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(54)发明名称

腺病毒载体及其用途

(57)摘要

本文提供了嵌合腺病毒载体。所提供的嵌合腺病毒载体可用于在受试者中诱导保护性免疫应答。

1. 一种腺病毒载体,该腺病毒载体包含编码六邻体多肽的核酸序列,该六邻体多肽包括含有选自SEQ ID NO:1或SEQ ID NO:2的氨基酸序列的含六邻体高变区多肽。

2. 如权利要求1所述的腺病毒载体,其中该六邻体多肽序列包含SEQ ID NO:3或SEQ ID NO:4。

3. 如权利要求1-2中任一项所述的腺病毒载体,其中该腺病毒载体进一步包含E1缺失。

4. 如权利要求1-3中任一项所述的腺病毒载体,其中该腺病毒载体进一步包含E3缺失。

5. 如权利要求1-4中任一项所述的腺病毒载体,其中该腺病毒载体进一步包含人腺病毒-5 (HAdV-5) E4 orf6。

6. 如权利要求1-5中任一项所述的腺病毒载体,其中该腺病毒载体包含选自SEQ ID NO:5或SEQ ID NO:6的核酸序列。

7. 如权利要求1-6中任一项所述的腺病毒载体,其中该腺病毒载体进一步包含至少一个转基因。

8. 如权利要求1-7中任一项所述的腺病毒载体,其中该转基因位于E1缺失处、E3缺失处、和/或右反向末端重复序列(rITR)附近。

9. 如权利要求1-8中任一项所述的腺病毒载体,其中该腺病毒载体包含来自人腺病毒-26 (Ad26)的一种或多种核酸序列。

10. 一种重组细胞,该重组细胞包含如权利要求1-9中任一项所述的腺病毒载体。

11. 一种生产腺病毒载体的方法,该方法包括:

(a) 使如权利要求10所述的重组细胞在用于生产该腺病毒载体的条件下生长;以及

(b) 从该重组细胞中分离该腺病毒载体。

12. 一种免疫原性组合物,该免疫原性组合物包含如权利要求1-9中任一项所述的腺病毒载体、以及药学上可接受的载剂。

13. 一种在有需要的受试者中诱导免疫应答的方法,该方法包括向该受试者施用如权利要求12所述的免疫原性组合物。

14. 一种生产免疫原性组合物的方法,该方法包括将如权利要求1-9中任一项所述的腺病毒载体与药学上可接受的载剂组合。

腺病毒载体及其用途

技术领域

[0001] 本发明涉及生物技术。更具体地说,涉及腺病毒载体诸如复制缺陷型腺病毒载体在宿主中递送抗原并引发免疫应答的领域和用途。

背景技术

[0002] 重组腺病毒载体广泛应用于基因治疗应用和疫苗。基于AdV-5载体的疫苗已显示出在多种动物模型中引发强有力的和保护性的免疫应答(参见例如W02001/02607;W02002/22080;Shiver等人,Nature[自然]415:331(2002);Letvin等人,Ann.Rev.Immunol.[免疫学年鉴]20:73(2002);Shiver和Emeni,Ann.Rev.Med.[医学年鉴]55:355(2004))。然而,基于重组AdV-5载体的疫苗的效用将可能受到人群中AdV-5特异性中和抗体(NAb)的高血清阳性率的限制。在小鼠、恒河猴和人的研究中,抗AdV-5免疫的存在已经显示出基本上抑制了基于AdV-5的疫苗的免疫原性。

[0003] 一种在先前已被最常见的人腺病毒(例如AdV-5)感染或治疗的个体中规避预先存在的免疫性的有前景的策略涉及开发来自腺病毒血清型的重组载体,这些腺病毒血清型未遇到这种预先存在的免疫性。一种这样的策略基于嵌合腺病毒的使用,这些嵌合腺病毒包括用来自具有低(或无)血清阳性率的腺病毒的衣壳蛋白序列(例如,六邻体蛋白序列和/或纤维蛋白序列)替换天然衣壳蛋白序列(例如,六邻体蛋白序列和/或纤维蛋白序列)。

[0004] 因此,本领域需要可大量生产的、在宿主中不会遇到预先存在的免疫、但仍具有免疫原性并能够诱导针对由插入载体中的异源核酸编码的抗原的强烈免疫应答的替代性腺病毒载体。

发明内容

[0005] 本文提供了腺病毒载体。该腺病毒载体可以包含编码六邻体多肽的核酸序列,该六邻体多肽包括含有选自SEQ ID NO:1或SEQ ID NO:2的氨基酸序列的含六邻体高变区多肽。在某些实施例中,该腺病毒载体可以包含含有SEQ ID NO:3或SEQ ID NO:4的六邻体多肽序列。

[0006] 在某些实施例中,该腺病毒载体进一步包含E1缺失。在某些实施例中,该腺病毒载体进一步包含E3缺失。该腺病毒载体可以进一步包含人腺病毒-5(HAdV-5)E4 orf6。该腺病毒载体可以例如包含选自SEQ ID NO:5或SEQ ID NO:6的核酸序列。

[0007] 在某些实施例中,该腺病毒载体进一步包含至少一个转基因。在某些实施例中,该至少一个转基因位于E1缺失处、E3缺失处、和/或右反向末端重复序列(rITR)附近。

[0008] 在某些实施例中,该腺病毒载体包含来自人腺病毒-26(Ad26)的一种或多种核酸序列。

[0009] 还提供了包含本文所述的腺病毒载体的重组细胞。还提供了产生这些腺病毒载体的方法。这些方法包括(a)使本文所述的重组细胞在用于生产该腺病毒载体的条件下生长;以及(b)从该重组细胞中分离该腺病毒载体。

[0010] 还提供了包含本文所述的腺病毒载体和药学上可接受的载剂的免疫原性组合物。还提供了在有需要的受试者中诱导免疫应答的方法。这些方法包括向该受试者施用本文所述的免疫原性组合物。还提供了生产免疫原性组合物的方法,这些方法包括将本文所述的腺病毒载体与药学上可接受的载剂组合。

附图说明

[0011] 当结合附图阅读时,将更好地理解前述发明内容以及本申请的优选实施例的以下详细描述。然而,应当理解,本申请不限于附图中所示的精确实施例。

[0012] 图1显示了本文所述的六邻体嵌合载体的六邻体序列替换的示意图。图1A显示示意图,示出了五个六邻体基因区段(灰色条)和七个短高变区(HVR)(黑色条)在全长HAdV-26六邻体基因(空白条)中的位置,这些HVR之前在HAdV-5与HAdV-48六邻体之间交换以生成六邻体嵌合HAdV-5载体Ad5HVR48(1-7)(Roberts等人,Nature[自然]441:239-43(2006))。图1B显示HAdV-26、PtroAdV-1、PtroAdV-12和PtroAdV-13的六邻体多肽序列的部分比对。灰色条对应于在HAdV-26与PtroAdV-1、PtroAdV-12或PtroAdV-13之间交换的五个六邻体基因区段。黑色条表示与在HAdV-5与HAdV-48之间交换的上述先前指定的HVR对应的序列。

