
aactcgcccagctgatctccgcagtcaacaaattgaccatgcgcgcggtacctcaacag
aagcctcgcagaaatcggaaaaacaagaagcaaaggcagaagaagcaggcgccgcaaaa
cgacccaaagcaaaagaagcaaccaccacaaaagaagccggctcaaaagaagaagaaac
caggccgtagggagagaatgtgcatgaaaattgaaaatgattgcatcttcgaagtcaag
catgaaggcaaagtgatgggctacgcatgcctggtgggggataaagtaatgaaaccagc
acatgtgaagggaactatcgacaatgccgatctggctaaactggcctttaagcggtcgt
ctaaatacgatcttgaatgtgcacagataccggtgcacatgaagtctgatgcctcgaag
tttacccacgagaaacccgaggggtactataactggcatcacggagcagtgcagtattc
aggaggccggttcactatcccgacgggtgcaggcaagccgggagacagcggcagaccga
tcttcgacaacaaaggacgggtggtggccatcgtcctaggaggggccaacgaaggtgcc
cgcacggccctctccgtggtgacgtggaacaaagacatcgtcacaaaaattacccctga
gggagccgaagagtggagcctcgccctcccggtcttgtgcctgttggcaaacactacat
tcccctgctctcagccgccttgcacaccctgctgctacgaaaaggaaccggaaagcacc

ttgcgcatgcttgaggacaacgtgatgagacccggatactaccagctactaaaagcatc
gctgacttgctctccccaccgccaaagacgcagtactaaggacaattttaatgtctata
aagccacaagaccatatctagctcattgtcctgactgcggagaagggcattcgtgccac
agccctatcgcattggagcgcatcagaaatgaagcaacggacggaacgctgaaaatcca
ggtctctttgcagatcgggataaagacagatgacagccacgattggaccaagctgcgct
atatggatagccatacgccagcggacgcggagcgagccggattgcttgtaaggacttca
gcaccgtgcacgatcaccgggaccatgggacactttattctcgcccgatgcccgaaagg
agagacgctgacagtgggatttacggacagcagaaagatcagccacacatgcacacacc
cgttccatcatgaaccacctgtgataggtagggagaggttccactctcgaccacaacat
ggtaaagagttaccttgcagcacgtacgtgcagagcaccgctgccactgctgaggagat
agaggtgcatatgcccccagatactcctgaccgcacgctgatgacgcagcagtctggca
acgtgaagatcacagttaatgggcagacggtgcggtacaagtgcaactgcggtggctca
aacgagggactgacaaccacagacaaagtgatcaataactgcaaaattgatcagtgcca
tgctgcagtcactaatcacaagaattggcaatacaactccccttttagtcccgcgcaacg
ctgaactcggggaccgtaaaggaaagatccacatcccattcccattggcaaacgtgact
tgcagagtgccaaaagcaagaaaccctacagtaacttacggaaaaaaccaagtcaccat
gctgctgtatcctgaccatccgacactcttgtcttaccgtaacatgggacaggaaccaa
attaccacgaggagtgggtgacacacaagaaggaggttaccttgaccgtgcctactgag
ggtctggaggtcacttggggcaacaacgaaccatacaagtactggccgcagatgtctac
gaacggtactgctcatggtcacccacatgagataatcttgtactattatgagctgtacc
ccactatgactgtagtcattgtgtcggtggcctcgttcgtgcttctgtcgatggtgggc
acagcagtgggaatgtgtgtgtgcgcacggcgcagatgcattacaccatatgaattaac
accaggagccactgttcccttcctgctcagcctgctatgctgcgtcagaacgaccaagg
cggccacatattacgaggctgcggcatatctatggaacgaacagcagcccctgttctgg
ttgcaggctcttatcccgctggccgccttgatcgtcctgtgcaactgtctgaaactctt
gccatgctgctgtaagaccctggctttttagccgtaatgagcatcggtgcccacactg
tgagcgcgtacgaacacgtaacagtgatcccgaacacggtgggagtaccgtataagact
cttgtcaacagaccgggttacagccccatggtgttggagatggagctacaatcagtcac
cttggaaccaacactgtcacttgactacatcacgtgcgagtacaaaactgtcatcccct
ccccgtacgtgaagtgctgtggtacagcagagtgcaaggacaagagcctaccagactac
agctgcaaggtctttactggagtctacccatttatgtggggcggcgcctactgcttttg
cgacgccgaaaatacgcaattgagcgaggcacatgtagagaaatctgaatcttgcaaaa
cagagtttgcatcggcctacagagcccacaccgcatcggcgtcggcgaagctccgcgtc
ctttaccaaggaaacaacattaccgtagctgcctacgctaacggtgaccatgccgtcac
agtaaaggacgccaagtttgtcgtgggcccaatgtcctccgcctggacacctttgaca
acaaaatcgtggtgtacaaaggcgacgtctacaacatggactacccacctttggcgca
ggaagaccaggacaatttggtgacattcaaagtcgtacaccggaaagtaaagacgttta
tgccaacactcagttggtactacagaggccagcagcaggcacggtacatgtaccatact
ctcaggcaccatctggcttcaagtattggctgaaggaacgaggagcatcgctacagcac
acggcaccgttcggttgccagattgcgacaaacccggtaagagctgtaaattgcgctgt
ggggaacataccaatttccatcgacataccggatgcggcctttactagggttgtcgatg
caccctctgtaacggacatgtcatgcgaagtaccagcctgcactcactcctccgacttt
gggggcgtcgccatcatcaaatacacagctagcaagaaaggtaaatgtgcagtacattc
gatgaccaacgccgttaccattcgagaagccgacgtagaagtagaggggaactcccagc
tgcaaatatccttctcaacagccctggcaagcgccgagtttcgcgtgcaagtgtgctcc
acacaagtacactgcgcagccgcatgccaccctccaaaggaccacatagtcaattaccc
agcatcacacaccacccttggggtccaggatatatccacaacggcaatgtcttgggtgc
agaagattacgggaggagtaggattaattgttgctgttgctgccttaattttaattgtg
gtgctatgcgtgtcgtttagcaggcactaa.

对于基孔肯雅病毒,编码衣壳-E3-E2-6K-E1的另一示例性的核苷酸序列描述如下(SEQ ID No.:12):

atggagttcatcccaacccaaacttttacaataggaggtaccagcctcgaccctggac
tccgcgccctactatccaagtcatcaggcccagaccgcgccctcagaggcaagctgggc
aacttgcccagctgatctcagcagttaataaactgacaatgcgcgcggtaccacaacag
aagccacgcaggaatcggaagaataagaagcaaaagcaaaaacaacaggcgccacaaaa
caacacaaatcaaaagaagcagccacctaaaaagaaaccggctcaaaagaaaaagaagc
cgggccgcagagagaggatgtgcatgaaaatcgaaaatgattgtattttcgaagtcaag
cacgaaggtaaggtaacaggttacgcgtgcctggtgggggacaaagtaatgaaaccagc
acacgtaaaggggaccatcgataacgcggacctggccaaactggcctttaagcggtcat
ctaagtatgaccttgaatgcgcgcagatacccgtgcacatgaagtccgacgcttcgaag
ttcacccatgagaaaccggaggggtactacaactggcaccacggagcagtacagtactc
aggaggccggttcaccatccctacaggtgctggcaaaccaggggacagcggcagaccga
tcttcgacaacaagggacgcgtggtggccatagtcttaggaggagctaatgaaggagcc
cgtacagccctctcggtggtgacctggaataaagacattgtcactaaaatcacccccga
gggggccgaagagtggagtcttgccatcccagttatgtgcctgttggcaaacaccacgt
tcccctgctcccagccccttgcacgccctgctgctacgaaaaggaaccggaggaaacc
ctacgcatgcttgaggacaacgtcatgagacctgggtactatcagctgctacaagcatc
cttaacatgttctccccaccgccagcgacgcagcaccaaggacaacttcaatgtctata
aagccacaagaccatacttagctcactgtcccgactgtggagaagggcactcgtgccat
agtcccgtagcactagaacgcatcagaaatgaagcgacagacgggacgctgaaaatcca
ggtctccttgcaaatcggaataaagacggatgacagccacgattggaccaagctgcgtt
atatggacaaccacatgccagcagacgcagagagggcggggctatttgtaagaacatca
gcaccgtgtacgattactggaacaatgggacacttcatcctggcccgatgtccaaaagg
ggaaactctgacggtgggattcactgacagtaggaagattagtcactcatgtacgcacc
catttcaccacgaccctcctgtgataggtcgggaaaaattccattcccgaccgcagcac
ggtaaagagctaccttgcagcacgtacgtgcagagcaccgccgcaactaccgaggagat
agaggtacacatgcccccagacacccctgatcgcacattaatgtcacaacagtccggca
acgtaaagatcacagtcaatggccagacggtgcggtacaagtgtaattgcggtggctca
aatgaaggactaacaactacagacaaagtgattaataactgcaaggttgatcaatgtca
tgccgcggtcaccaatcacaaaaagtggcagtataactcccctctggtcccgcgtaatg
ctgaacttggggaccgaaaaggaaaaattcacatcccgtttccgctggcaaatgtaaca
tgcagggtgcctaaagcaaggaaccccaccgtgacgtacgggaaaaaccaagtcatcat
gctactgtatcctgaccacccaacactcctgtcctaccggaatatgggagaagaaccaa
actatcaagaagagtgggtgatgcataagaaggaagtcgtgctaaccgtgccgactgaa
gggctcgaggtcacgtggggcaacaacgagccgtataagtattggccgcagttatctac
aaacggtacagcccatggccacccgcatgagataattctgtattattatgagctgtacc
ccactatgactgtagtagttgtgtcagtggccacgttcatactcctgtcgatggtgggt
atggcagcggggatgtgcatgtgtgcacgacgcagatgcatcacaccgtatgaactgac
accaggagctaccgtccctttcctgcttagcctaatatgctgcatcagaacagctaaag
cggccacataccaagaggctgcgatatacctgtggaacgagcagcaacctttgttttgg
ctacaagcccttattccgctggcagccctgattgttctatgcaactgtctgagactctt
accatgctgctgtaaaacgttggctttttagccgtaatgagcgtcggtgcccacactg
tgagcgcgtacgaacacgtaacagtgatcccgaacacggtgggagtaccgtataagact
ctagtcaatagacctggctacagccccatggtattggagatggaactactgtcagtcac
tttggagccaacactatcgcttgattacatcacgtgcgagtacaaaaccgtcatcccgt
ctccgtacgtgaagtgctgcggtacagcagagtgcaaggacaaaaacctacctgactac
agctgtaaggtcttcaccggcgtctacccatttatgtggggcggcgcctactgcttctg
cgacgctgaaaacacgcagttgagcgaagcacacgtggagaagtccgaatcatgcaaaa
cagaatttgcatcagcatacagggctcataccgcatctgcatcagctaagctccgcgtc
ctttaccaaggaaataacatcactgtaactgcctatgcaaacggcgaccatgccgtcac
agttaaggacgccaaattcattgtggggccaatgtcttcagcctggacacctttcgaca
acaaaattgtggtgtacaaaggtgacgtctataacatggactacccgccctttggcgca
ggaagaccaggacaatttggcgatatccaaagtcgcacacctgagagtaaagacgtcta

tgctaatacacaactggtactgcagagaccggctgtgggtacggtacacgtgccatact
ctcaggcaccatctggctttaagtattggctaaaagaacgcggggcgtcgctgcagcac
acagcaccatttggctgccaaatagcaacaaacccggtaagagcggtgaactgcgccgt
agggaacatgcccatctccatcgacataccggaagcggccttcactagggtcgtcgacg
cgccctctttaacggacatgtcgtgcgaggtaccagcctgcacccattcctcagacttt
gggggcgtcgccattattaaatatgcagccagcaagaaaggcaagtgtgcggtgcattc
gatgactaacgccgtcactattcgggaagctgagatagaagttgaagggaattctcagc
tgcaaatctctttctcgacggccttagccagcgccgaattccgcgtacaagtctgttct
acacaagtacactgtgcagccgagtgccacccccgaaggaccacatagtcaactaccc
ggcgtcacataccaccctcggggtccaggacatctccgctacggcgatgtcatgggtgc
agaagatcacgggaggtgtgggactggttgttgctgttgccgcactgattctaatcgtg
gtgctatgcgtgtcgttcagcaggcactaa.

在一个实施方案中,本发明提供包含如上所述的核酸分子的载体,其中所述载体任选包含与所述核酸分子操作性连接的表达控制序列。

[0078] 表达控制序列的实例包括但不限于:启动子例如CMV启动子、噬菌体λ PL启动子、大肠杆菌lac、phoA和tac启动子、SV40早期和晚期启动子、和逆转录病毒LTR的启动子。

[0079] 根据WO/2012/006180,本领域技术人员可以制备表达载体,所述参考文献的全部公开内容都通过引用结合到本文中。

[0080] 可用于表达衍生自基孔肯雅病毒(CHIKV)的多肽和抗原多肽的融合蛋白的载体的实例包括示于以下的载体:VLP_CHI 512载体(SEQ ID No.:23),其含有CHIKV VLP多核苷酸(SEQ ID No. 28;SEQ ID No.:29所示的相应氨基酸序列);和VLP_CHI 532载体(SEQ ID No.: 24),其含有CHIKV VLP多核苷酸(SEQ ID No. 30;SEQ ID No.:31所示的相应氨基酸序列)。

[0081] 根据US2012/0003266,本领域技术人员可以制备表达载体,所述参考文献的全部公开内容都通过引用结合到本文中。

[0082] 可用于表达衍生自委内瑞拉马脑炎病毒(VEEV)的多肽和抗原多肽的融合蛋白的载体实例包括示于以下的载体:VLP_VEEV VLP 518载体(SEQ ID No.:25),其含有VEEV VLP多核苷酸(SEQ ID No. 32;SEQ ID No.:33所示的相应氨基酸序列);VLP_VEEV VLP 519载体(SEQ ID No.26),其含有VEEV VLP多核苷酸(SEQ ID No. 34;SEQ ID No.:35所示的相应氨基酸序列);和VLP_VEEV VLP 538载体(SEQ ID No.: 27),其含有VEEV VLP多核苷酸(SEQ ID No. 36;SEQ ID No.:37所示的相应氨基酸序列)。

[0083] 在一个实施方案中,本发明提供:

i) 核酸分子,所述核酸分子编码衍生自基孔肯雅病毒(CHIKV)的多肽和衍生自TNF-α的多肽的融合蛋白,其由SEQ ID No.13所示的核苷酸序列组成;

ii) 核酸分子,所述核酸分子编码衍生自基孔肯雅病毒(CHIKV)的多肽和衍生自CD20的多肽的融合蛋白,其由SEQ ID No.14所示的核苷酸序列组成;

iii) 核酸分子,所述核酸分子编码衍生自委内瑞拉马脑炎病毒(VEEV)的多肽和衍生自TNF-α的多肽的融合蛋白,其由SEQ ID No.15所示的核苷酸序列组成;

iv) 核酸分子,所述核酸分子编码衍生自委内瑞拉马脑炎病毒(VEEV)的多肽和衍生自CD20的多肽的融合蛋白,其由SEQ ID No.16所示的核苷酸序列组成;或

v) 核酸分子,所述核酸分子编码衍生自委内瑞拉马脑炎病毒(VEEV)的多肽和衍生自CTLA4的多肽的融合蛋白,其由SEQ ID No.17所示的氨基酸序列组成。

[0084] 在一个实施方案中，本发明提供核酸分子，其是自具有SEQ ID No.13-17的任一个所示的核苷酸序列的核酸分子修饰而来。所述修饰的核酸分子与具有SEQ ID No.13-17的任一个所示的核苷酸序列的核酸分子可具有至少70%、75%、80%、85%、90%、95%或98%核苷酸序列同一性。而且，所述修饰的核酸分子可以是突变体，其中基于具有SEQ ID No.13-17的任一个所示的核苷酸序列的核酸分子，至多10%的氨基酸被缺失、置换和/或添加。

[0085] (3)组合物

在第三方面，本发明提供组合物，包含在本发明第一方面中提供的颗粒和/或在本发明第二方面中提供的核酸分子。

[0086] 在一个实施方案中，本发明提供组合物，包含如上所述的基孔肯雅或委内瑞拉马脑炎病毒样颗粒或如上所述的核酸分子。

[0087] 所述组合物可以进一步包含药学上可接受的载体和/或佐剂。佐剂的实例包括但不限于Ribi溶液(Sigma佐剂系统, Sigma-Aldrich)。

[0088] 本发明的药物组合物可含有单一活性成分或两种或更多种活性成分的组合，只要它们不违背本发明的目标。例如，包括趋化因子在内的细胞因子、细胞因子的抗体例如抗TNF抗体(例如英夫利昔单抗、阿达木单抗)、抗VEGF抗体(例如贝伐单抗和雷珠单抗)、细胞因子受体拮抗剂例如抗HER2抗体(例如曲妥单抗)、抗EGF受体抗体(例如西妥昔单抗)、抗VEGF适体(例如哌加他尼)和免疫调节剂例如环孢菌素、他克莫司、乌苯美司，可以用于联合治疗。

[0089] 在多种活性成分的组合中，鉴于它们的治疗效果和安全性，可适当增加或减少它们各自的含量。

[0090] 本文所用的术语“组合”是指将两种或更多种活性成分以单一实体或剂量的形式同时给予患者，或将两者作为单独的实体同时或序贯地没有具体时间限制地给予患者，其中这样的给予在机体内提供了治疗有效水平的两种组分，优选在同一时间。

[0091] 在一个实施方案中，所述组合物是疫苗组合物，包括DNA疫苗。在一个实施方案中，本发明提供的DNA疫苗包含含有CpG的寡核苷酸。

[0092] (4)产生抗体的方法，免疫调节的方法，治疗自身免疫性疾病的方法，在哺乳动物中诱导和/或增强针对抗原的免疫应答的方法，治疗癌症的方法，被动免疫的方法，在巨噬细胞上呈递抗原的方法，和产生颗粒的方法

在第四方面，本发明提供产生抗体的方法，包括使在本发明第一方面中提供的颗粒和/或在本发明第二方面中提供的核酸分子与哺乳动物接触。

[0093] 可使用常规技术，使在本发明第四方面产生的抗体人源化。因此，在一个实施方案中，在本发明第四方面中提供的方法进一步包括使非人类哺乳动物产生的抗体人源化的步骤。

[0094] 可将在本发明第一方面中提供的颗粒和/或在本发明第二方面中提供的核酸分子直接给予患者，给予受累器官或全身，或离体施加到衍生自所述患者或人细胞系的细胞并且随后再给予所述患者，或在体外用于从衍生自所述患者的免疫细胞例如B细胞和T细胞中选择亚群体，然后再将其重新给予所述患者。

[0095] 依照本发明，所述病毒样颗粒可以用于免疫治疗。

[0096] 在第五方面，本发明提供免疫调节的方法、治疗自身免疫性疾病的方法、在哺乳动

物中诱导和/或增强针对抗原的免疫应答的方法和治疗癌症的方法，包括将在本发明第三方面中提供的组合物给予哺乳动物。

[0097] 在第六方面，本发明提供被动免疫的方法，包括将在本发明第四方面中提供的抗体给予哺乳动物。

[0098] 在第七方面，本发明提供在巨噬细胞上呈递抗原的方法，包括使在本发明第一方面中提供的颗粒和/或在本发明第二方面中提供的核酸分子与哺乳动物接触。

[0099] 在第八方面，本发明提供产生在本发明第一方面中提供的颗粒的方法，包括：制备包含编码所述颗粒的核苷酸序列的基因；培养已用所述基因转染的细胞，以表达所述颗粒；和回收所述颗粒。

[0100] 在一个实施方案中，本发明提供产生抗体的方法，包括使如上所述的基孔肯雅或委内瑞拉马脑炎病毒样颗粒和/或如上所述的核酸分子与哺乳动物接触。所产生的抗体可以是可与基孔肯雅或委内瑞拉马脑炎病毒样颗粒中包含的抗原或所述核酸分子编码的抗原特异性结合的抗体。产生本发明提供的抗体的方法可以是可用于产生针对抗原(例如TNFα、CD20和CLTA4)的单克隆抗体或多克隆抗体的方法。

[0101] 在一个实施方案中，通过产生本发明的抗体的方法所获得的抗体用于被动免疫。被动免疫的方法可包括将所获抗体给予哺乳动物。

[0102] 依照本发明，本发明的组合物可用于免疫调节。尤其是，所述免疫调节用于治疗自身免疫性疾病、神经性疾病、炎性疾病例如炎性肺病包括急性呼吸窘迫综合征、慢性阻塞性肺病和哮喘、血管生成相关疾病包括肿瘤。

[0103] 在一个优选的实施方案中，本发明提供的免疫调节是在哺乳动物中诱导和/或增强针对抗原的免疫应答。因此，在一个实施方案中，本发明提供在哺乳动物中诱导和/或增强针对抗原的免疫应答的方法，包括将有效量的上述组合物给予所述哺乳动物。哺乳动物的实例包括但不限于人。

[0104] 因为许多抗体可用于治疗疾病，所以本发明提供的方法和组合物可用于治疗疾病。例如，与表1中列举的靶标特异性结合的抗体或与表1中列举的靶标上的表位结合的抗体可用于治疗表1中列举的疾病。

[0105] 在一个实施方案中，用于本发明的至少一种抗原是表1中列举的至少一种靶标。当用于本发明的至少一种抗原是表1中列举的至少一种靶标时，本发明提供的颗粒、分离的核酸、载体、组合物和方法可用于治疗表1中列举的疾病或病况(参见表1的“用途”)。

[0106] 例如，当用于本发明的至少一种抗原是一种或多种癌抗原时，本发明提供的颗粒、分离的核酸、载体、组合物和方法可用于治疗癌症。

[0107] 癌抗原的实例包括但不限于VEGF、表皮生长因子受体、CD33、CD20和ErbB2。当将包含两种或更多种癌抗原的本发明的组合物给予哺乳动物时，针对这两种或更多种癌抗原的抗体就可以攻击癌症。

[0108] 例如，当用于本发明的至少一种抗原是淀粉样蛋白β时，本发明提供的分离的核酸、载体、组合物和方法可用于治疗阿尔茨海默病。

[0109] 例如，当用于本发明的至少一种抗原是TNFα时，本发明提供的分离的核酸、载体、组合物和方法可用于治疗：炎症；自身免疫疾病，包括类风湿性关节炎；银屑病、克罗恩病；溃疡性结肠炎等。

[0110] 例如，当用于本发明的至少一种抗原是CD20时，本发明提供的分离的核酸、载体、组合物和方法可用于治疗：自身免疫疾病，包括类风湿性关节炎和SLE；癌症，包括非霍奇金淋巴瘤等。

[0111] 例如，当用于本发明的至少一种抗原是CTLA4时，本发明提供的分离的核酸、载体、组合物和方法可用于治疗癌症包括黑素瘤；和用于活化T细胞等。

[0112] 考虑到感染基孔肯雅或委内瑞拉马脑炎的患者的症状以及基孔肯雅或委内瑞拉马脑炎的异常大的分子，该VLP可以有效地及高效地起作用以靶向巨噬细胞及其组成例如细胞因子和免疫调节性化合物。

[0113] 在一方面，本发明提供在巨噬细胞上呈递抗原的方法，包括将如上所述的基孔肯雅或委内瑞拉马脑炎病毒样颗粒和/或如上所述的核酸分子给予哺乳动物。本发明提供的基孔肯雅或委内瑞拉马脑炎病毒样颗粒良好地靶向巨噬细胞。在一个实施方案中，本发明提供的基孔肯雅或委内瑞拉马脑炎病毒样颗粒是至少一种抗原的一类递送系统(递送到巨噬细胞)，所述抗原包含在基孔肯雅或委内瑞拉马脑炎病毒样颗粒中。

[0114] 在一个实施方案中，本发明提供用于产生在本发明第一方面中提供的基孔肯雅或委内瑞拉马脑炎病毒样颗粒的方法，包括：制备包含编码所述颗粒的核苷酸序列的基因；培养已用所述基因转染的细胞，以表达所述颗粒；和回收所述颗粒。在该实施方案中，可使用常规方法进行转染。用于转染的细胞可以是293细胞。VLP的回收可包括在用包含基因的质粒转染细胞后收集条件培养基，并且可进一步包括用超速离心从条件培养基中纯化VLP。在一个实施方案中，在本发明第八方面中提供的产生基孔肯雅或委内瑞拉马脑炎病毒样颗粒的方法中可以包括进一步的步骤，其中设计编码抗原的多核苷酸，使得当在抗原或含有所述抗原的天然存在的蛋白或源自其的修饰的蛋白的晶体中测定距离时，抗原的N-末端残基和C-末端残基之间的空间距离为30Å或更小(例如5 Å至15 Å、5 Å至12 Å、5 Å至11 Å、5 Å至10 Å、5 Å至8 Å、8 Å至15 Å、8 Å至13 Å、8 Å至12 Å、8 Å至11 Å、9 Å至12 Å、9 Å至11 Å、9 Å至10 Å、或10 Å至11 Å)。

[0115] 免疫系统经发展而识别外源抗原，以杀伤病原体例如病毒或细菌。它也经发展而不能识别自身蛋白，以保护自身蛋白。这称为免疫耐受系统。因此通过传统免疫方法诱导针对自身抗原的抗体是困难的。为了克服免疫耐受性，我们开发出新的疫苗方法，使用含有自身抗原的自我装配亚基。自我装配亚基自发装配并形成稳定的有组织的单元，其将高度重复的抗原展示在表面。与单一抗原免疫原例如传统免疫方法相比，高度重复的抗原免疫原在B细胞中增强了信号途径并导致对抗体应答的刺激。将该机制用于疫苗开发，不仅增加针对靶免疫原的抗体应答，而且克服自身抗原耐受性。

[0116] 参考以下实施例，将详细描述本发明，然而以下实施例无意限制本发明的范围。

实施例

[0117] (1) 制备基孔肯雅病毒样颗粒，其包含病毒结构多肽和人TNFα片段

预计与基孔肯雅病毒结构多肽融合的TNFα多肽单体难以稳定表达，因为发现TNFα在天然条件下是三聚体。然而，使用融合蛋白，其中TNFα单体肽(TNFα单体肽的片段)通过接头在TNFα-衍生肽的N-和C-末端(用于将TNFα-衍生肽与基孔肯雅病毒结构多肽连接)与基孔肯雅病毒结构多肽融合，导致基孔肯雅病毒样颗粒的稳定表达，所述颗粒包含病毒结构

多肽和TNFα单体-衍生肽。

[0118] 详细地讲，编码原始人TNFα的多核苷酸经修饰以制备编码修饰的TNFα-衍生肽的多核苷酸，其中作为原始TNFα-衍生肽的N-末端序列的RTPSD被SGG置换和将TRGGS连接到TNFα的C-末端(参见图1所示的SEQ ID No.18-20)。将所得多核苷酸插入到编码SEQ ID No.2的519-位置的G和520-位置的Q的密码子之间，以构建质粒(以下称为CHIKV-TNFa4)，用于表达基孔肯雅病毒样颗粒，其中将修饰的TNFα-衍生肽插入到基孔肯雅病毒结构多肽的E2 (C-E3-E2-6K-E1)。随后，用250μg CHIKV-TNFa4转染293F细胞(1.5x10^6细胞/ml)。培养4天后，收集上清液。将所得上清液覆盖到Opti Prep (Sigma D1556)上，然后进行超速离心(20000rpm, 120min)，使用SW28转子，以浓缩VLP (即病毒样颗粒)。将浓缩的VLP与Opti Prep混合形成密度梯度，然后进行超速离心(75000rpm, 4小时)，使用NVT100转子。超速离心后，收集纯化的VLP。包含与基孔肯雅病毒结构多肽缀合的TNFα的VLP的表达经蛋白质印迹得以证实，使用CHIVK特异性抗体(ATCC: VR-1241AF)和TNFα特异性抗体(Cell Signal: #6945)。

[0119] 当在TNFα晶体中测定距离时，TNFα-衍生肽的N-末端残基和C-末端残基之间的空间距离为8.27Å。

[0120] (2) 制备委内瑞拉马脑炎病毒样颗粒，其包含病毒结构多肽和人TNFα-衍生肽(称为"VEEV-TNFa VLP")

按照上述(1)，制备与编码委内瑞拉马脑炎病毒结构多肽的多核苷酸融合的编码修饰的TNFα-衍生肽的多核苷酸(参见SEQ ID No.15)，以构建表达载体，接着在293F细胞中转染。

[0121] 通过密度梯度离心纯化VEEV-TNFa VLP。如泳道4所示，TNFα-衍生肽和VEEV表达经蛋白质印迹得以证实，分别使用TNFa单克隆抗体(上图)和VEEV多克隆抗体(下图) (参见图2)。

[0122] 当在TNFα晶体中测定距离时，TNFα-衍生肽的N-末端残基和C-末端残基之间的空间距离为8.27Å。

[0123] (3) 在免疫的小鼠中检测抗人TNFα抗体

将小鼠分为3组(每组n=5)。将按照上述(1)制备的包含病毒结构多肽和人TNFα-衍生多肽的基孔肯雅病毒样颗粒(以下称为“CHIKV-TNFα”)、不包含人TNFα-衍生多肽的基孔肯雅病毒样颗粒(以下称为“CHIKV-VLP”)、按照上述(2)制备的包含病毒结构多肽和人TNFα-衍生多肽的委内瑞拉马脑炎病毒样颗粒(以下称为“VEEV-TNFα”)、不包含人TNFα-衍生多肽的委内瑞拉马脑炎病毒样颗粒(以下称为“VEEV-VLP”)或溶媒(即PBS)，经肌内给予各组小鼠。在实验开始时(以下称为“0周”)和第一次给予后3周(以下称为“3周”)给予小鼠，如下所述：组1：VEEV-TNFα (0周)、CHIKV-TNFα (3周)；组2：VEEV-VLP (0周)、CHIKV-VLP (3周)；和组3：PBS (0周)、PBS (3周)。

[0124] 实验开始后6周，从每只小鼠获取血液样品并制备血清。使用在ELISA板上包被有TNFα蛋白的ELISA，检测所产生的抗人TNFα抗体。结果表明，包含病毒结构多肽和人TNFα-衍生多肽的病毒样颗粒在小鼠中诱导抗人TNFα抗体(参见图9)。