[0013] 图2显示嵌合pAd26载体的示意图。图2A显示pAd26.HVRPtr12.luc(SEQ ID NO:21)的一般特征的示意图。图2B显示pAd26.HVRPtr13.luc(SEQ ID NO:22)的一般特征的示意图。

[0014] 图3显示pAd26.ApoA1.RSVF-2A-GLuc(SEQ ID NO:29)的一般特征的示意图。

[0015] 图4显示用于生成腺病毒载体Ad26HVRPtr12.RSVF-2A-GLuc和Ad26HVRPtr13.RSVF-2A-GLuc(在补充E1的细胞中)的同源重组策略的示意图。

[0016] 图5显示由Ad26HVRPtr12.FLuc和Ad26HVRPtr13.FLuc诱导的细胞和体液免疫应答。图5A显示了实验设置。图5B显示由Ad26.FLuc、Ad26HVRPtr12.FLuc和Ad26HVRPtr13.FLuc诱导的针对载体编码的抗原(即Fluc,萤火虫萤光素酶)的免疫反应的图,如通过干扰素 γ (IFN- γ)ELISPOT分析所测定的。y轴显示每 10^6 个脾细胞的点形成单位(SFU)的数量,虚线表示培养基刺激的95%百分位数。

[0017] 图6显示由Ad26HVRPtr12.RSVF-2A-GLuc和Ad26HVRPtr13.RSVF-2A-GLuc诱导的细胞和体液免疫应答。图6A显示实验设置。图6B显示在用Ad26.RSVF-2A-GLuc、Ad26HVRPtr12.RSVF-2A-GLuc和Ad26HVRPtr13.RSVF-2A-GLuc免疫后八周时进行的RSV A2病毒中和试验(VNA)的结果。图6C显示由Ad26.RSVF-2A-GLuc、Ad26HVRPtr12.RSVF-2A-GLuc和Ad26HVRPtr13.RSVF-2A-GLuc诱导的针对载体编码的抗原RSV F的细胞免疫应答,如通过IFN- γ ELISPOT分析所测定的。y轴显示每 10^6 个脾细胞的点形成单位(SFU)的数量,虚线表示培养基刺激的95%百分位数。图6D显示由免疫后8周免疫小鼠血清中的Ad26.RSVF-2A-GLuc、Ad26HVRPtr12.RSVF-2A-GLuc和Ad26HVRPtr13.RSVF-2A-GLuc诱导的RSVF特异性IgG结合抗体的图。该图描绘以终点滴度(\log_{10})计算的IgG ELISA滴度。

[0018] 图7显示在用腺病毒载体Ad35、Ad26、Ad5、Ad4、Ad26HVRPtr12和Ad26HVRPtr13免疫的小鼠中诱导的同源和异源腺病毒中和滴度。

[0019] 图8显示Ad26、Ad5、Ad26HVRPtr12和Ad26HVRPtr13在200个来自年龄为18-55岁、生活在美国(US)和欧盟(EU)的成人的人类群组血清样品中的血清阳性率。将这些血清中针对

每种载体测得的中和滴度分成四个类别(<16(无中和)、16至300、300至1,000、1000至4000和>4000),如在所示的图表中表示的。

[0020] 图9显示新型衣壳嵌合载体AdHVRPtr12.FLuc和Ad26HVRPtr13.FLuc在生产细胞系sPER.C6中的生产率。

具体实施方式

[0021] 本披露至少部分地基于包含人骨架且包含嵌合六邻体多肽序列或纤维多肽序列中的至少一者的嵌合腺病毒载体的创建。腺病毒载体能够引起免疫应答,同时保持低血清阳性率。这些腺病毒载体可以被配制成药苗并用于诱导针对感兴趣的特异性抗原的保护性免疫。

[0022] 在背景技术和整个说明书中引用或描述了各种出版物、文章和专利;这些参考文献各自通过援引以其全文并入本文。包括在本说明书中的对文件、法案、材料、装置、制品等的讨论用于提供本发明的背景的目的。这种讨论不承认任何或所有这些事项形成关于所披露或要求保护的发明的现有技术的一部分。

[0023] 除非另外定义,否则本文所用的所有科学和技术术语具有如本发明所属领域的普通技术人员通常理解的含义。否则,本文所用的某些术语具有说明书中阐述的含义。

[0024] 必须注意,除非上下文另外明确规定,否则如本文和所附权利要求中所用,单数形式“一个/一种”和“该”包括复数指示物。

[0025] 除非另有说明,否则任何数值,诸如本文所述的浓度或浓度范围,应被理解为在所有情况下都被术语“约”修饰。因此,数值典型地包括列举值 $\pm 10\%$ 。例如,1mg/mL的浓度包括0.9mg/mL至1.1mg/mL。同样地,1%至10%(w/v)的浓度范围包括0.9%(w/v)至11%(w/v)。如本文所用,数值范围的使用明确地包括所有可能的子范围,该范围内的所有单个数值,包括值的这些范围内的整数和分数,除非上下文另有明确指示。

[0026] 除非另外指明,否则在一系列要素前面的术语“至少”应被理解为指该系列中的每一个要素。本领域技术人员将认识到或能够仅使用常规实验便确定本文所述的本发明的具体实施例的许多等同方案。这些等同方案也旨在包括在本发明中。

[0027] 如本文所用,术语“包括”、“包含”、“具有”、“含有”或它们的任何其他变化,将被理解为意味着包括所述整数或整数组,而不排除任何其他整数或整数组,并且旨在是非排他性的或开放性的。例如,包含元件的清单的组合物、混合物、工艺、方法、物品或设备不一定限制于仅那些元件,而可以包括不是此类组合物、混合物、工艺、方法、物品或设备明确列出的或固有的其他元件。此外,除非明确地说明是相反的,否则“或”是指包括在内的或,而不是指排他性的或。例如,以下项中的任一者满足条件A或B:A是真(或存在)并且B是假(或不存在的),A是假(或不存在的)并且B是真(或存在的),以及A和B二者都是真(或存在的)。

[0028] 如本文所用,多个引用的要素之间的连接术语“和/或”应被理解为涵盖单独的和组合的选项两者。例如,当两种要素由和/或连接时,第一选项是指在不具有第二要素的情况下第一要素的应用。第二选项是指在不具有第一要素的情况下第二要素的应用。第三选项是指第一要素和第二要素一起的应用。这些选项中的任何一个应被理解为属于该含义之内,并且因此满足如本文所用的术语“和/或”的要求。这些选项中的多于一个的同时应用也应被理解为属于该含义之内,并且因此满足术语“和/或”的要求。