[0125] (4) 制备委内瑞拉马脑炎病毒样颗粒，其包含病毒结构多肽和人CD20片段

按照上述(1)和(2)，通过密度梯度离心纯化VEEV-CD20 VLP，并且CD20和VEEV的片

段表达经蛋白酶印迹得以证实。作为CD20片段的IYNCEPANPSEKNSPSTQYCYSIQ (SEQ ID No.: 21),用作与委内瑞拉马脑炎病毒结构多肽融合的抗原。

[0126] 当在CD20晶体中测定距离时,CD20片段的N-末端残基和C-末端残基之间的空间距离为10.07Å。

[0127] (5) 制备委内瑞拉马脑炎病毒样颗粒,其包含病毒结构多肽和人CTLA4片段

根据全长CTLA4氨基酸序列而选择CTLA4片段:CKVELMYPPPYYLGIG (SEQ ID No.: 22),使得当在CLTA4晶体中测定距离时,所述片段(其与委内瑞拉马脑炎病毒结构多肽E2融合)的N-末端残基和C-末端残基之间的空间距离为大约5.6Å。

[0128] 将编码CTLA4片段的多核苷酸引入VLP_VEEV VLP 518载体,以构建质粒,用于表达与由SEQ ID No.:8的氨基酸序列组成的委内瑞拉马脑炎病毒结构多肽融合的CTLA4片段。

[0129] (6) 制备委内瑞拉马脑炎病毒样颗粒,其包含病毒结构多肽和全长人CTLA4

将编码全长人CTLA4的多核苷酸引入VLP_VEEV VLP 518载体,以构建质粒,用于表达与委内瑞拉马脑炎病毒结构多肽融合的CTLA4。

[0130] 当在CLTA4晶体中测定距离时,全长人CTLA4的N-末端残基和C-末端残基之间的空间距离为大约39.6Å。

[0131] 在用所制备的质粒转染293细胞后,通过ELISA不能检测出与委内瑞拉马脑炎病毒结构多肽融合的CTLA4的表达。

[0132] (7) 制备基孔肯雅病毒样颗粒,其包含病毒结构多肽和人或小鼠CD20片段,和检测抗人或小鼠CD20抗体

使用VLP_CHI 532载体和人或小鼠TNFα抗体片段,制备包含病毒结构多肽和人或小鼠CD20片段的基孔肯雅病毒样颗粒。人和小鼠TNFα抗体片段描述如下:CD20人iyncepanpseknspstqycysiq (SEQ ID No.:21);CD20小鼠ydcepsnsseknspstqycnsi (SEQ ID No.:41)。

[0133] 接头(例如SGG、SG、GS或GGS)用于将如下所述的CD20片段插入SEQ ID No.2的519-位置的G和520-位置的Q之间:

CD20人:SGGiyncepanpseknspstqycysiqGS (SEQ ID No.:42)

CD20小鼠形式2:SGydcepsnsseknspstqycnsiGGS (SEQ ID No.:43)

CD20小鼠形式3:SGGydcepsnsseknspstqycnsiGS (SEQ ID No.:44)。

[0134] 质粒:VLP_CHI VLP 532 CD20H、VLP_CHI VLP 532 CD20-2小鼠和VLP_CHI VLP 532 CD20-3小鼠用于表达基孔肯雅病毒样颗粒,其包含病毒结构多肽和人或小鼠CD20片段(SEQ ID No.: 45 (所表达的多肽的氨基酸序列示于SEQ ID No.: 46)、SEQ ID No.: 47 (所表达的多肽的氨基酸序列示于SEQ ID No.: 48)和SEQ ID No.: 49 (所表达的多肽的氨基酸序列示于SEQ ID No.: 50)。

[0135] 按照(1)中所述方法纯化病毒样颗粒。用100μg纯化VLP;100μg人或小鼠CD20片段;或PBS (对照),对小鼠免疫接种一次。免疫接种后10天,自小鼠中获得血液样品并制备血清。通过包被有人CD20片段的ELISA来检测经免疫诱导的抗人CD20抗体,并通过包被有小鼠CD20片段的ELISA来检测经免疫诱导的抗小鼠CD20抗体。结果表明,通过给予包含与病毒结构多肽融合的人或小鼠CD20片段的基孔肯雅病毒样颗粒,充分诱导出抗人CD20抗体和抗小鼠CD20抗体。而且,结果表明,通过给予包含与病毒结构多肽融合的自身抗原片段的基孔肯

雅病毒样颗粒,可以充分诱导出自身抗原特异性抗体(参见图10和图11)。

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<151> 2012-02-16
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Asn Lys Leu Thr Met Arg Ala Val Pro Gln Gln Lys Pro Arg Arg Asn
50 55 60
Arg Lys Asn Lys Lys Gln Lys Gln Lys Gln Gln Ala Pro Gln Asn Asn
65 70 75 80
Thr Asn Gln Lys Lys Gln Pro Pro Lys Lys Lys Pro Ala Gln Lys Lys
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Lys Lys Pro Gly Arg Arg Glu Arg Met Cys Met Lys Ile Glu Asn Asp
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Cys Ile Phe Glu Val Lys His Glu Gly Lys Val Thr Gly Tyr Ala Cys
115 120 125
Leu Val Gly Asp Lys Val Met Lys Pro Ala His Val Lys Gly Thr Ile
130 135 140
Asp Asn Ala Asp Leu Ala Lys Leu Ala Phe Lys Arg Ser Ser Lys Tyr
145 150 155 160
Asp Leu Glu Cys Ala Gln Ile Pro Val His Met Lys Ser Asp Ala Ser
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Lys Phe Thr His Glu Lys Pro Glu Gly Tyr Tyr Asn Trp His His Gly
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Ala Val Gln Tyr Ser Gly Gly Arg Phe Thr Ile Pro Thr Gly Ala Gly
195 200 205

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

515 520 525

Gly Gly Ser Asn Glu Gly Leu Thr Thr Thr Asp Lys Val Ile Asn Asn

530 535 540

Cys Lys Val Asp Gln Cys His Ala Ala Val Thr Asn His Lys Lys Trp

545 550 555 560

Gln Tyr Asn Ser Pro Leu Val Pro Arg Asn Ala Glu Leu Gly Asp Arg

565 570 575

Lys Gly Lys Ile His Ile Pro Phe Pro Leu Ala Asn Val Thr Cys Arg

580 585 590

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

595 600 605

Ile Met Leu Leu Tyr Pro Asp His Pro Thr Leu Leu Ser Tyr Arg Asn

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Met Gly Glu Glu Pro Asn Tyr Gln Glu Glu Trp Val Met His Lys Lys

625 630 635 640

Glu Val Val Leu Thr Val Pro Thr Glu Gly Leu Glu Val Thr Trp Gly

645 650 655

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

660 665 670

Ala His Gly His Pro His Glu Ile Ile Leu Tyr Tyr Tyr Glu Leu Tyr

675 680 685

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

690 695 700

Ser Met Val Gly Met Ala Ala Gly Met Cys Met Cys Ala Arg Arg Arg

705 710 715 720

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

725 730 735

Leu Ser Leu Ile Cys Cys Ile Arg Thr Ala Lys Ala Ala Thr Tyr Gln

740 745 750

Glu Ala Ala Ile Tyr Leu Trp Asn Glu Gln Gln Pro Leu Phe Trp Leu

755 760 765

Gln Ala Leu Ile Pro Leu Ala Ala Leu Ile Val Leu Cys Asn Cys Leu

770 775 780

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

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Cys His Pro Pro Lys Asp His Ile Val Asn Tyr Pro Ala Ser His
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50 55 60
Arg Lys Asn Lys Lys Gln Arg Gln Lys Lys Gln Ala Pro Gln Asn Asp
65 70 75 80
Pro Lys Gln Lys Lys Gln Pro Pro Gln Lys Lys Pro Ala Gln Lys Lys
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Lys Lys Pro Gly Arg Arg Glu Arg Met Cys Met Lys Ile Glu Asn Asp
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Cys Ile Phe Glu Val Lys His Glu Gly Lys Val Met Gly Tyr Ala Cys
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Asp Leu Glu Cys Ala Gln Ile Pro Val His Met Lys Ser Asp Ala Ser
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Lys Phe Thr His Glu Lys Pro Glu Gly Tyr Tyr Asn Trp His His Gly
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195 200 205
Lys Pro Gly Asp Ser Gly Arg Pro Ile Phe Asp Asn Lys Gly Arg Val
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His Arg Gln Arg Arg Ser Thr Lys Asp Asn Phe Asn Val Tyr Lys Ala
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370 375 380
Asp Ser His Asp Trp Thr Lys Leu Arg Tyr Met Asp Ser His Thr Pro
385 390 395 400
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675 680 685
Pro Thr Met Thr Val Val Ile Val Ser Val Ala Ser Phe Val Leu Leu
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Ser Ala Trp Thr Pro Phe Asp Asn Lys Ile Val Val Tyr Lys Gly Asp
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Val Tyr Asn Met Asp Tyr Pro Pro Phe Gly Ala Gly Arg Pro Gly Gln
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Gly Lys Leu Phe Arg Pro Met His Val Glu Gly Lys Ile Asp Asn Asp
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Val Leu Ala Ala Leu Lys Thr Lys Lys Ala Ser Lys Tyr Asp Leu Glu
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Tyr Ala Asp Val Pro Gln Asn Met Arg Ala Asp Thr Phe Lys Tyr Thr
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His Glu Lys Pro Gln Gly Tyr Tyr Ser Trp His His Gly Ala Val Gln
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Tyr Glu Asn Gly Arg Phe Thr Val Pro Lys Gly Val Gly Ala Lys Gly
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Glu Gln Trp Ser Leu Val Thr Thr Met Cys Leu Leu Ala Asn Val Thr
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Phe Pro Cys Ala Gln Pro Pro Ile Cys Tyr Asp Arg Lys Pro Ala Glu
290 295 300
Thr Leu Ala Met Leu Ser Val Asn Val Asp Asn Pro Gly Tyr Asp Glu
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Leu Leu Glu Ala Ala Val Lys Cys Pro Gly Arg Lys Arg Arg Ser Thr
325 330 335
Glu Glu Leu Phe Asn Glu Tyr Lys Leu Thr Arg Pro Tyr Met Ala Arg
340 345 350
Cys Ile Arg Cys Ala Val Gly Ser Cys His Ser Pro Ile Ala Ile Glu
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Ala Val Lys Ser Asp Gly His Asp Gly Tyr Val Arg Leu Gln Thr Ser
370 375 380
Ser Gln Tyr Gly Leu Asp Ser Ser Gly Asn Leu Lys Gly Arg Thr Met
385 390 395 400
Arg Tyr Asp Met His Gly Thr Ile Lys Glu Ile Pro Leu His Gln Val

405 410 415
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Phe Leu Leu Ala Arg Cys Pro Ala Gly Asp Ser Ile Thr Met Glu Phe
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Lys Lys Asp Ser Val Arg His Ser Cys Ser Val Pro Tyr Glu Val Lys
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Ala Tyr Val Glu Met His Leu Pro Gly Ser Glu Val Asp Ser Ser Leu
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Val Ser Leu Ser Gly Ser Ser Val Thr Val Thr Pro Pro Asp Gly Thr
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Ser Ala Leu Val Glu Cys Glu Cys Gly Gly Thr Lys Ile Ser Glu Thr
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Phe Leu Leu Ala Asp Gly Lys Cys Thr Val Pro Leu Ala Pro Glu Pro
595 600 605
Met Ile Thr Phe Gly Phe Arg Ser Val Ser Leu Lys Leu His Pro Lys
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Asn Pro Thr Tyr Leu Ile Thr Arg Gln Leu Ala Asp Glu Pro His Tyr
625 630 635 640
Thr His Glu Leu Ile Ser Glu Pro Ala Val Arg Asn Phe Thr Val Thr
645 650 655
Glu Lys Gly Trp Glu Phe Val Trp Gly Asn His Pro Pro Lys Arg Phe
660 665 670
Trp Ala Gln Glu Thr Ala Pro Gly Asn Pro His Gly Leu Pro His Glu
675 680 685
Val Ile Thr His Tyr Tyr His Arg Tyr Pro Met Ser Thr Ile Leu Gly
690 695 700
Leu Ser Ile Cys Ala Ala Ile Ala Thr Val Ser Val Ala Ala Ser Thr
705 710 715 720

Trp Leu Phe Cys Arg Ser Arg Val Ala Cys Leu Thr Pro Tyr Arg Leu
725 730 735
Thr Pro Asn Ala Arg Ile Pro Phe Cys Leu Ala Val Leu Cys Cys Ala
740 745 750
Arg Thr Ala Arg Ala Glu Thr Thr Trp Glu Ser Leu Asp His Leu Trp
755 760 765
Asn Asn Asn Gln Gln Met Phe Trp Ile Gln Leu Leu Ile Pro Leu Ala
770 775 780
Ala Leu Ile Val Val Thr Arg Leu Leu Arg Cys Val Cys Cys Val Val
785 790 795 800
Pro Phe Leu Val Met Ala Gly Ala Ala Gly Ala Gly Ala Tyr Glu His
805 810 815
Ala Thr Thr Met Pro Ser Gln Ala Gly Ile Ser Tyr Asn Thr Ile Val
820 825 830
Asn Arg Ala Gly Tyr Ala Pro Leu Pro Ile Ser Ile Thr Pro Thr Lys
835 840 845
Ile Lys Leu Ile Pro Thr Val Asn Leu Glu Tyr Val Thr Cys His Tyr
850 855 860
Lys Thr Gly Met Asp Ser Pro Ala Ile Lys Cys Cys Gly Ser Gln Glu
865 870 875 880
Cys Thr Pro Thr Tyr Arg Pro Asp Glu Gln Cys Lys Val Phe Thr Gly
885 890 895
Val Tyr Pro Phe Met Trp Gly Gly Ala Tyr Cys Phe Cys Asp Thr Glu
900 905 910
Asn Thr Gln Val Ser Lys Ala Tyr Val Met Lys Ser Asp Asp Cys Leu
915 920 925
Ala Asp His Ala Glu Ala Tyr Lys Ala His Thr Ala Ser Val Gln Ala
930 935 940
Phe Leu Asn Ile Thr Val Gly Glu His Ser Ile Val Thr Thr Val Tyr
945 950 955 960
Val Asn Gly Glu Thr Pro Val Asn Phe Asn Gly Val Lys Ile Thr Ala
965 970 975
Gly Pro Leu Ser Thr Ala Trp Thr Pro Phe Asp Arg Lys Ile Val Gln
980 985 990
Tyr Ala Gly Glu Ile Tyr Asn Tyr Asp Phe Pro Glu Tyr Gly Ala Gly
995 1000 1005
Gln Pro Gly Ala Phe Gly Asp Ile Gln Ser Arg Thr Val Ser Ser
1010 1015 1020
Ser Asp Leu Tyr Ala Asn Thr Asn Leu Val Leu Gln Arg Pro Lys

1025 1030 1035

Ala Gly Ala Ile His Val Pro Tyr Thr Gln Ala Pro Ser Gly Phe

1040 1045 1050

Glu Gln Trp Lys Lys Asp Lys Ala Pro Ser Leu Lys Phe Thr Ala

1055 1060 1065

Pro Phe Gly Cys Glu Ile Tyr Thr Asn Pro Ile Arg Ala Glu Asn

1070 1075 1080

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

1085 1090 1095

Leu Phe Thr Arg Val Ser Glu Thr Pro Thr Leu Ser Ala Ala Glu

1100 1105 1110

Cys Thr Leu Asn Glu Cys Val Tyr Ser Ser Asp Phe Gly Gly Ile

1115 1120 1125

Ala Thr Val Lys Tyr Ser Ala Ser Lys Ser Gly Lys Cys Ala Val

1130 1135 1140

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

1145 1150 1155

Leu Thr Glu Gln Gly Ser Ala Thr Ile His Phe Ser Thr Ala Asn

1160 1165 1170

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

1175 1180 1185

Cys Lys Gly Asp Cys His Pro Pro Lys Asp His Ile Val Thr His

1190 1195 1200

Pro Gln Tyr His Ala Gln Thr Phe Thr Ala Ala Val Ser Lys Thr

1205 1210 1215

Ala Trp Thr Trp Leu Thr Ser Leu Leu Gly Gly Ser Ala Val Ile

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

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

625 630 635 640
Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe
645 650 655
Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu Thr Arg Gly
660 665 670
Gly Ser Gly Gly Gln Thr Val Arg Tyr Lys Cys Asn Cys Gly Gly Ser
675 680 685
Asn Glu Gly Leu Thr Thr Thr Asp Lys Val Ile Asn Asn Cys Lys Ile
690 695 700
Asp Gln Cys His Ala Ala Val Thr Asn His Lys Asn Trp Gln Tyr Asn
705 710 715 720
Ser Pro Leu Val Pro Arg Asn Ala Glu Leu Gly Asp Arg Lys Gly Lys
725 730 735
Ile His Ile Pro Phe Pro Leu Ala Asn Val Thr Cys Arg Val Pro Lys
740 745 750
Ala Arg Asn Pro Thr Val Thr Tyr Gly Lys Asn Gln Val Thr Met Leu
755 760 765
Leu Tyr Pro Asp His Pro Thr Leu Leu Ser Tyr Arg Asn Met Gly Gln
770 775 780
Glu Pro Asn Tyr His Glu Glu Trp Val Thr His Lys Lys Glu Val Thr
785 790 795 800
Leu Thr Val Pro Thr Glu Gly Leu Glu Val Thr Trp Gly Asn Asn Glu
805 810 815
Pro Tyr Lys Tyr Trp Pro Gln Met Ser Thr Asn Gly Thr Ala His Gly
820 825 830
His Pro His Glu Ile Ile Leu Tyr Tyr Tyr Glu Leu Tyr Pro Thr Met
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Thr Val Val Ile Val Ser Val Ala Ser Phe Val Leu Leu Ser Met Val
850 855 860
Gly Thr Ala Val Gly Met Cys Val Cys Ala Arg Arg Arg Cys Ile Thr
865 870 875 880
Pro Tyr Glu Leu Thr Pro Gly Ala Thr Val Pro Phe Leu Leu Ser Leu
885 890 895
Leu Cys Cys Val Arg Thr Thr Lys Ala Ala Thr Tyr Tyr Glu Ala Ala
900 905 910
Ala Tyr Leu Trp Asn Glu Gln Gln Pro Leu Phe Trp Leu Gln Ala Leu
915 920 925
Ile Pro Leu Ala Ala Leu Ile Val Leu Cys Asn Cys Leu Lys Leu Leu
930 935 940

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

1235 1240 1245
Pro Asp Ala Ala Phe Thr Arg Val Val Asp Ala Pro Ser Val Thr
1250 1255 1260
Asp Met Ser Cys Glu Val Pro Ala Cys Thr His Ser Ser Asp Phe
1265 1270 1275
Gly Gly Val Ala Ile Ile Lys Tyr Thr Ala Ser Lys Lys Gly Lys
1280 1285 1290
Cys Ala Val His Ser Met Thr Asn Ala Val Thr Ile Arg Glu Ala
1295 1300 1305
Asp Val Glu Val Glu Gly Asn Ser Gln Leu Gln Ile Ser Phe Ser
1310 1315 1320
Thr Ala Leu Ala Ser Ala Glu Phe Arg Val Gln Val Cys Ser Thr
1325 1330 1335
Gln Val His Cys Ala Ala Ala Cys His Pro Pro Lys Asp His Ile
1340 1345 1350
Val Asn Tyr Pro Ala Ser His Thr Thr Leu Gly Val Gln Asp Ile
1355 1360 1365
Ser Thr Thr Ala Met Ser Trp Val Gln Lys Ile Thr Gly Gly Val
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35 40 45
Asn Lys Leu Thr Met Arg Ala Val Pro Gln Gln Lys Pro Arg Arg Asn
50 55 60
Arg Lys Asn Lys Lys Gln Arg Gln Lys Lys Gln Ala Pro Gln Asn Asp

65 70 75 80
Pro Lys Gln Lys Lys Gln Pro Pro Gln Lys Lys Pro Ala Gln Lys Lys
85 90 95
Lys Lys Pro Gly Arg Arg Glu Arg Met Cys Met Lys Ile Glu Asn Asp
100 105 110
Cys Ile Phe Glu Val Lys His Glu Gly Lys Val Met Gly Tyr Ala Cys
115 120 125
Leu Val Gly Asp Lys Val Met Lys Pro Ala His Val Lys Gly Thr Ile
130 135 140
Asp Asn Ala Asp Leu Ala Lys Leu Ala Phe Lys Arg Ser Ser Lys Tyr
145 150 155 160
Asp Leu Glu Cys Ala Gln Ile Pro Val His Met Lys Ser Asp Ala Ser
165 170 175
Lys Phe Thr His Glu Lys Pro Glu Gly Tyr Tyr Asn Trp His His Gly
180 185 190
Ala Val Gln Tyr Ser Gly Gly Arg Phe Thr Ile Pro Thr Gly Ala Gly
195 200 205
Lys Pro Gly Asp Ser Gly Arg Pro Ile Phe Asp Asn Lys Gly Arg Val
210 215 220
Val Ala Ile Val Leu Gly Gly Ala Asn Glu Gly Ala Arg Thr Ala Leu
225 230 235 240
Ser Val Val Thr Trp Asn Lys Asp Ile Val Thr Lys Ile Thr Pro Glu
245 250 255
Gly Ala Glu Glu Trp Ser Leu Ala Leu Pro Val Leu Cys Leu Leu Ala
260 265 270
Asn Thr Thr Phe Pro Cys Ser Gln Pro Pro Cys Thr Pro Cys Cys Tyr
275 280 285
Glu Lys Glu Pro Glu Ser Thr Leu Arg Met Leu Glu Asp Asn Val Met
290 295 300
Arg Pro Gly Tyr Tyr Gln Leu Leu Lys Ala Ser Leu Thr Cys Ser Pro
305 310 315 320
His Arg Gln Arg Arg Ser Thr Lys Asp Asn Phe Asn Val Tyr Lys Ala
325 330 335
Thr Arg Pro Tyr Leu Ala His Cys Pro Asp Cys Gly Glu Gly His Ser
340 345 350
Cys His Ser Pro Ile Ala Leu Glu Arg Ile Arg Asn Glu Ala Thr Asp
355 360 365
Gly Thr Leu Lys Ile Gln Val Ser Leu Gln Ile Gly Ile Lys Thr Asp
370 375 380

Asp Ser His Asp Trp Thr Lys Leu Arg Tyr Met Asp Ser His Thr Pro
385 390 395 400
Ala Asp Ala Glu Arg Ala Gly Leu Leu Val Arg Thr Ser Ala Pro Cys
405 410 415
Thr Ile Thr Gly Thr Met Gly His Phe Ile Leu Ala Arg Cys Pro Lys
420 425 430
Gly Glu Thr Leu Thr Val Gly Phe Thr Asp Ser Arg Lys Ile Ser His
435 440 445
Thr Cys Thr His Pro Phe His His Glu Pro Pro Val Ile Gly Arg Glu
450 455 460
Arg Phe His Ser Arg Pro Gln His Gly Lys Glu Leu Pro Cys Ser Thr
465 470 475 480
Tyr Val Gln Ser Thr Ala Ala Thr Ala Glu Glu Ile Glu Val His Met
485 490 495
Pro Pro Asp Thr Pro Asp Arg Thr Leu Met Thr Gln Gln Ser Gly Asn
500 505 510
Val Lys Ile Thr Val Asn Gly Gln Thr Val Arg Tyr Lys Cys Asn Cys
515 520 525
Gly Gly Ser Gly Gly Ile Tyr Asn Cys Glu Pro Ala Asn Pro Ser Glu
530 535 540
Lys Asn Ser Pro Ser Thr Gln Tyr Cys Tyr Ser Ile Gln Gly Ser Asn
545 550 555 560
Glu Gly Leu Thr Thr Thr Asp Lys Val Ile Asn Asn Cys Lys Ile Asp
565 570 575
Gln Cys His Ala Ala Val Thr Asn His Lys Asn Trp Gln Tyr Asn Ser
580 585 590
Pro Leu Val Pro Arg Asn Ala Glu Leu Gly Asp Arg Lys Gly Lys Ile
595 600 605
His Ile Pro Phe Pro Leu Ala Asn Val Thr Cys Arg Val Pro Lys Ala
610 615 620
Arg Asn Pro Thr Val Thr Tyr Gly Lys Asn Gln Val Thr Met Leu Leu
625 630 635 640
Tyr Pro Asp His Pro Thr Leu Leu Ser Tyr Arg Asn Met Gly Gln Glu
645 650 655
Pro Asn Tyr His Glu Glu Trp Val Thr His Lys Lys Glu Val Thr Leu
660 665 670
Thr Val Pro Thr Glu Gly Leu Glu Val Thr Trp Gly Asn Asn Glu Pro
675 680 685
Tyr Lys Tyr Trp Pro Gln Met Ser Thr Asn Gly Thr Ala His Gly His

690 695 700

Pro His Glu Ile Ile Leu Tyr Tyr Tyr Glu Leu Tyr Pro Thr Met Thr
705 710 715 720

Val Val Ile Val Ser Val Ala Ser Phe Val Leu Leu Ser Met Val Gly
725 730 735

Thr Ala Val Gly Met Cys Val Cys Ala Arg Arg Arg Cys Ile Thr Pro
740 745 750

Tyr Glu Leu Thr Pro Gly Ala Thr Val Pro Phe Leu Leu Ser Leu Leu
755 760 765

Cys Cys Val Arg Thr Thr Lys Ala Ala Thr Tyr Tyr Glu Ala Ala Ala
770 775 780

Tyr Leu Trp Asn Glu Gln Gln Pro Leu Phe Trp Leu Gln Ala Leu Ile
785 790 795 800

Pro Leu Ala Ala Leu Ile Val Leu Cys Asn Cys Leu Lys Leu Leu Pro
805 810 815

Cys Cys Cys Lys Thr Leu Ala Phe Leu Ala Val Met Ser Ile Gly Ala
820 825 830

His Thr Val Ser Ala Tyr Glu His Val Thr Val Ile Pro Asn Thr Val
835 840 845

Gly Val Pro Tyr Lys Thr Leu Val Asn Arg Pro Gly Tyr Ser Pro Met
850 855 860

Val Leu Glu Met Glu Leu Gln Ser Val Thr Leu Glu Pro Thr Leu Ser
865 870 875 880

Leu Asp Tyr Ile Thr Cys Glu Tyr Lys Thr Val Ile Pro Ser Pro Tyr
885 890 895

Val Lys Cys Cys Gly Thr Ala Glu Cys Lys Asp Lys Ser Leu Pro Asp
900 905 910

Tyr Ser Cys Lys Val Phe Thr Gly Val Tyr Pro Phe Met Trp Gly Gly
915 920 925

Ala Tyr Cys Phe Cys Asp Ala Glu Asn Thr Gln Leu Ser Glu Ala His
930 935 940

Val Glu Lys Ser Glu Ser Cys Lys Thr Glu Phe Ala Ser Ala Tyr Arg
945 950 955 960

Ala His Thr Ala Ser Ala Ser Ala Lys Leu Arg Val Leu Tyr Gln Gly
965 970 975

Asn Asn Ile Thr Val Ala Ala Tyr Ala Asn Gly Asp His Ala Val Thr
980 985 990

Val Lys Asp Ala Lys Phe Val Val Gly Pro Met Ser Ser Ala Trp Thr
995 1000 1005

Pro Phe Asp Asn Lys Ile Val Val Tyr Lys Gly Asp Val Tyr Asn
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Met Asp Tyr Pro Pro Phe Gly Ala Gly Arg Pro Gly Gln Phe Gly
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Asp Ile Gln Ser Arg Thr Pro Glu Ser Lys Asp Val Tyr Ala Asn
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Thr Gln Leu Val Leu Gln Arg Pro Ala Ala Gly Thr Val His Val
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Pro Tyr Ser Gln Ala Pro Ser Gly Phe Lys Tyr Trp Leu Lys Glu
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Arg Gly Ala Ser Leu Gln His Thr Ala Pro Phe Gly Cys Gln Ile
1085 1090 1095
Ala Thr Asn Pro Val Arg Ala Val Asn Cys Ala Val Gly Asn Ile
1100 1105 1110
Pro Ile Ser Ile Asp Ile Pro Asp Ala Ala Phe Thr Arg Val Val
1115 1120 1125
Asp Ala Pro Ser Val Thr Asp Met Ser Cys Glu Val Pro Ala Cys
1130 1135 1140
Thr His Ser Ser Asp Phe Gly Gly Val Ala Ile Ile Lys Tyr Thr
1145 1150 1155
Ala Ser Lys Lys Gly Lys Cys Ala Val His Ser Met Thr Asn Ala
1160 1165 1170
Val Thr Ile Arg Glu Ala Asp Val Glu Val Glu Gly Asn Ser Gln
1175 1180 1185
Leu Gln Ile Ser Phe Ser Thr Ala Leu Ala Ser Ala Glu Phe Arg
1190 1195 1200
Val Gln Val Cys Ser Thr Gln Val His Cys Ala Ala Ala Cys His
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Pro Pro Lys Asp His Ile Val Asn Tyr Pro Ala Ser His Thr Thr
1220 1225 1230
Leu Gly Val Gln Asp Ile Ser Thr Thr Ala Met Ser Trp Val Gln
1235 1240 1245
Lys Ile Thr Gly Gly Val Gly Leu Ile Val Ala Val Ala Ala Leu
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35 40 45
Thr Phe Lys Gln Arg Arg Asp Ala Pro Pro Glu Gly Pro Ser Ala Asn
50 55 60
Lys Pro Lys Lys Glu Ala Ser Gln Lys Gln Lys Gly Gly Gly Gln Gly
65 70 75 80
Lys Lys Lys Lys Asn Gln Gly Lys Lys Lys Ala Lys Thr Gly Pro Pro
85 90 95
Asn Pro Lys Ala Gln Asn Gly Asn Lys Lys Lys Thr Asn Lys Lys Pro
100 105 110
Gly Lys Arg Gln Arg Met Val Met Lys Leu Glu Ser Asp Lys Thr Phe
115 120 125
Pro Ile Met Leu Glu Gly Lys Ile Asn Gly Tyr Ala Cys Val Val Gly
130 135 140
Gly Lys Leu Phe Arg Pro Met His Val Glu Gly Lys Ile Asp Asn Asp
145 150 155 160
Val Leu Ala Ala Leu Lys Thr Lys Lys Ala Ser Lys Tyr Asp Leu Glu
165 170 175
Tyr Ala Asp Val Pro Gln Asn Met Arg Ala Asp Thr Phe Lys Tyr Thr
180 185 190
His Glu Lys Pro Gln Gly Tyr Tyr Ser Trp His His Gly Ala Val Gln
195 200 205
Tyr Glu Asn Gly Arg Phe Thr Val Pro Lys Gly Val Gly Ala Lys Gly
210 215 220
Asp Ser Gly Arg Pro Ile Leu Asp Asn Gln Gly Arg Val Val Ala Ile
225 230 235 240
Val Leu Gly Gly Val Asn Glu Gly Ser Arg Thr Ala Leu Ser Val Val
245 250 255
Met Trp Asn Glu Lys Gly Val Thr Val Lys Tyr Thr Pro Glu Asn Cys
260 265 270
Glu Gln Trp Ser Leu Val Thr Thr Met Cys Leu Leu Ala Asn Val Thr