[0029] 如本文所用,贯穿说明书和权利要求书所用的术语“由……组成”指示包括任何列举的整数或整数组,但不能将另外的整数或整数组添加至指定的方法、结构或组合物。

[0030] 如本文所用,贯穿说明书和权利要求书所用的术语“基本上由……组成”指示包括任何列举的整数或整数组,并且任选地包括不实质性改变所指定的方法、结构或组合物的基本或新颖特性的任何列举的整数或整数组。参见M.P.E.P. §2111.03。

[0031] 如本文所用,“受试者”是指任何动物,优选哺乳动物,最优选人,其将或已经通过根据本发明实施例的方法接种。如本文所用的术语“哺乳动物”涵盖任何哺乳动物。哺乳动物的实例包括但不限于牛、马、羊、猪、猫、狗、小鼠、大鼠、兔、豚鼠、猴、人等,更优选地是人。

[0032] 词语“右”、“左”、“下”和“上”表示所参考的附图中的方向。

[0033] 应当理解的是,当提及优选的发明的组分的规格或特征时,在此使用的术语“约”、“大约”、“总体上”、“基本上”、以及类似术语,指示描述的规格/特征不具有严格的界限或参数,并且并不从其排除功能上相同或相似的微小变化,如本领域普通技术人员将理解的那样。在最低程度上,包括数值参数的此类引用将包括将不改变最低有效位数的变化,使用本领域接受的数学的和产业的原理(例如化整误差、测量误差或其他系统误差、制造公差等)。

[0034] 在两个或更多个核酸或多肽序列(例如六邻体和纤维多肽以及编码它们的多核苷酸)的上下文中,术语“相同的”或“同一性”百分比是指当进行比较和比对以获得最大对应性时,两个或更多个序列或子序列是相同的或具有指定百分比的相同氨基酸残基或核苷酸,如使用以下序列比较算法之一或通过目视检查所测量的。

[0035] 对于序列比较,典型地,一个序列作为参考序列,测试序列与其进行比较。当使用序列比较算法时,将测试序列和参考序列输入计算机;如果需要,指定子序列坐标;以及指定序列算法程序参数。然后,序列比较算法基于指定的程序参数计算测试序列相对于参考序列的序列同一性百分比。

[0036] 用于比较的序列的最佳比对可以例如通过Smith&Waterman, Adv. Appl. Math. [应用数学进展]2:482 (1981) 的局部同源性算法、通过Needleman&Wunsch, J. Mol. Biol. [分子生物学杂志]48:443 (1970) 的同源性比对算法、通过Pearson&Lipman, Proc. Nat'l Acad. Sci. USA [美国国家科学院院刊]85:2444 (1988) 的类似性搜索方法、通过这些算法的计算机化实现形式(GAP、BESTFIT、FASTA和TFASTA,威斯康星遗传学软件包(Wisconsin Genetics Software Package),遗传学计算机课题组(Genetics Computer Group),威斯康星州麦迪逊科学大道575号(575 Science Dr., Madison, WI))、或通过目视检查(一般参见Current Protocols in Molecular Biology [分子生物学实验室指南], F.M. Ausubel 等人编, Current Protocols [实验室指南], 格林出版联合公司(Greene Publishing Associates, Inc.) 和约翰威利父子公司(John Wiley & Sons, Inc.) 的合资公司, (1995年增刊)(Ausubel)) 来进行。

[0037] 适于确定序列同一性百分比和序列相似性百分比的算法的实例是BLAST和BLAST 2.0算法,这些算法描述于Altschul等人(1990) J. Mol. Biol. [分子生物学杂志]215:403-410和Altschul等人(1977) Nucleic Acids Res. [核酸研究]25:3389-3402。用于进行BLAST分析的软件可通过国家生物技术信息中心(National Center for Biotechnology Information) 公开获得。该算法涉及首先通过鉴定查询序列中长度为W的短字来鉴定高分序列对(HSP), 当与数据库序列中相同长度的字进行比对时,这些序列对匹配或满足一些

正值阈值得分 T 。 T 被称为邻近字分值阈值(Altschul等人,同上)。这些初始的邻近字命中将作为种子,以用于启动搜索以发现包含它们的更长的HSP。然后,只要累积比对得分可以增加,字命中就沿着每个序列在两个方向上延伸。

[0038] 对于核苷酸序列,累积得分使用参数 M (一对匹配残基的奖励得分;总是 >0)和 N (错配残基的罚分;总是 <0)来计算。对于氨基酸序列,使用评分矩阵来计算累积得分。当存在以下情况时,停止字命中在每个方向上的扩展:累积比对得分从其最大获得值下降数量 X ;由于一个或多个负得分残基比对的累积,累积得分变为零或更低;或者到达任一序列的末端。BLAST算法参数 W 、 T 和 X 决定比对的灵敏度和速度。BLASTN程序(用于核苷酸序列)使用11的字长(W)、10的期望值(E)、 $M=5$ 、 $N=-4$ 以及两条链的比较作为默认值。对于氨基酸序列,BLASTP程序使用3的字长(W)、10的期望值(E)和BLOSUM62评分矩阵作为默认值(参见Henikoff&Henikoff,Proc.Natl.Acad.Sci.USA[美国国家科学院院刊]89:10915(1989))。

[0039] 除了计算序列同一性百分比之外,BLAST算法还进行两个序列之间相似性的统计学分析(参见例如Karlin&Altschul,Proc.Nat'l.Acad.Sci.USA[美国国家科学院院刊]90:5873-5787(1993))。BLAST算法提供的相似性的一种量度是最小和概率($P(N)$),其提供两个核苷酸或氨基酸序列之间偶然发生匹配的概率的指示。例如,如果在测试核酸与参考核酸的比较中最小和概率小于约0.1,更优选小于约0.01,最优选小于约0.001,则认为该核酸与参考序列相似。

[0040] 两个核酸序列或多肽基本上相同的另一个指示是由第一个核酸编码的多肽与由第二个核酸编码的多肽具有免疫交叉反应性,如下所述。因此,例如,如果某多肽和第二多肽仅因保守取代而不同,则两种肽通常基本上相同。两个核酸序列基本上相同的另一个指示是两个分子在严格条件下彼此杂交,如下所述。

[0041] 如本文所用,术语“保护性免疫”或“保护性免疫应答”是指该接种疫苗的受试者能够控制对其进行了疫苗接种的致病因子的感染。致病因子可以是例如抗原基因产物或抗原蛋白,或其片段。通常,已经出现了“保护性免疫应答”的受试者仅出现轻度至中度临床症状或根本没有症状。通常,对某种因子具有“保护性免疫应答”或“保护性免疫”的受试者不会由于所述因子的感染而死亡。