275 280 285

Phe Pro Cys Ala Gln Pro Pro Ile Cys Tyr Asp Arg Lys Pro Ala Glu
290 295 300

Thr Leu Ala Met Leu Ser Val Asn Val Asp Asn Pro Gly Tyr Asp Glu
305 310 315 320

Leu Leu Glu Ala Ala Val Lys Cys Pro Gly Arg Lys Arg Arg Ser Thr
325 330 335

Glu Glu Leu Phe Asn Glu Tyr Lys Leu Thr Arg Pro Tyr Met Ala Arg
340 345 350

Cys Ile Arg Cys Ala Val Gly Ser Cys His Ser Pro Ile Ala Ile Glu
355 360 365

Ala Val Lys Ser Asp Gly His Asp Gly Tyr Val Arg Leu Gln Thr Ser
370 375 380

Ser Gln Tyr Gly Leu Asp Ser Ser Gly Asn Leu Lys Gly Arg Thr Met
385 390 395 400

Arg Tyr Asp Met His Gly Thr Ile Lys Glu Ile Pro Leu His Gln Val
405 410 415

Ser Leu Tyr Thr Ser Arg Pro Cys His Ile Val Asp Gly His Gly Tyr
420 425 430

Phe Leu Leu Ala Arg Cys Pro Ala Gly Asp Ser Ile Thr Met Glu Phe
435 440 445

Lys Lys Asp Ser Val Arg His Ser Cys Ser Val Pro Tyr Glu Val Lys
450 455 460

Phe Asn Pro Val Gly Arg Glu Leu Tyr Thr His Pro Pro Glu His Gly
465 470 475 480

Val Glu Gln Ala Cys Gln Val Tyr Ala His Asp Ala Gln Asn Arg Gly
485 490 495

Ala Tyr Val Glu Met His Leu Pro Gly Ser Glu Val Asp Ser Ser Leu
500 505 510

Val Ser Leu Ser Gly Ser Ser Gly Gly Lys Pro Val Ala His Val Val
515 520 525

Ala Asn Pro Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg Ala
530 535 540

Asn Ala Leu Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu Val
545 550 555 560

Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe Lys
565 570 575

Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile Ser
580 585 590

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

900 905 910
Glu Thr Thr Trp Glu Ser Leu Asp His Leu Trp Asn Asn Asn Gln Gln
915 920 925
Met Phe Trp Ile Gln Leu Leu Ile Pro Leu Ala Ala Leu Ile Val Val
930 935 940
Thr Arg Leu Leu Arg Cys Val Cys Cys Val Val Pro Phe Leu Val Met
945 950 955 960
Ala Gly Ala Ala Gly Ala Gly Ala Tyr Glu His Ala Thr Thr Met Pro
965 970 975
Ser Gln Ala Gly Ile Ser Tyr Asn Thr Ile Val Asn Arg Ala Gly Tyr
980 985 990
Ala Pro Leu Pro Ile Ser Ile Thr Pro Thr Lys Ile Lys Leu Ile Pro
995 1000 1005
Thr Val Asn Leu Glu Tyr Val Thr Cys His Tyr Lys Thr Gly Met
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Asp Ser Pro Ala Ile Lys Cys Cys Gly Ser Gln Glu Cys Thr Pro
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Pro Phe Met Trp Gly Gly Ala Tyr Cys Phe Cys Asp Thr Glu Asn
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Thr Gln Val Ser Lys Ala Tyr Val Met Lys Ser Asp Asp Cys Leu
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Ala Asp His Ala Glu Ala Tyr Lys Ala His Thr Ala Ser Val Gln
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Ala Phe Leu Asn Ile Thr Val Gly Glu His Ser Ile Val Thr Thr
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Val Tyr Val Asn Gly Glu Thr Pro Val Asn Phe Asn Gly Val Lys
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Glu Tyr Gly Ala Gly Gln Pro Gly Ala Phe Gly Asp Ile Gln Ser
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Arg Thr Val Ser Ser Ser Asp Leu Tyr Ala Asn Thr Asn Leu Val
1175 1180 1185
Leu Gln Arg Pro Lys Ala Gly Ala Ile His Val Pro Tyr Thr Gln
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Leu Lys Phe Thr Ala Pro Phe Gly Cys Glu Ile Tyr Thr Asn Pro
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Asp Ile Pro Asp Ala Leu Phe Thr Arg Val Ser Glu Thr Pro Thr
1250 1255 1260
Leu Ser Ala Ala Glu Cys Thr Leu Asn Glu Cys Val Tyr Ser Ser
1265 1270 1275
Asp Phe Gly Gly Ile Ala Thr Val Lys Tyr Ser Ala Ser Lys Ser
1280 1285 1290
Gly Lys Cys Ala Val His Val Pro Ser Gly Thr Ala Thr Leu Lys
1295 1300 1305
Glu Ala Ala Val Glu Leu Thr Glu Gln Gly Ser Ala Thr Ile His
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Phe Ser Thr Ala Asn Ile His Pro Glu Phe Arg Leu Gln Ile Cys
1325 1330 1335
Thr Ser Tyr Val Thr Cys Lys Gly Asp Cys His Pro Pro Lys Asp
1340 1345 1350
His Ile Val Thr His Pro Gln Tyr His Ala Gln Thr Phe Thr Ala
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Ala Val Ser Lys Thr Ala Trp Thr Trp Leu Thr Ser Leu Leu Gly
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Gly Lys Leu Phe Arg Pro Met His Val Glu Gly Lys Ile Asp Asn Asp
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Val Leu Ala Ala Leu Lys Thr Lys Lys Ala Ser Lys Tyr Asp Leu Glu
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Tyr Ala Asp Val Pro Gln Asn Met Arg Ala Asp Thr Phe Lys Tyr Thr
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His Glu Lys Pro Gln Gly Tyr Tyr Ser Trp His His Gly Ala Val Gln
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Tyr Glu Asn Gly Arg Phe Thr Val Pro Lys Gly Val Gly Ala Lys Gly
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Asp Ser Gly Arg Pro Ile Leu Asp Asn Gln Gly Arg Val Val Ala Ile
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Val Leu Gly Gly Val Asn Glu Gly Ser Arg Thr Ala Leu Ser Val Val
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Met Trp Asn Glu Lys Gly Val Thr Val Lys Tyr Thr Pro Glu Asn Cys
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Glu Gln Trp Ser Leu Val Thr Thr Met Cys Leu Leu Ala Asn Val Thr
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Thr Leu Ala Met Leu Ser Val Asn Val Asp Asn Pro Gly Tyr Asp Glu
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Arg Tyr Asp Met His Gly Thr Ile Lys Glu Ile Pro Leu His Gln Val

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Ser Leu Tyr Thr Ser Arg Pro Cys His Ile Val Asp Gly His Gly Tyr

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Phe Leu Leu Ala Arg Cys Pro Ala Gly Asp Ser Ile Thr Met Glu Phe

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Lys Lys Asp Ser Val Arg His Ser Cys Ser Val Pro Tyr Glu Val Lys

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Phe Asn Pro Val Gly Arg Glu Leu Tyr Thr His Pro Pro Glu His Gly

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Val Glu Gln Ala Cys Gln Val Tyr Ala His Asp Ala Gln Asn Arg Gly

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Ala Tyr Val Glu Met His Leu Pro Gly Ser Glu Val Asp Ser Ser Leu

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

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Asn Pro Ser Glu Lys Asn Ser Pro Ser Thr Gln Tyr Cys Tyr Ser Ile

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Gln Gly Ser Ser Val Thr Val Thr Pro Pro Asp Gly Thr Ser Ala Leu

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Thr Lys Gln Phe Ser Gln Cys Thr Lys Lys Glu Gln Cys Arg Ala Tyr

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Arg Leu Gln Asn Asp Lys Trp Val Tyr Asn Ser Asp Lys Leu Pro Lys

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Trp Glu Phe Val Trp Gly Asn His Pro Pro Lys Arg Phe Trp Ala Gln
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Glu Thr Ala Pro Gly Asn Pro His Gly Leu Pro His Glu Val Ile Thr
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755 760 765
Ala Arg Ile Pro Phe Cys Leu Ala Val Leu Cys Cys Ala Arg Thr Ala
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Arg Ala Glu Thr Thr Trp Glu Ser Leu Asp His Leu Trp Asn Asn Asn
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Ala Glu Ala Tyr Lys Ala His Thr Ala Ser Val Gln Ala Phe Leu Asn

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His Glu Lys Pro Gln Gly Tyr Tyr Ser Trp His His Gly Ala Val Gln
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Tyr Glu Asn Gly Arg Phe Thr Val Pro Lys Gly Val Gly Ala Lys Gly
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Gln Cys Thr Lys Lys Glu Gln Cys Arg Ala Tyr Arg Leu Gln Asn Asp
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Val Ser Leu Lys Leu His Pro Lys Asn Pro Thr Tyr Leu Ile Thr Arg
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Gln Leu Ala Asp Glu Pro His Tyr Thr His Glu Leu Ile Ser Glu Pro
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675 680 685

Gly Asn His Pro Pro Lys Arg Phe Trp Ala Gln Glu Thr Ala Pro Gly
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Asn Pro His Gly Leu Pro His Glu Val Ile Thr His Tyr Tyr His Arg
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Tyr Pro Met Ser Thr Ile Leu Gly Leu Ser Ile Cys Ala Ala Ile Ala
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755 760 765

Cys Leu Ala Val Leu Cys Cys Ala Arg Thr Ala Arg Ala Glu Thr Thr
770 775 780

Trp Glu Ser Leu Asp His Leu Trp Asn Asn Asn Gln Gln Met Phe Trp
785 790 795 800

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885 890 895
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Tyr Glu Asn Gly Arg Phe Thr Val Pro Lys Gly Val Gly Ala Lys Gly
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35 40 45
Asn Lys Leu Thr Met Arg Ala Val Pro Gln Gln Lys Pro Arg Arg Asn
50 55 60
Arg Lys Asn Lys Lys Gln Arg Gln Lys Lys Gln Ala Pro Gln Asn Asp
65 70 75 80
Pro Lys Gln Lys Lys Gln Pro Pro Gln Lys Lys Pro Ala Gln Lys Lys
85 90 95
Lys Lys Pro Gly Arg Arg Glu Arg Met Cys Met Lys Ile Glu Asn Asp

100 105 110

Cys Ile Phe Glu Val Lys His Glu Gly Lys Val Met Gly Tyr Ala Cys

115 120 125

Leu Val Gly Asp Lys Val Met Lys Pro Ala His Val Lys Gly Thr Ile

130 135 140

Asp Asn Ala Asp Leu Ala Lys Leu Ala Phe Lys Arg Ser Ser Lys Tyr

145 150 155 160

Asp Leu Glu Cys Ala Gln Ile Pro Val His Met Lys Ser Asp Ala Ser

165 170 175

Lys Phe Thr His Glu Lys Pro Glu Gly Tyr Tyr Asn Trp His His Gly

180 185 190

Ala Val Gln Tyr Ser Gly Gly Arg Phe Thr Ile Pro Thr Gly Ala Gly

195 200 205

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

210 215 220

Val Ala Ile Val Leu Gly Gly Ala Asn Glu Gly Ala Arg Thr Ala Leu

225 230 235 240

Ser Val Val Thr Trp Asn Lys Asp Ile Val Thr Lys Ile Thr Pro Glu

245 250 255

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

260 265 270

Asn Thr Thr Phe Pro Cys Ser Gln Pro Pro Cys Thr Pro Cys Cys Tyr

275 280 285

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

290 295 300

Arg Pro Gly Tyr Tyr Gln Leu Leu Lys Ala Ser Leu Thr Cys Ser Pro

305 310 315 320

His Arg Gln Arg Arg Ser Thr Lys Asp Asn Phe Asn Val Tyr Lys Ala

325 330 335

Thr Arg Pro Tyr Leu Ala His Cys Pro Asp Cys Gly Glu Gly His Ser

340 345 350

Cys His Ser Pro Ile Ala Leu Glu Arg Ile Arg Asn Glu Ala Thr Asp

355 360 365

Gly Thr Leu Lys Ile Gln Val Ser Leu Gln Ile Gly Ile Lys Thr Asp

370 375 380

Asp Ser His Asp Trp Thr Lys Leu Arg Tyr Met Asp Ser His Thr Pro

385 390 395 400

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

405 410 415

Thr Ile Thr Gly Thr Met Gly His Phe Ile Leu Ala Arg Cys Pro Lys
420 425 430
Gly Glu Thr Leu Thr Val Gly Phe Thr Asp Ser Arg Lys Ile Ser His
435 440 445
Thr Cys Thr His Pro Phe His His Glu Pro Pro Val Ile Gly Arg Glu
450 455 460
Arg Phe His Ser Arg Pro Gln His Gly Lys Glu Leu Pro Cys Ser Thr
465 470 475 480
Tyr Val Gln Ser Thr Ala Ala Thr Ala Glu Glu Ile Glu Val His Met
485 490 495
Pro Pro Asp Thr Pro Asp Arg Thr Leu Met Thr Gln Gln Ser Gly Asn
500 505 510
Val Lys Ile Thr Val Asn Gly Ser Gly Gly Ser Gly Gly Gln Thr Val
515 520 525
Arg Tyr Lys Cys Asn Cys Gly Gly Ser Asn Glu Gly Leu Thr Thr Thr
530 535 540
Asp Lys Val Ile Asn Asn Cys Lys Ile Asp Gln Cys His Ala Ala Val
545 550 555 560
Thr Asn His Lys Asn Trp Gln Tyr Asn Ser Pro Leu Val Pro Arg Asn
565 570 575
Ala Glu Leu Gly Asp Arg Lys Gly Lys Ile His Ile Pro Phe Pro Leu
580 585 590
Ala Asn Val Thr Cys Arg Val Pro Lys Ala Arg Asn Pro Thr Val Thr
595 600 605
Tyr Gly Lys Asn Gln Val Thr Met Leu Leu Tyr Pro Asp His Pro Thr
610 615 620
Leu Leu Ser Tyr Arg Asn Met Gly Gln Glu Pro Asn Tyr His Glu Glu
625 630 635 640
Trp Val Thr His Lys Lys Glu Val Thr Leu Thr Val Pro Thr Glu Gly
645 650 655
Leu Glu Val Thr Trp Gly Asn Asn Glu Pro Tyr Lys Tyr Trp Pro Gln
660 665 670
Met Ser Thr Asn Gly Thr Ala His Gly His Pro His Glu Ile Ile Leu
675 680 685
Tyr Tyr Tyr Glu Leu Tyr Pro Thr Met Thr Val Val Ile Val Ser Val
690 695 700
Ala Ser Phe Val Leu Leu Ser Met Val Gly Thr Ala Val Gly Met Cys
705 710 715 720
Val Cys Ala Arg Arg Arg Cys Ile Thr Pro Tyr Glu Leu Thr Pro Gly

725 730 735
Ala Thr Val Pro Phe Leu Leu Ser Leu Leu Cys Cys Val Arg Thr Thr
740 745 750
Lys Ala Ala Thr Tyr Tyr Glu Ala Ala Ala Tyr Leu Trp Asn Glu Gln
755 760 765
Gln Pro Leu Phe Trp Leu Gln Ala Leu Ile Pro Leu Ala Ala Leu Ile
770 775 780
Val Leu Cys Asn Cys Leu Lys Leu Leu Pro Cys Cys Cys Lys Thr Leu
785 790 795 800
Ala Phe Leu Ala Val Met Ser Ile Gly Ala His Thr Val Ser Ala Tyr
805 810 815
Glu His Val Thr Val Ile Pro Asn Thr Val Gly Val Pro Tyr Lys Thr
820 825 830
Leu Val Asn Arg Pro Gly Tyr Ser Pro Met Val Leu Glu Met Glu Leu
835 840 845
Gln Ser Val Thr Leu Glu Pro Thr Leu Ser Leu Asp Tyr Ile Thr Cys
850 855 860
Glu Tyr Lys Thr Val Ile Pro Ser Pro Tyr Val Lys Cys Cys Gly Thr
865 870 875 880
Ala Glu Cys Lys Asp Lys Ser Leu Pro Asp Tyr Ser Cys Lys Val Phe
885 890 895
Thr Gly Val Tyr Pro Phe Met Trp Gly Gly Ala Tyr Cys Phe Cys Asp
900 905 910
Ala Glu Asn Thr Gln Leu Ser Glu Ala His Val Glu Lys Ser Glu Ser
915 920 925
Cys Lys Thr Glu Phe Ala Ser Ala Tyr Arg Ala His Thr Ala Ser Ala
930 935 940
Ser Ala Lys Leu Arg Val Leu Tyr Gln Gly Asn Asn Ile Thr Val Ala
945 950 955 960
Ala Tyr Ala Asn Gly Asp His Ala Val Thr Val Lys Asp Ala Lys Phe
965 970 975
Val Val Gly Pro Met Ser Ser Ala Trp Thr Pro Phe Asp Asn Lys Ile
980 985 990
Val Val Tyr Lys Gly Asp Val Tyr Asn Met Asp Tyr Pro Pro Phe Gly
995 1000 1005
Ala Gly Arg Pro Gly Gln Phe Gly Asp Ile Gln Ser Arg Thr Pro
1010 1015 1020
Glu Ser Lys Asp Val Tyr Ala Asn Thr Gln Leu Val Leu Gln Arg
1025 1030 1035

Pro Ala Ala Gly Thr Val His Val Pro Tyr Ser Gln Ala Pro Ser
1040 1045 1050
Gly Phe Lys Tyr Trp Leu Lys Glu Arg Gly Ala Ser Leu Gln His
1055 1060 1065
Thr Ala Pro Phe Gly Cys Gln Ile Ala Thr Asn Pro Val Arg Ala
1070 1075 1080
Val Asn Cys Ala Val Gly Asn Ile Pro Ile Ser Ile Asp Ile Pro
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Asp Ala Ala Phe Thr Arg Val Val Asp Ala Pro Ser Val Thr Asp
1100 1105 1110
Met Ser Cys Glu Val Pro Ala Cys Thr His Ser Ser Asp Phe Gly
1115 1120 1125
Gly Val Ala Ile Ile Lys Tyr Thr Ala Ser Lys Lys Gly Lys Cys
1130 1135 1140
Ala Val His Ser Met Thr Asn Ala Val Thr Ile Arg Glu Ala Asp
1145 1150 1155
Val Glu Val Glu Gly Asn Ser Gln Leu Gln Ile Ser Phe Ser Thr
1160 1165 1170
Ala Leu Ala Ser Ala Glu Phe Arg Val Gln Val Cys Ser Thr Gln
1175 1180 1185
Val His Cys Ala Ala Ala Cys His Pro Pro Lys Asp His Ile Val
1190 1195 1200
Asn Tyr Pro Ala Ser His Thr Thr Leu Gly Val Gln Asp Ile Ser
1205 1210 1215
Thr Thr Ala Met Ser Trp Val Gln Lys Ile Thr Gly Gly Val Gly
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Gln Tyr Cys Asn Ser Ile
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Ser Pro Ser Thr Gln Tyr Cys Tyr Ser Ile Gln Gly Ser
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Ser Thr Gln Tyr Cys Asn Ser Ile Gly Gly Ser
20 25

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Pro Ser Thr Gln Tyr Cys Asn Ser Ile Gly Ser
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<400> 46

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35 40 45
Asn Lys Leu Thr Met Arg Ala Val Pro Gln Gln Lys Pro Arg Arg Asn
50 55 60
Arg Lys Asn Lys Lys Gln Arg Gln Lys Lys Gln Ala Pro Gln Asn Asp
65 70 75 80
Pro Lys Gln Lys Lys Gln Pro Pro Gln Lys Lys Pro Ala Gln Lys Lys
85 90 95
Lys Lys Pro Gly Arg Arg Glu Arg Met Cys Met Lys Ile Glu Asn Asp
100 105 110
Cys Ile Phe Glu Val Lys His Glu Gly Lys Val Met Gly Tyr Ala Cys
115 120 125
Leu Val Gly Asp Lys Val Met Lys Pro Ala His Val Lys Gly Thr Ile
130 135 140
Asp Asn Ala Asp Leu Ala Lys Leu Ala Phe Lys Arg Ser Ser Lys Tyr
145 150 155 160
Asp Leu Glu Cys Ala Gln Ile Pro Val His Met Lys Ser Asp Ala Ser
165 170 175
Lys Phe Thr His Glu Lys Pro Glu Gly Tyr Tyr Asn Trp His His Gly
180 185 190
Ala Val Gln Tyr Ser Gly Gly Arg Phe Thr Ile Pro Thr Gly Ala Gly
195 200 205
Lys Pro Gly Asp Ser Gly Arg Pro Ile Phe Asp Asn Lys Gly Arg Val
210 215 220
Val Ala Ile Val Leu Gly Gly Ala Asn Glu Gly Ala Arg Thr Ala Leu
225 230 235 240
Ser Val Val Thr Trp Asn Lys Asp Ile Val Thr Lys Ile Thr Pro Glu
245 250 255
Gly Ala Glu Glu Trp Ser Leu Ala Leu Pro Val Leu Cys Leu Leu Ala
260 265 270
Asn Thr Thr Phe Pro Cys Ser Gln Pro Pro Cys Thr Pro Cys Cys Tyr
275 280 285
Glu Lys Glu Pro Glu Ser Thr Leu Arg Met Leu Glu Asp Asn Val Met
290 295 300
Arg Pro Gly Tyr Tyr Gln Leu Leu Lys Ala Ser Leu Thr Cys Ser Pro
305 310 315 320
His Arg Gln Arg Arg Ser Thr Lys Asp Asn Phe Asn Val Tyr Lys Ala
325 330 335
Thr Arg Pro Tyr Leu Ala His Cys Pro Asp Cys Gly Glu Gly His Ser

340 345 350

Cys His Ser Pro Ile Ala Leu Glu Arg Ile Arg Asn Glu Ala Thr Asp
355 360 365

Gly Thr Leu Lys Ile Gln Val Ser Leu Gln Ile Gly Ile Lys Thr Asp
370 375 380

Asp Ser His Asp Trp Thr Lys Leu Arg Tyr Met Asp Ser His Thr Pro
385 390 395 400

Ala Asp Ala Glu Arg Ala Gly Leu Leu Val Arg Thr Ser Ala Pro Cys
405 410 415

Thr Ile Thr Gly Thr Met Gly His Phe Ile Leu Ala Arg Cys Pro Lys
420 425 430

Gly Glu Thr Leu Thr Val Gly Phe Thr Asp Ser Arg Lys Ile Ser His
435 440 445

Thr Cys Thr His Pro Phe His His Glu Pro Pro Val Ile Gly Arg Glu
450 455 460

Arg Phe His Ser Arg Pro Gln His Gly Lys Glu Leu Pro Cys Ser Thr
465 470 475 480

Tyr Val Gln Ser Thr Ala Ala Thr Ala Glu Glu Ile Glu Val His Met
485 490 495

Pro Pro Asp Thr Pro Asp Arg Thr Leu Met Thr Gln Gln Ser Gly Asn
500 505 510

Val Lys Ile Thr Val Asn Gly Gln Thr Val Arg Tyr Lys Cys Asn Cys
515 520 525

Gly Gly Ser Gly Gly Ile Tyr Asn Cys Glu Pro Ala Asn Pro Ser Glu
530 535 540

Lys Asn Ser Pro Ser Thr Gln Tyr Cys Tyr Ser Ile Gln Gly Ser Asn
545 550 555 560

Glu Gly Leu Thr Thr Thr Asp Lys Val Ile Asn Asn Cys Lys Ile Asp
565 570 575

Gln Cys His Ala Ala Val Thr Asn His Lys Asn Trp Gln Tyr Asn Ser
580 585 590

Pro Leu Val Pro Arg Asn Ala Glu Leu Gly Asp Arg Lys Gly Lys Ile
595 600 605

His Ile Pro Phe Pro Leu Ala Asn Val Thr Cys Arg Val Pro Lys Ala
610 615 620

Arg Asn Pro Thr Val Thr Tyr Gly Lys Asn Gln Val Thr Met Leu Leu
625 630 635 640

Tyr Pro Asp His Pro Thr Leu Leu Ser Tyr Arg Asn Met Gly Gln Glu
645 650 655

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

965 970 975

Asn Asn Ile Thr Val Ala Ala Tyr Ala Asn Gly Asp His Ala Val Thr

980 985 990

Val Lys Asp Ala Lys Phe Val Val Gly Pro Met Ser Ser Ala Trp Thr

995 1000 1005

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

1010 1015 1020

Met Asp Tyr Pro Pro Phe Gly Ala Gly Arg Pro Gly Gln Phe Gly

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Asp Ile Gln Ser Arg Thr Pro Glu Ser Lys Asp Val Tyr Ala Asn

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Thr Gln Leu Val Leu Gln Arg Pro Ala Ala Gly Thr Val His Val

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Ala Thr Asn Pro Val Arg Ala Val Asn Cys Ala Val Gly Asn Ile

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Pro Ile Ser Ile Asp Ile Pro Asp Ala Ala Phe Thr Arg Val Val

1115 1120 1125

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

1130 1135 1140

Thr His Ser Ser Asp Phe Gly Gly Val Ala Ile Ile Lys Tyr Thr

1145 1150 1155

Ala Ser Lys Lys Gly Lys Cys Ala Val His Ser Met Thr Asn Ala

1160 1165 1170

Val Thr Ile Arg Glu Ala Asp Val Glu Val Glu Gly Asn Ser Gln

1175 1180 1185

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

1190 1195 1200

Val Gln Val Cys Ser Thr Gln Val His Cys Ala Ala Ala Cys His

1205 1210 1215

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

1220 1225 1230

Leu Gly Val Gln Asp Ile Ser Thr Thr Ala Met Ser Trp Val Gln

1235 1240 1245

Lys Ile Thr Gly Gly Val Gly Leu Ile Val Ala Val Ala Ala Leu

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

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

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

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

Ile Arg Glu Ala Asp Val Glu Val Glu Gly Asn Ser Gln Leu Gln
1175 1180 1185
Ile Ser Phe Ser Thr Ala Leu Ala Ser Ala Glu Phe Arg Val Gln
1190 1195 1200
Val Cys Ser Thr Gln Val His Cys Ala Ala Ala Cys His Pro Pro
1205 1210 1215
Lys Asp His Ile Val Asn Tyr Pro Ala Ser His Thr Thr Leu Gly
1220 1225 1230
Val Gln Asp Ile Ser Thr Thr Ala Met Ser Trp Val Gln Lys Ile
1235 1240 1245
Thr Gly Gly Val Gly Leu Ile Val Ala Val Ala Ala Leu Ile Leu
1250 1255 1260
Ile Val Val Leu Cys Val Ser Phe Ser Arg His
1265 1270

原始 **TNF**α序列

RTPSDkpvahvvanpqaegqlqwlnrranallangvelrdnqlvvpseglyliysqvlfkgqgcp
sthvllthtisriavsyqtkvnllsaikspcqretpegaeakpwyepiylggvfqlekgdrlsaeinrp
dyldfaesgqvyfgiial

插入 **CHIKV** 中的修饰的 **TNF**α序列

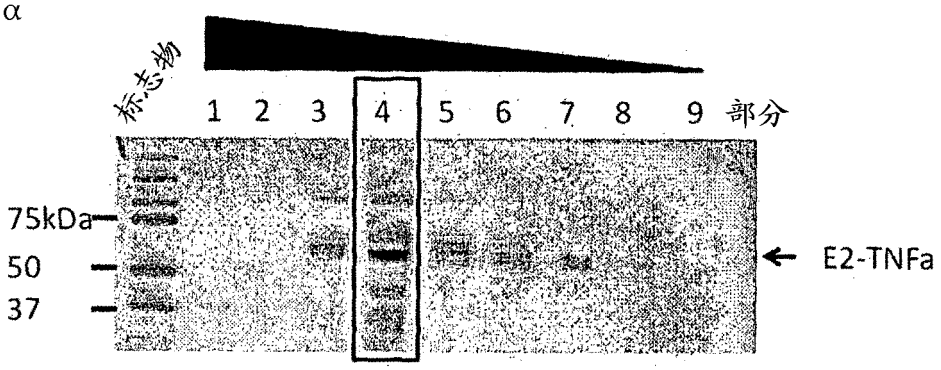
SGGkpvahvvanpqaegqlqwlnrranallangvelrdnqlvvpseglyliysqvlfkgqgcpst
hvllthtisriavsyqtkvnllsaikspcqretpegaeakpwyepiylggvfqlekgdrlsaeinrpdy
ldfaesgqvyfgiialTRGGS

编码修饰的 **TNF**α的核苷酸序列

Tccggaggtaagcctgtagcccatgttgtagcaaaccctcaagctgaggggcagctccagtggctgaaccgc
cgggccaatgccctcctggccaatggcgtggagctgagagataaccagctggtggtgccatcagagggcctg
tacctcatctactcccaggtcctcttcaagggccaaggctgcccctccacccatgtgctcctcacccacaccatc
agccgcatcgccgtctcctaccagaccaaggtcaacctcctctctgccatcaagagcccctgccagagggaga
ccccagagggggctgaggccaagccctggtatgagcccatctatctgggaggggtcttccagctggagaagg
gtgaccgactcagcgctgagatcaatcggcccgactatctcgactttgccgagtctgggcaggtctactttggg
atcattgccctgacgcgtggaggatcc