[0042] 术语“佐剂”定义为一种或多种引起免疫系统刺激的物质。在此上下文中,使用佐剂来增强对本发明的腺病毒载体的免疫应答。

[0043] 如本文所用,术语“抗原基因产物或其片段”或“抗原蛋白”可包括细菌、病毒、寄生虫、或真菌蛋白、或其片段。优选地,抗原性蛋白或抗原性基因产物能够在宿主中产生保护性免疫应答,例如诱导针对疾病或感染(例如细菌、病毒、寄生虫或真菌疾病或感染)的免疫应答,和/或在受试者中产生针对疾病或感染的免疫(即,接种疫苗),其保护受试者抵抗疾病或感染。

[0044] 如本文所用,术语“嵌合”是指包含两种或更多种通常不关联在一起的基因、核酸、蛋白质、肽或多肽的基因、核酸、蛋白质、肽或多肽。“嵌合”基因、核酸或蛋白质可以是两种或更多种不相关序列(例如,编码两种或更多种不同蛋白质的两种或更多种不同核酸)之间的融合体。“嵌合”基因、核酸或蛋白质可以是两种或更多种相关序列之间的融合体(例如,核酸编码相同的蛋白质,然而,核酸来自不同的来源材料,即,一种核酸是人的,另一种核酸是猿猴的)。

[0045] 腺病毒载体

[0046] 暴露于某些腺病毒已经导致针对某些腺病毒血清型的免疫应答,这可以影响腺病毒载体的功效。因为人腺病毒感染在人类中是常见的,所以在人群中抗人腺病毒的中和抗体的流行率高。预计个体中存在这种中和抗体会降低基于人腺病毒骨架的基因转移载体的功效。一种避免功效降低的方法是替换腺病毒衣壳蛋白上的表位,这些表位是中和抗体的靶标。衣壳蛋白上的靶序列可以用来自其他腺病毒(例如,猿猴腺病毒)的蛋白序列替换,这些腺病毒具有低流行性,并因此而言,针对这些腺病毒的中和抗体在人群中很少。

[0047] “衣壳蛋白”是指腺病毒衣壳上的蛋白或其功能片段或衍生物,其参与确定特定腺病毒的血清型和/或向性。衣壳蛋白典型地包括纤维蛋白、五邻体蛋白和/或六邻体蛋白。在某些实施例中,衣壳蛋白是腺病毒的完整或全长衣壳蛋白。在其他实施例中,衣壳蛋白是腺病毒的全长衣壳蛋白的片段或衍生物。在某些实施例中,由本发明的腺病毒载体编码的六邻体、五邻体和纤维具有相同或不同的腺病毒背景。

[0048] “六邻体多肽”指腺病毒六邻体外壳蛋白、其功能片段和衍生物。

[0049] “纤维多肽”指腺病毒纤维蛋白、其功能片段和衍生物。

[0050] 针对腺病毒的中和抗体的一个靶标是主要外壳蛋白,即六邻体蛋白。用来自人群中罕见的腺病毒的六邻体蛋白或六邻体蛋白内的可变序列,替换六邻体蛋白或六邻体蛋白内的定义血清型并与中和抗体结合的可变序列,可以允许构建对通常在人在发现的抗体的中和不太敏感的腺病毒载体。

[0051] 六邻体高变区(HVR)是六邻体多肽的表示不同腺病毒血清型中最高的变异性的区域。通常,这些HVR被认为与六邻体蛋白三聚体的溶剂暴露表面相对应(在完整的病毒颗粒的情况下),并且相关地,预期它们是抗体介导的腺病毒中和的重要决定因素(Roberts等人,Nature[自然]441:239-43(2006))。因此,将给定的腺病毒载体的六邻体HVR用在人类中具有低(或无)血清阳性率的腺病毒的六邻体HVR替换是在人类目标群体中规避预先存在的抗载体体液免疫的一种可能手段。因此,已经有许多研究探索六邻体嵌合性的概念,主要涉及基于HAdV-5的载体内的六邻体序列替换(Roy等人,J Virol.[病毒学杂志]72:6875-9(1998);Gall等人,J Virol.[病毒学杂志]72:10260-4(1998);Youil等人,Hum.Gene Ther.[人类基因治疗]13:311-20(2002);Wu等人J Virol.[病毒学杂志]76:12775-82(2002);Roy等人,Virology.[病毒学]333:207-14(2005);Roberts等人,Nature[自然]441:239-43(2006);Bradley等人,J Virol.[病毒学杂志]86:1267-72(2012);Yu等人,Biochem Biophys Res Commun.[生物化学与生物物理研究通讯]421:170-6(2012);Bruder等人,PLoS One.[公共科学图书馆:综合]7(4):e33920(2012))。

[0052] 针对腺病毒的中和抗体的第二个靶标是纤维蛋白。用来自非人类来源的稀有腺病毒的纤维序列替换纤维蛋白,更优选替换纤维蛋白内的可变序列,还可以允许构建对通常在人在发现的抗体的中和不太敏感的腺病毒载体。上述纤维替换与六邻体替换的组合可赋予对通常在人在发现的抗体的中和的额外抗性。

[0053] 本披露提供了包含转基因和嵌合六邻体核酸序列的嵌合腺病毒载体。这些腺病毒载体可以例如包含编码六邻体多肽的核酸序列,该六邻体多肽包括含有选自SEQ ID NO:1或SEQ ID NO:2的氨基酸序列的含六邻体高变区多肽。在某些实施例中,六邻体多肽序列包含SEQ ID NO:3或SEQ ID NO:4。腺病毒载体可以例如包含来自人腺病毒-4、人腺病毒-5、人

腺病毒-26或人腺病毒-35的一种或多种核酸序列。在某些实施例中，腺病毒载体包含选自SEQ ID NO:5或SEQ ID NO:6的核酸序列。

[0054] “腺病毒载体”指衍生自或包含腺病毒基因组的至少一部分的重组载体。

[0055] 典型地，本发明的腺病毒载体包含在例如质粒、粘粒或杆状病毒载体上的完整重组腺病毒基因组。本发明的核酸分子可以呈RNA形式或呈通过克隆而获得或以合成方式而产生的DNA形式。DNA可以是双链的或单链的。

[0056] 普通技术人员将认识到，衍生自多种血清型的元件可以组合在单个腺病毒载体中，例如人或猿猴腺病毒。因此，可以产生组合了来自不同血清型的期望性质的嵌合腺病毒载体。因此，在一些实施例中，本发明的嵌合腺病毒载体可以将不存在预先存在的嵌合六邻体和/或纤维多肽序列免疫性与现有腺病毒载诸如rAd4、rAd5、rAd26或rAd35的高水平抗原递送和呈递能力相结合。