图 1

抗-TNFα



抗委内瑞拉马脑炎

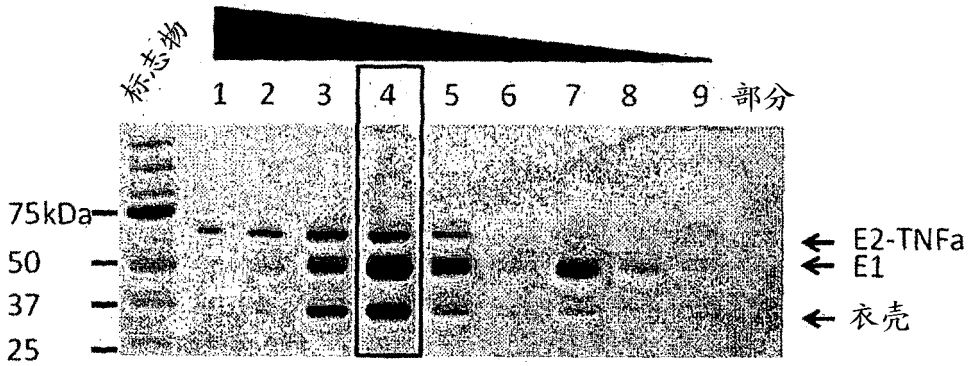


图 2

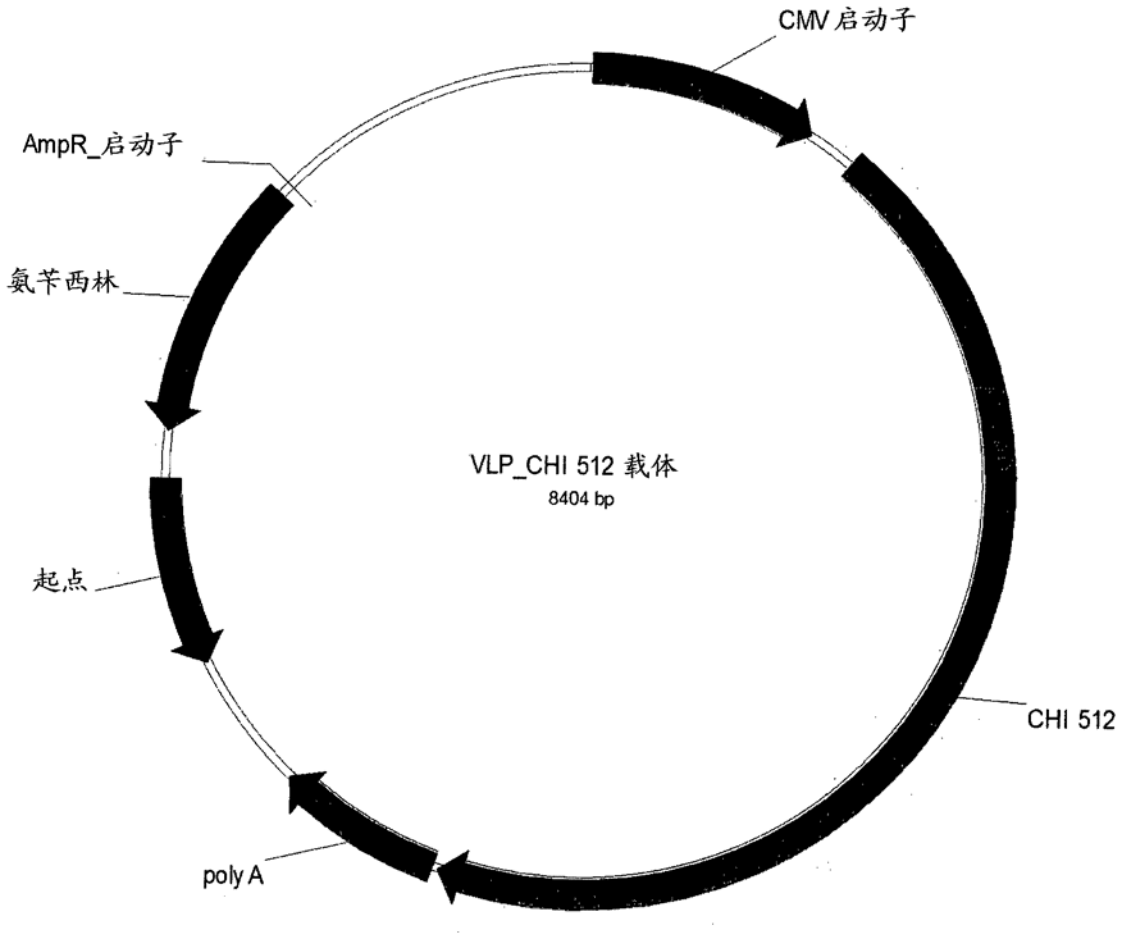


图 3

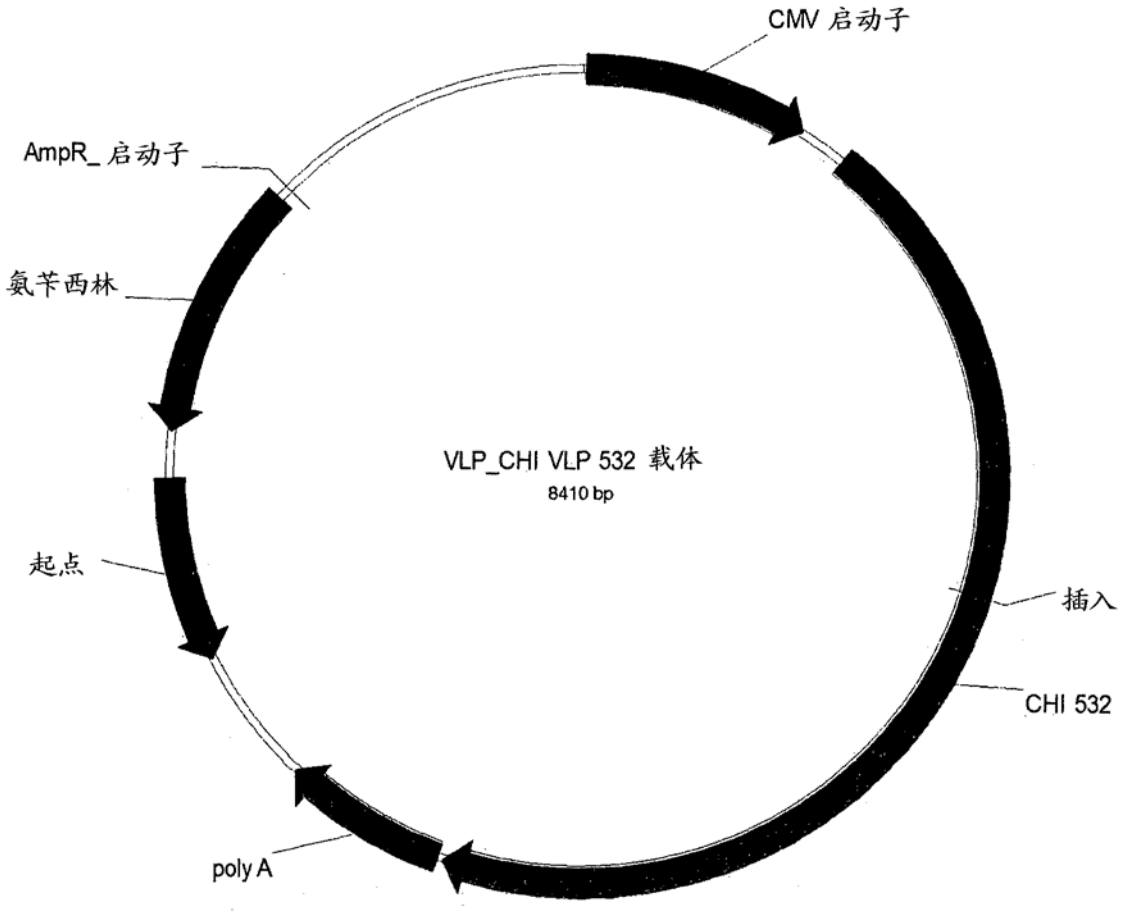

CMV 启动子
AmpR_ 启动子
氨苄西林
VLP_CHI VLP 532 载体
8410 bp
起点
插入
CHI 532
poly A

图 4

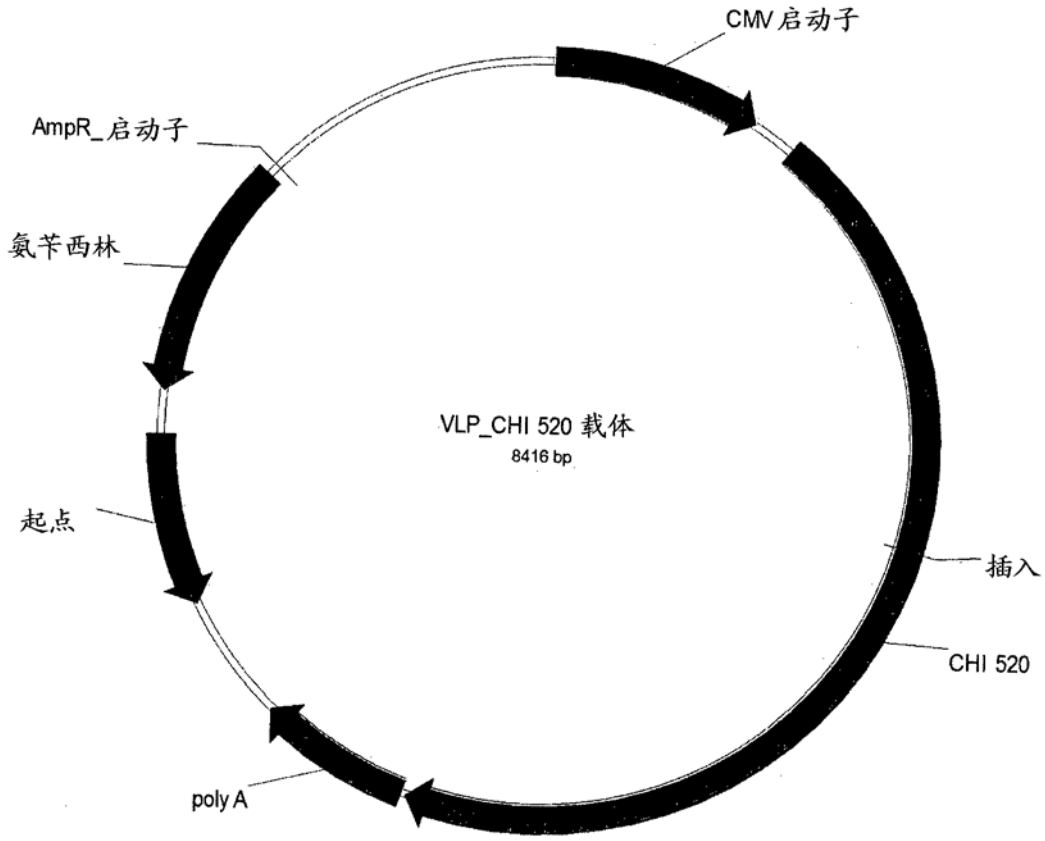


图 5

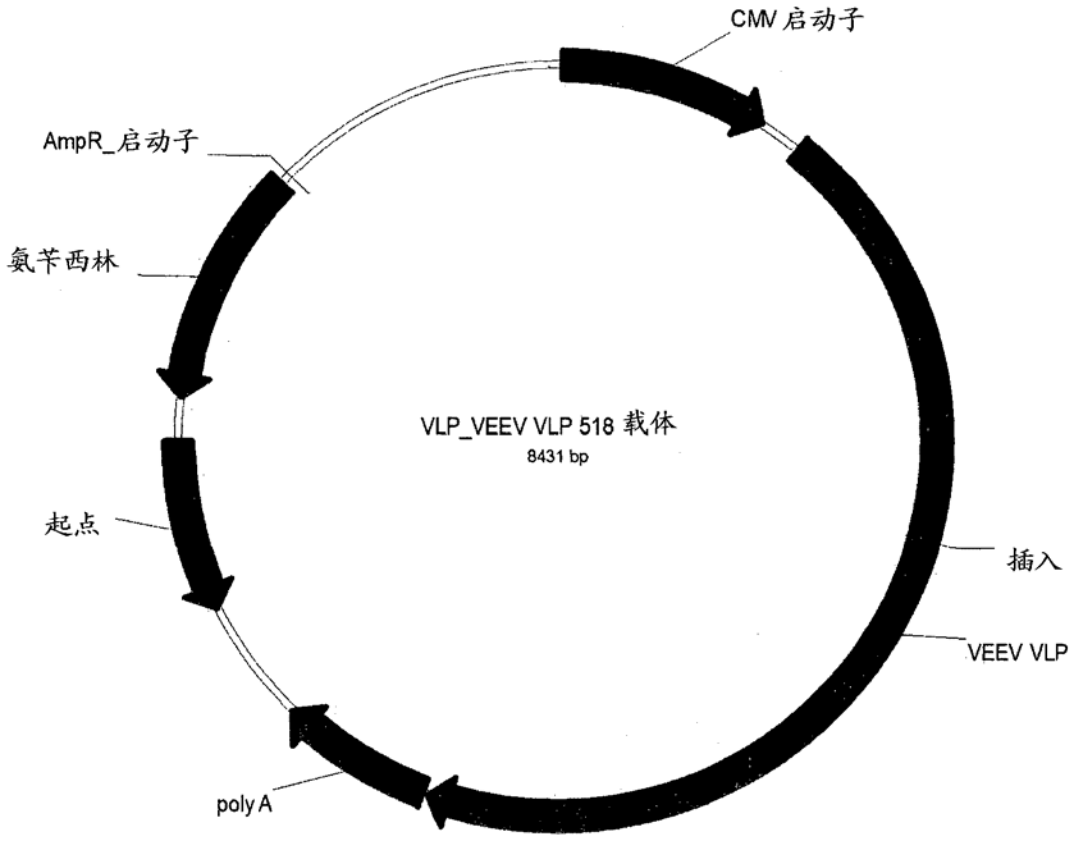

CMV 启动子
AmpR_启动子
氨苄西林
VLP_VEEV VLP 518 载体
8431 bp
起点
插入
VEEV VLP
poly A

图 6

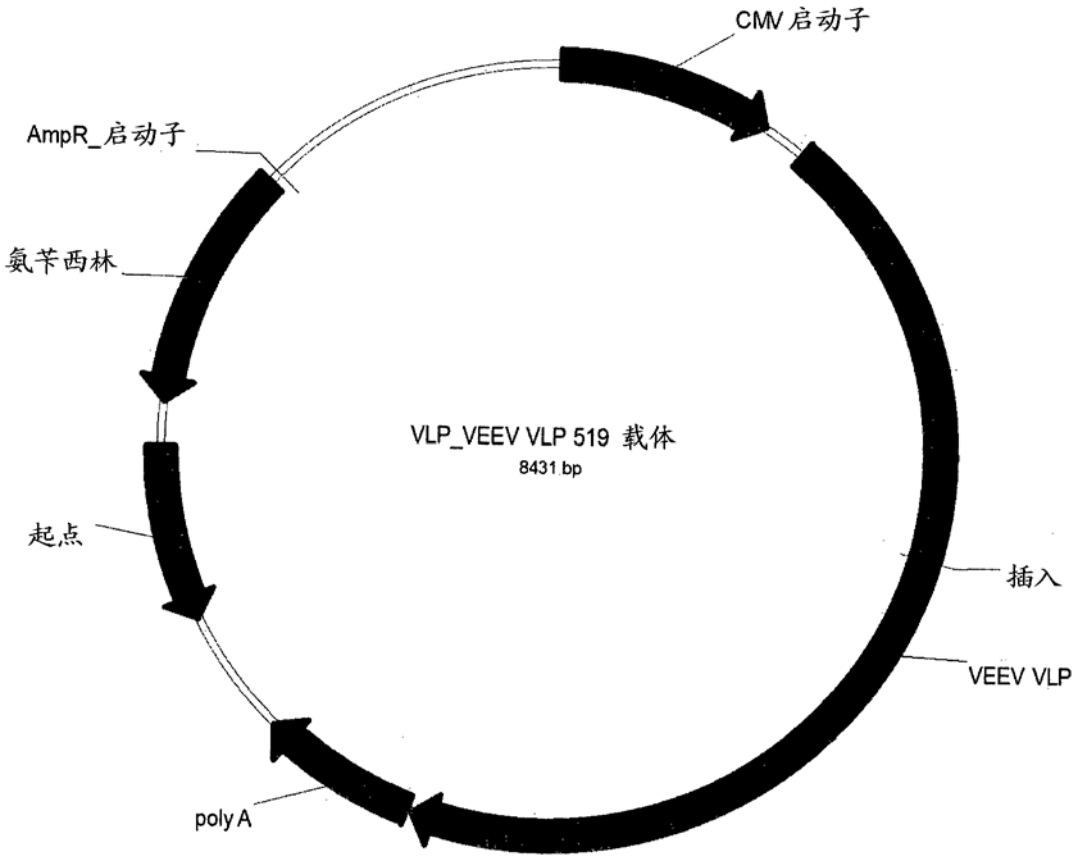

CMV 启动子
AmpR_启动子
氨苄西林
VLP_VEEV VLP 519 载体
8431 bp
起点
插入
VEEV VLP
poly A

图 7

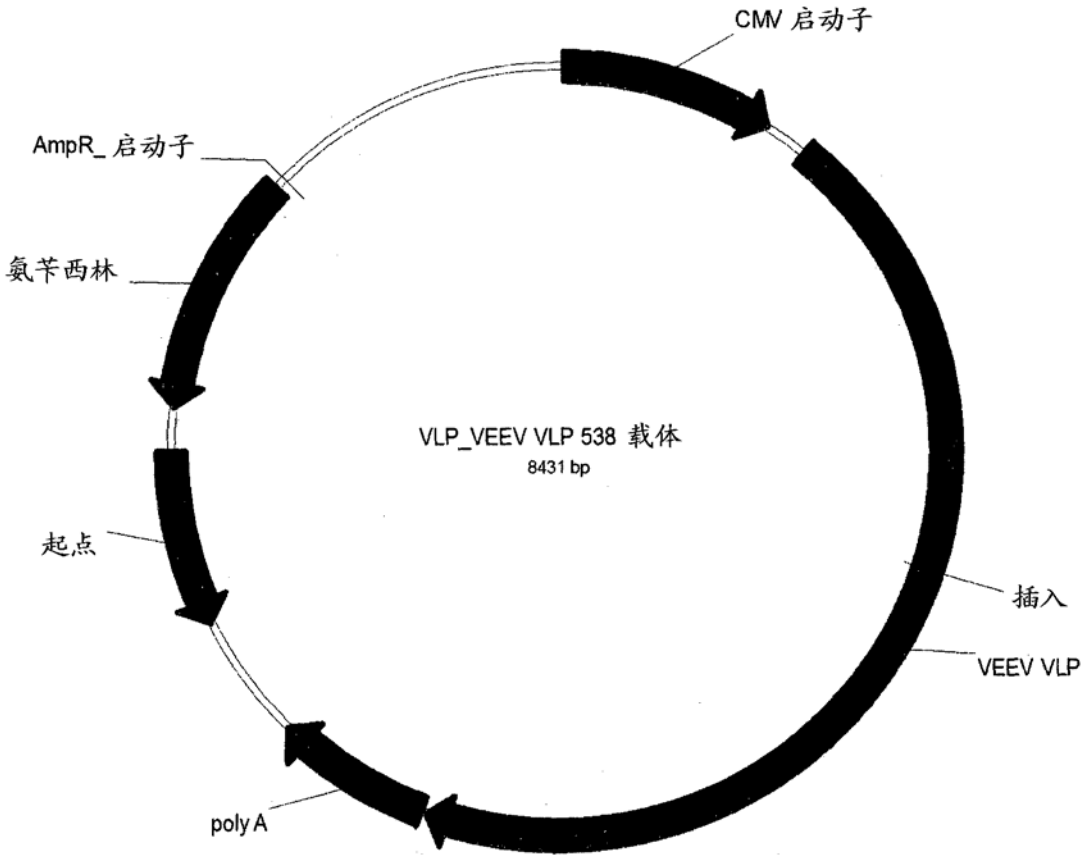

CMV 启动子
AmpR_ 启动子
氨苄西林
VLP_VEEV VLP 538 载体