[0057] 用作疫苗的腺病毒载体的优点包括易于操纵、良好的大规模可制造性以及基于多年的研究、开发、制造和临床试验经验的优异安全记录，这些临床试验使用了许多已报道的腺病毒载体。被用作疫苗的腺病毒载体通常提供对转基因编码的蛋白或转基因编码的抗原基因产物的良好免疫应答，包括细胞免疫应答。根据本发明的腺病毒载体可以基于任何类型的腺病毒，并且在某些实施例中是人腺病毒，其可以属于任何组或血清型。在优选的实施例中，重组腺病毒基于来自A、B、C、D、E、F或G组的人腺病毒。在其他优选的实施例中，重组腺病毒基于人腺病毒血清型5、11、26、34、35、48、49或50。在其他实施例中，它是可以为任何血清型的猿猴腺病毒，诸如黑猩猩或大猩猩腺病毒。在某些实施例中，重组腺病毒基于黑猩猩腺病毒1、3、7、8、21、22、23、24、25、26、27.1、28.1、29、30、31.1、32、33、34、35.1、36、37.2、39、40.1、41.1、42.1、43、44、45、46、48、49、50、67型或SA7P。

[0058] 在更优选的实施例中，第二组合物的黑猩猩腺病毒载体是ChAdV3。重组黑猩猩腺病毒血清型3 (ChAd3或cAd3) 是亚群C腺病毒，其性质类似于人腺病毒血清型5 (Ad5) 的性质。ChAd3在评估丙型肝炎病毒 (HCV) 候选疫苗的人类研究中已显示出是安全的和免疫原性的 (Barnes E等人2012*Science translational medicine* [科学转化医学] 4:115ra1)。据报道，基于ChAd3的疫苗能够诱导与人Ad5载体疫苗相当的免疫应答。参见例如Peruzzi D等人2009*Vaccine* [疫苗] 27:1293-300和Quinn KM等人2013*J Immunol* [免疫学杂志] 190:2720-35;WO 2005/071093;WO 2011/0130627等。

[0059] 腺病毒载体、其构建方法及其繁殖方法是本领域所熟知的，并且描述于例如美国专利号5,559,099、5,837,511、5,846,782、5,851,806、5,994,106、5,994,128、5,965,541、5,981,225、6,040,174、6,020,191和6,113,913，以及Thomas Shenk, “Adenoviridae and their Replication” [腺病毒及其复制], M.S.Horwitz, “Adenoviruses” [腺病毒], 分别第67和68章, 见于Virology [病毒学], B.N.Fields等人编, 第3版, 纽约雷文出版社有限公司 (Raven Press, Ltd., New York) (1996), 以及本文提及的其他参考文献。典型地, 腺病毒载体的构建涉及使用标准分子生物学技术, 诸如以下文献中所述的那些技术: Sambrook等人, *Molecular Cloning, a Laboratory Manual* [分子克隆, 实验室手册], 第2版, 纽约冷泉港的冷泉港出版社 (Cold Spring Harbor Press, Cold Spring Harbor, N.Y.) (1989); Watson等人, *Recombinant DNA* [重组DNA], 第2版, Scientific American Books [科学美国人] (1992); 和Ausubel等人, *Current Protocols in Molecular Biology* [分子生物学实验室

指南],纽约威利国际科学出版公司(Wiley Interscience Publishers,NY) (1995);以及本文提及的其他参考文献。

[0060] 在某些实施例中,腺病毒载体包含E1缺失和/或E3缺失。E1或E3缺失可以例如包括基因的完全缺失或部分缺失,其使得E1或E3基因产物具有功能缺陷。因此,在某些实施例中,腺病毒是复制缺陷型的,例如因为它在基因组的E1区含有缺失。如技术人员已知的,在缺失来自腺病毒基因组的必需区域的情况下,由这些区域编码的功能必须优选的是由生产细胞反式提供,即,当E1、E2和/或E4区域的部分或全部从腺病毒中缺失时,这些区域必须存在于生产细胞中,例如整合到其基因组中,或呈所谓的辅助腺病毒或辅助质粒形式。这些腺病毒还可以具有在E3区域中的缺失,该缺失对于复制是非必要的,因此不必补充这种缺失。E1、E2、E3和E4区域中的一个或多个也可以通过其他方法失活,诸如通过将感兴趣的转基因(通常与启动子连接)插入待失活的区域。

[0061] 可以使用的生产细胞(有时在本领域中以及在本文还称为‘包装细胞’或‘补充细胞’)可以是可在其中繁殖所希望的腺病毒的任何生产细胞。例如,在生产细胞中完成重组腺病毒载体的繁殖,这些生产细胞补充腺病毒中的缺陷。此类生产细胞优选地在其基因组中至少具有腺病毒E1序列,并因而能够补充在E1区域中具有缺失的重组腺病毒。可以使用任何补充E1的生产细胞,诸如由E1永生化的类人视网膜细胞,例如911或PER.C6细胞(参见美国专利5,994,128)、E1转化的羊水细胞(参见欧洲专利1230354)、E1转化的A549细胞(参见例如W0 98/39411、美国专利5,891,690)、GH329:HeLa(Gao等人,2000,Hum Gene Ther[人类基因治疗]11:213-19)、293等。在某些实施例中,生产细胞是例如HEK293细胞、或PER.C6细胞、或911细胞、或IT293SF细胞等。在(Kovesdi等人,2010,Viruses[病毒]2:1681-703)中对生产细胞中的腺病毒载体的生产进行了综述。

[0062] 在某些实施例中,腺病毒载体是包含一个或多个腺病毒核酸序列的嵌合腺病毒载体。人腺病毒核酸可以选自例如人腺病毒-4(Ad-4)、人腺病毒-5(Ad-5)、人腺病毒-26(Ad-26)或人腺病毒-35(Ad-35)。在某些实施例中,E1缺陷型腺病毒载体包含人Ad5的腺病毒的E4-orf6编码序列。这使得此类腺病毒可在表达Ad5的E1基因的熟知的补充细胞系中繁殖,诸如293细胞或PER.C6细胞(参见例如Fallaux等人,1998,Hum Gene Ther[人类基因治疗]9:1909-17;Havenga等人,2006,J Gen Virol[普通病毒学杂志]87:2135-43;W0 03/104467,它们通过援引以其全文并入本文)。

[0063] 在某些实施例中,腺病毒载体包含转基因。“转基因”是指源核酸,它是不天然存在于载体中的核酸,并且根据本发明,转基因可编码在受试者中引发免疫应答的抗原性基因产物或抗原性蛋白。转基因可以例如通过标准分子生物学技术引入载体中。例如,可将转基因克隆到腺病毒载体的缺失的E1或E3区域中,或E4区域与rITR之间的区域中。通常,转基因可操作地连接至表达控制序列。在优选的实施例中,转基因在转基因插入位点被插入。