8431 bp
起点
插入
VEEV VLP
poly A

图 8

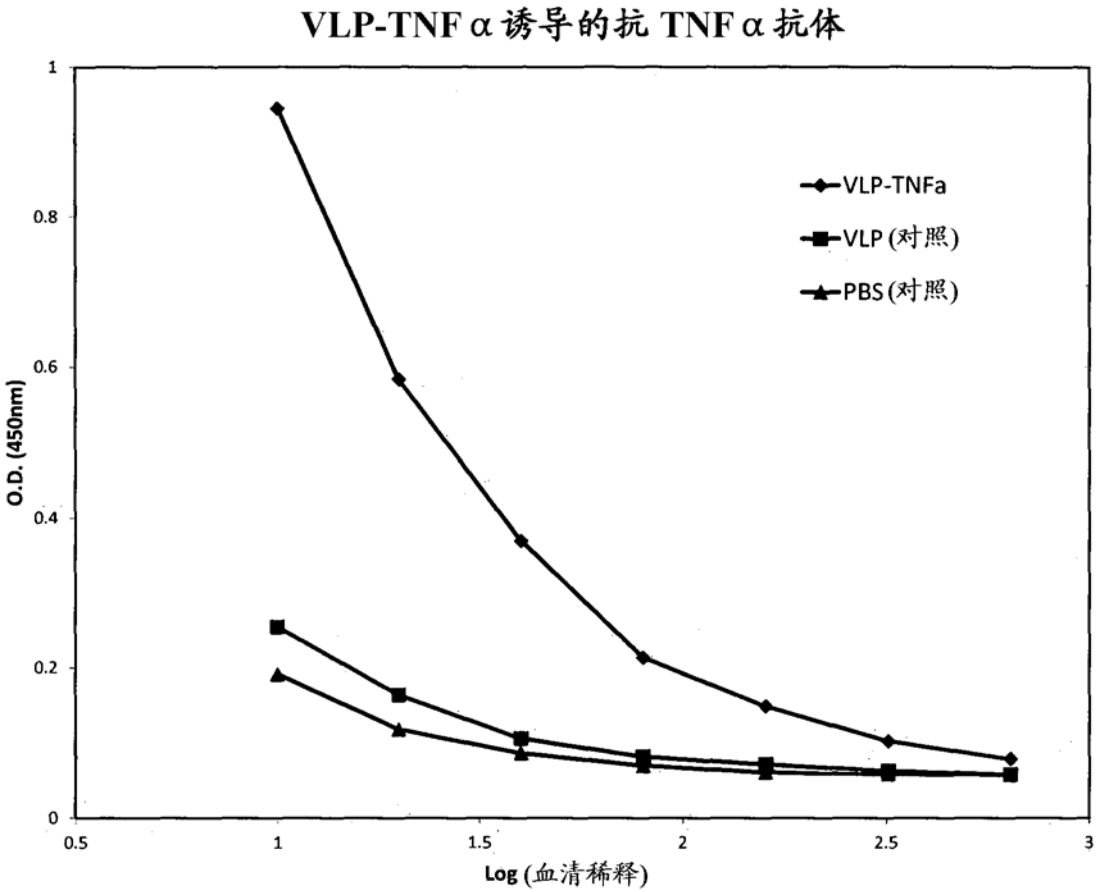

VLP-TNFα诱导的抗 TNFα抗体
O.D. (450nm)
Log (血清稀释)
VLP-TNFa
VLP (对照)
PBS (对照)
0
0.2
0.4
0.6
0.8
1
0.5
1
1.5
2
2.5
3

图 9

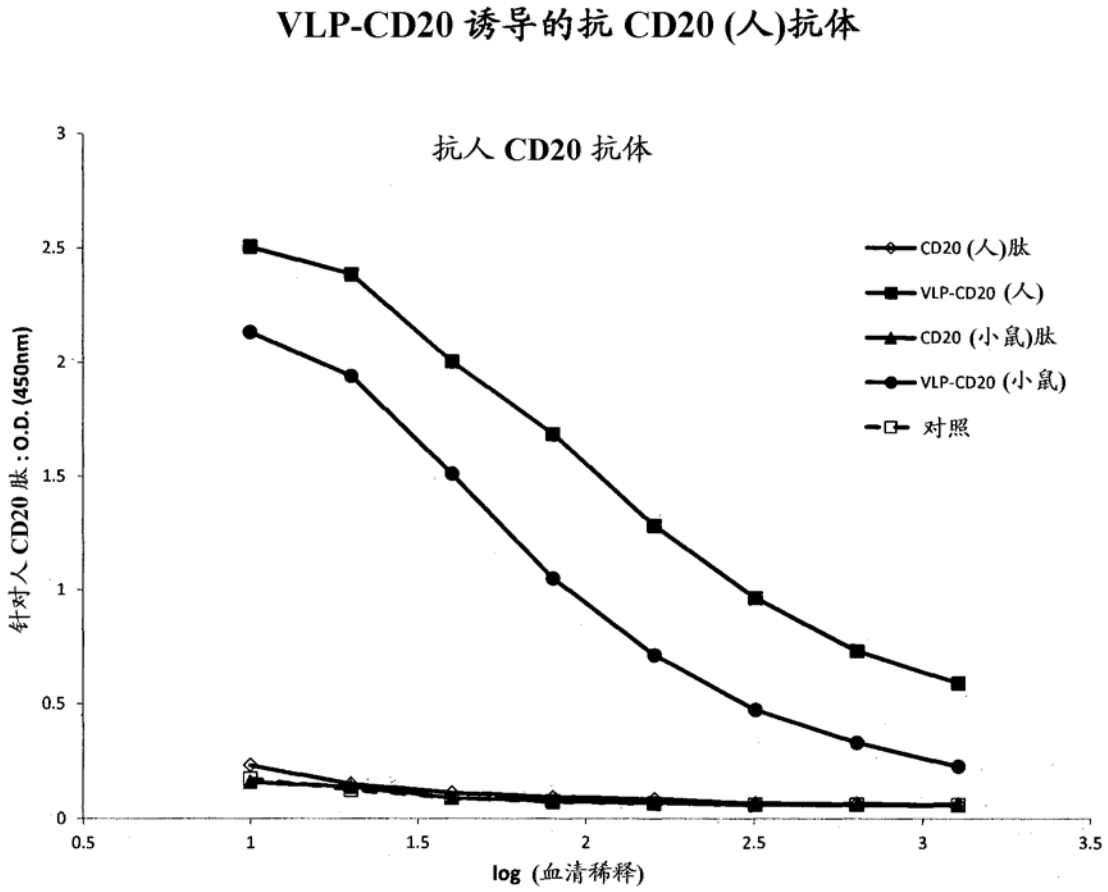

VLP-CD20 诱导的抗 CD20 (人)抗体
抗人 CD20 抗体
针对人 CD20 肽 : O.D. (450nm)
log (血清稀释)
CD20 (人)肽
VLP-CD20 (人)
CD20 (小鼠)肽
VLP-CD20 (小鼠)
对照
3
2.5
2
1.5
1
0.5
0
0.5
1
1.5
2
2.5
3
3.5

图 10

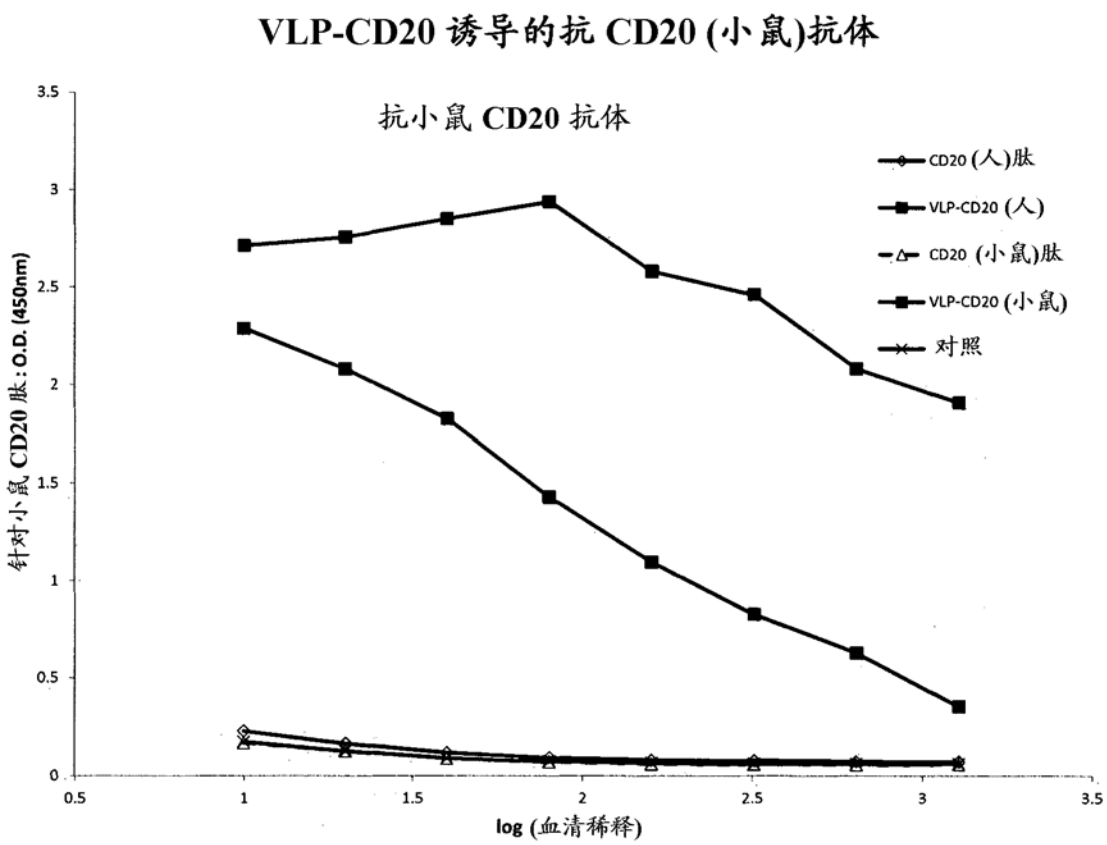

VLP-CD20 诱导的抗 CD20 (小鼠)抗体
抗小鼠 CD20 抗体
CD20 (人)肽
VLP-CD20 (人)
CD20 (小鼠)肽
VLP-CD20 (小鼠)
对照
针对小鼠 CD20 肽: O.D. (450nm)
log (血清稀释)
0
0.5
1
1.5
2
2.5
3
3.5

图 11