[0064] 如果需要,可以对根据本发明实施例的六邻体或纤维核酸序列和/或对转基因进行密码子优化,以确保在治疗的宿主(例如人)中的正确表达。密码子优化是广泛应用于本领域的技术。

[0065] 转基因可以在腺病毒衍生的启动子(例如,主要晚期启动子)的控制下(即,可操作地连接),或者可以在异源启动子的控制下。合适的异源启动子的实例包括CMV启动子和RSV启动子。优选地,启动子位于表达盒内的感兴趣的异源基因的上游。

[0066] 在优选的实施例中,腺病毒载体包含选自SEQ ID NO:5或SEQ ID NO:6的核酸序列。

[0067] 免疫原性组合物

[0068] 免疫原性组合物是用于本发明的包含免疫有效量的纯化的或部分纯化的人腺病毒载体的组合物。所述组合物可以根据本领域熟知的方法被配制成药苗(也称为“免疫原性组合物”)。此类组合物可以包含佐剂以增强免疫应答。鉴于本披露,可以通过本领域技术人员熟知的技术确定制剂中每种组分的最佳比率。

[0069] 鉴于本披露,根据本发明的实施例的免疫原性组合物可以使用本领域技术人员已知的方法制备。液体药物组合物通常包含液体载剂,诸如水、石油、动物或植物油、矿物油或合成油。可以包括生理盐水溶液、葡萄糖或其他糖溶液或二醇,诸如乙二醇、丙二醇或聚乙二醇。

[0070] 可用于本发明的免疫原性组合物可以包含佐剂。适于根据本发明共同施用的佐剂应该是在人中潜在安全、耐受良好且有效的佐剂,包括QS-21、Detox-PC、MPL-SE、MoGM-CSF、TiterMax-G、CRL-1005、GERBU、TERamide、PSC97B、Adjumer、PG-026、GSK-I、AS01、AS03、AS04、AS15、GcMAF、B-aletine、MPC-026、Adjuvax、CpG ODN、Betafectin、Alum和MF59。

[0071] 其他可以施用的佐剂包括凝集素、生长因子、细胞因子和淋巴因子,诸如 α -干扰素、 γ -干扰素、血小板衍生生长因子(PDGF)、粒细胞集落刺激因子(gCSF)、粒细胞巨噬细胞集落刺激因子(gMCSF)、肿瘤坏死因子(TNF)、表皮生长因子(EGF)、IL-1、IL-2、IL-4、IL-6、IL-8、IL-10和IL-12或其编码核酸。

[0072] 本发明的组合物可以包含药学上可接受的赋形剂、载剂、缓冲剂、稳定剂或本领域技术人员熟知的其他材料。此类材料应该是无毒的,并且不应该干扰活性成分的功效。载剂或其他材料的确切性质可以取决于施用途径,例如肌内、皮下、经口、静脉内、皮肤、粘膜内(例如,肠)、鼻内或腹膜内途径。

[0073] 诱导保护性免疫的方法

[0074] 本发明的另一个一般方面涉及在需要的受试者中诱导免疫应答的方法。这些方法可以例如包括向受试者施用包含本文所述的腺病毒载体和药学上可接受的载剂的疫苗。本文还提供了生产疫苗的方法。这些方法包括将本文所述的腺病毒载体与药学上可接受的载剂组合。

[0075] 根据本发明的实施例的任何免疫原性组合物(包括但不限于本文所述的那些)均可在本发明方法中用作疫苗。

[0076] 包含载体的免疫原性组合物/疫苗的施用典型地是肌内或皮下。然而,也可以设想其他施用方式,诸如静脉内、皮肤、皮内或鼻。免疫原性组合物的肌内施用可以通过使用针注射腺病毒载体的混悬液来实现。一种替代方案是使用无针注射装置来施用组合物(使用例如Biojector™)或含有疫苗的冷冻干燥粉末。

[0077] 对于静脉内、皮肤或皮下注射,或在病痛部位的注射,载体将呈肠胃外可接受的水溶液的形式,它是无热原的并具有合适的pH、等渗性和稳定性。本领域技术人员完全能够使用例如等渗媒介物诸如氯化钠注射液、林格氏注射液、乳酸盐林格氏注射液来制备适合的溶液。根据需要,可以包括防腐剂、稳定剂、缓冲剂、抗氧化剂和/或其他添加剂。还可以使用缓释制剂。

[0078] 典型地,施用将具有预防性目的,以在感染或发展症状之前产生针对感兴趣的抗原(例如,细菌、病毒、寄生虫和/或真菌病原体)的免疫应答。可根据本发明治疗或预防的疾病和病症包括免疫应答可在其中起到保护或治疗作用的那些。在其他实施例中,腺病毒载体可被施用用于暴露后预防。

[0079] 将含有嵌合人腺病毒载体的免疫原性组合物施用给受试者,从而在受试者中产生对感兴趣的抗原的免疫应答。足以诱导可检测的免疫应答的组合物的量被定义为组合物的“免疫有效剂量”或“有效量”。本发明的免疫原性组合物可以诱导体液以及细胞介导的免疫应答。在典型的实施例中,免疫应答是保护性免疫应答。

[0080] 施用的实际量以及施用的速率和时程将取决于正治疗的疾病的性质和严重程度。治疗处方(例如剂量等的决定)是在全科医生和其他医师、或在兽医环境中是兽医的职责范围内的,并且典型地考虑了待治疗的病症、个体患者的状况、递送部位、施用方法以及医师已知的其他因素。以上提及的这些技术和方案的实例可以在Remington's Pharmaceutical Sciences[雷明顿药学大全],第16版,Osol, A. 编,1980中找到。

[0081] 在产生腺病毒载体和任选将此类颗粒配制成组合物后,可以将这些载体施用给个体,特别是人或其他灵长类动物。可以对人或另一种哺乳动物施用,例如小鼠、大鼠、仓鼠、豚鼠、兔、绵羊、山羊、猪、马、牛、驴、猴、狗或猫。向非人哺乳动物的递送不必是为了治疗目的,而是可以用于实验环境,例如研究对腺病毒载体的免疫应答机制。

[0082] 在一个示例性方案中,腺病毒载体以约100 μ l至约10ml范围内的体积施用(例如肌内),该体积的浓度为约10⁴至10¹²个病毒颗粒/ml。优选地,腺病毒载体以0.1-2.0ml范围内的体积施用。例如,腺病毒载体可以100 μ l、500 μ l、1ml、2ml施用。更优选地,腺病毒载体以0.5ml的体积施用。任选地,腺病毒载体以10⁷vp/ml、10⁸vp/ml、10⁹vp/ml、10¹⁰vp/ml、5x10¹⁰vp/ml、10¹¹vp/ml或10¹²vp/ml的浓度施用。典型地,在一次施用期间,腺病毒载体以约10⁹至约10¹²个病毒颗粒(vp)的量,更典型地以约10¹⁰至约10¹²个vp的量施用于人受试者。初始疫苗接种后如上所述进行加强免疫。

[0083] 初始疫苗接种之后可以是包含编码感兴趣抗原的相同腺病毒载体的疫苗/组合物或包含编码相同感兴趣抗原的不同腺病毒载体的疫苗/组合物的加强或激发。

[0084] 如果需要,组合物可以存在于试剂盒、包装或分配器中,该试剂盒、包装或分配器可以包含一个或多个含有活性成分的单位剂型。例如,试剂盒可以包括金属或塑料箔,诸如泡罩包装。试剂盒、包装或分配器可附有施用说明书。

[0085] 本发明的组合物可以单独施用或与其他治疗联合施用(同时地或按顺序),这取决于待治疗的病状。

[0086] 实施例

[0087] 实施例1是一种腺病毒载体,该腺病毒载体包含编码六邻体多肽的核酸序列,该六邻体多肽包括含有选自SEQ ID NO:1或SEQ ID NO:2的氨基酸序列的含六邻体高变区多肽。

[0088] 实施例2是如实施例1所述的腺病毒载体,其中该六邻体多肽序列包含SEQ ID NO:3或SEQ ID NO:4。

[0089] 实施例3是如实施例1或2所述的腺病毒载体,其中该腺病毒载体进一步包含E1缺失。

[0090] 实施例4是如实施例1-3中任一项所述的腺病毒载体,其中该腺病毒载体进一步包

含E3缺失。

[0091] 实施例5是如实施例1-4中任一项所述的腺病毒载体,其中该腺病毒载体进一步包含人腺病毒-5 (HAdV-5) E4 orf6。

[0092] 实施例6是如实施例1-5中任一项所述的腺病毒载体,其中该腺病毒载体包含选自SEQ ID NO:5或SEQ ID NO:6的核酸序列。

[0093] 实施例7是如实施例1-6中任一项所述的腺病毒载体,其中该腺病毒载体进一步包含至少一个转基因。

[0094] 实施例8是如实施例1-7中任一项所述的腺病毒载体,其中该转基因位于E1缺失处、E3缺失处、和/或右反向末端重复序列(rITR)附近。

[0095] 实施例9是如实施例1-8中任一项所述的腺病毒载体,其中该腺病毒载体包含来自人腺病毒-26 (Ad26)的一种或多种核酸序列。

[0096] 实施例10是一种重组细胞,该重组细胞包含如实施例1-9中任一项所述的腺病毒载体。

[0097] 实施例11是一种生产腺病毒载体的方法,该方法包括:(a)使如实施例10所述的重组细胞在用于生产该腺病毒载体的条件下生长;以及(b)从该重组细胞中分离该腺病毒载体。

[0098] 实施例12是一种免疫原性组合物,该免疫原性组合物包含如实施例1-9中任一项所述的腺病毒载体和药学上可接受的载剂。

[0099] 实施例13是一种在有需要的受试者中诱导免疫应答的方法,该方法包括向该受试者施用如实施例12所述的免疫原性组合物。

[0100] 实施例14是一种生产免疫原性组合物的方法,该方法包括将如实施例1-9中任一项所述的腺病毒载体与药学上可接受的载剂组合。

[0101] 实例

[0102] 实例1:六邻体嵌合腺病毒载体Ad26HVRPtr1、Ad26HVRPtr12和Ad26HVRPtr13的设计。

[0103] 在此实例中描述的是Ad26HVRPtr1、Ad26HVRPtr12和Ad26HVRPtr13的设计,它们是携带从黑猩猩腺病毒获得的某些六邻体序列替换的新的基于HAdV-26的载体。设计这些六邻体嵌合腺病毒载体的目的是生成可能的新的基于腺病毒的(疫苗)载体,这些载体是可制造的,在血清学上与HAdV-26不同,并且在人类人群中针对这些载体存在低(或无)预先存在的免疫。

[0104] 将分别包含腺病毒载体基因组序列SEQ ID NO:4、SEQ ID NO:5和SEQ ID NO:6的Ad26HVRPtr1、Ad26HVRPtr12和Ad26HVRPtr13设计为先前描述(WO2007104792 A2;Abbink等人,2007)的重组HAdV-26载体的六邻体嵌合形式。因此,这些载体被设计成携带与先前指定的(WO 2007104792 A2;Abbink等人,2007)相同的E1缺失、E3缺失和E4 orf6替换(被HAdV-5中的替换)。

[0105] 如以下实例所述,本文生成和检查的六邻体嵌合载体的特定变体是Ad26HVRPtr1.Fluc、Ad26HVRPtr12.Fluc、Ad26HVRPtr13.Fluc、Ad26HVRPtr12.RSVF-2A-GLuc和Ad26HVRPtr13.RSVF-2A-GLuc,它们分别包含病毒基因组序列SEQ ID NO:7、SEQ ID NO:8、SEQ ID NO:9、SEQ ID NO:10和SEQ ID NO:11。如其载体名称所示,生成这些载体以在

其E1缺失的位置处携带CMV启动子驱动的表达盒,该表达盒编码萤火虫萤光素酶(FLuc)或嵌合蛋白“RSV-F_{A2}-2A-GLuc”(RSVF-2A-GLuc),后者是呼吸道合胞病毒株A2融合糖蛋白(RSV-F_{2A})、口蹄疫病毒2A肽和高斯(Gaussia)萤光素酶(GLuc)的融合体。FLuc表达盒和RSVF-2A-GLuc表达盒均由CMV启动子驱动,并携带SV40聚腺苷酸化信号。RSVF-2A-GLuc的盒进一步在其5'未翻译区内包含一个序列,该序列包含人载脂蛋白A1(ApoA1)基因的内含子2。

[0106] 腺病毒载体Ad26HVRPtr1、Ad26HVRPtr12和Ad26HVRPtr13(分别包含SEQ ID NO:4、SEQ ID NO:5和SEQ ID NO:6)在其基于HAdV-26的基因组内的某些六邻体基因区段被其他腺病毒的相应六邻体基因区段替换的意义上被设计为六邻体嵌合的。充当Ad26HVRPtr1、Ad26HVRPtr12和Ad26HVRPtr13的六邻体序列供体的病毒分别是PtroAdV-1、PtroAdV-12和PtroAdV-13。这些病毒是在野生黑猩猩的粪便样品中鉴定出来的,并且已分配给人类腺病毒E种(HAdV-E)(Wevers等人,J.Virol.[病毒学杂志]85(20):10774-84(2011))。这些病毒的部分六邻体基因序列分别以GenBank登录号JN163971、JN163982和JN163983公开提供。考虑到六邻体序列的受体载体基于HAdV-26,即人腺病毒D种(HAdV-D)的成员,而三种六邻体序列供体病毒属于HAdV-E,本文产生的载体代表交叉腺病毒种六邻体嵌合载体。

[0107] HAdV-26六邻体基因区段(在本文被替换以生成六邻体嵌合载体Ad26HVRPtr1、Ad26HVRPtr12和Ad26HVRPtr13(及其在本文构建的含有转基因表达盒的衍生物))对应于以Genbank登录号EF153474(版本1)保藏的HAdV-26的野生型完整基因组的核苷酸18178至18357、18379至18438、18556至18633、18685至18723和19027至19158。这五个HAdV-26六邻体基因区段以及它们相应的衍生自PtroAdV-1、PtroAdV-12或PtroAdV-13的替换区段在很大程度上但并非完全对应于编码高变区(HVR)的序列。这显示在图1A中,其中在HAdV-26六邻体基因的示意图中指出了这五个区段的位置以及之前指定的HVR的位置。此外,这更详细地通过用HAdV-26、PtroAdV-1、PtroAdV-12和PtroAdV-13的(部分)六邻体多肽序列进行的氨基酸比对来说明,其中在本文进行交换的特定区段在先前指定的HVR的旁边特别突出显示(图1B)。

[0108] 值得注意的是,HAdV-26的五个六邻体基因区段(在本文被替换以生成Ad26HVRPtr1、Ad26HVRPtr12和Ad26HVRPtr13)并不完全对应于在描述六邻体嵌合的基于HAdV-5的载体的先前报告中被替换的含六邻体HVR的序列(Roberts等人,Nature[自然]441:239-43(2006);Bradley等人,J.Virol.[病毒学杂志]86:1267-72(2012);Yu等人,Biochem Biophys Res Commun.[生物化学与生物物理研究通讯]421:170-6(2012);Bruder等人,PLoS One.[公共科学图书馆:综合]7(4):e33920(2012))。例如,如图1A和图1B所示,五个六邻体基因区段未能完全对应于七个氨基酸段(先前被交换以生成Ad5HVR48(1-7)),Ad5HVR48(1-7)是基于HAdV-5并包含HAdV-48的六邻体HVR的六邻体嵌合载体(Roberts等人,Nature[自然]441:239-43(2006))。

[0109] 腺病毒载体Ad26HVRPtr1、Ad26HVRPtr12和Ad26HVRPtr13的完整嵌合六邻体基因核苷酸序列分别在SEQ ID NO:13、SEQ ID NO:14和SEQ ID NO:15中列出。这些载体的完整嵌合六邻体多肽序列分别在SEQ ID NO:12、SEQ ID NO:3和SEQ ID NO:4中列出。

[0110] 实例2:携带Ad26HVRPtr1.Fluc、Ad26HVRPtr12.Fluc和Ad26HVRPtr13.Fluc的完整腺病毒载体基因组的质粒的分子构建

[0111] 使用与先前针对生成六邻体嵌合的编码Fluc的载体“Ad26.HVR5C”所述的相同方法和策略(Ma等人, *J. Canc. Res. Clin. Oncol.* [癌症研究与临床肿瘤学杂志]141(3):419-29(2015), 补充图4), 构建含有Ad26HVRPtr1、Ad26HVRPtr12和Ad26HVRPtr13载体基因组的质粒, 这些质粒在腺病毒E1区域中携带CMV启动子驱动的FLuc表达盒。简而言之, 首先在中间“六邻体穿梭”质粒pHex26-Shuttle.BamHI的背景下引入对六邻体基因的所需改变。这通过标准基因合成和亚克隆程序(由加利福尼亚州卡尔斯巴德的生命科技公司(Life Technologies, Carlsbad, CA)的GeneArt进行)完成, 并产生了修饰的六邻体穿梭质粒, 这些质粒携带SEQ ID NO:13、SEQ ID NO:14和SEQ ID NO:15所示的上述嵌合六邻体基因序列。然后, 通过在大肠杆菌(*E. coli*) BJ5183 (Stratagene/加利福尼亚州圣克拉拉的安捷伦科技公司(Agilent Technologies, Santa Clara, CA))中进行同源重组, 将嵌合六邻体基因从六邻体穿梭质粒穿梭到pAd26.luc.dH中, pAd26.luc.dH是一种在两个PacI限制性位点之间携带六邻体基因缺失型重组HAdV-26载体基因组的质粒, 该载体基因组在其E1缺失位置处装有CMV启动子驱动的编码Fluc的表达盒。上述分子克隆程序导致生成了质粒pAd26.HVRPtr1.luc (SEQ ID NO:20)、pAd26.HVRPtr12.luc (SEQ ID NO:21; 图2A) 和pAd26.HVRPtr13.luc (SEQ ID NO:22; 图2B)。

[0112] 还以与如上所述完全相同的方式构建了三个匹配的对比六邻体嵌合腺病毒载体质粒。在这些名为pAd26.HVR5.luc (SEQ ID NO:17)、pAd26.HVR35.luc (SEQ ID NO:18) 和pAd26.HVR52.luc (SEQ ID NO:19) 的质粒中, 分别用相应的HAdV-5、HAdV-35和HAdV-52区段组替换上述五种HAdV-26六邻体基因区段组。这些质粒分别包含SEQ ID NO:23、SEQ ID NO:24和SEQ ID NO:25所示的嵌合六邻体基因核苷酸序列。这些六邻体基因分别编码SEQ ID NO:26、SEQ ID NO:27和SEQ ID NO:28所示的嵌合六邻体多肽序列。

[0113] 实例3: 初步评估腺病毒载体Ad26HVRPtr1.Fluc、Ad26HVRPtr12.Fluc和Ad26HVRPtr13.Fluc的活力、生长效率和生产率

[0114] 先前的研究已表明, 包含腺病毒物种之间的六邻体序列交换的嵌合腺病毒载体通常是不能存活的, 或可能显示出延迟的生长动力学并产生较低的产量(Youil等人, *Hum. Gene Ther.* [人类基因治疗]13:311-20(2002); Wu等人 *J. Virol.* [病毒学杂志]76:12775-82(2002); Bradley等人, *J. Virol.* [病毒学杂志]86:1267-72(2012); Bruder等人, *PLoS One.* [公共科学图书馆:综合]7(4):e33920(2012))。因此, 应测试新的六邻体嵌合腺病毒(疫苗)载体的基本生长特性、产量和颗粒质量。

[0115] 评估本文设计和构建的六邻体嵌合腺病毒载体的活力、生长效率、生产率和颗粒感染性, 将它们与其基于亲本HAdV-26的载体进行比较。为此, 通过根据标准程序, 使用Lipofectamine转染试剂(加利福尼亚州卡尔斯巴德的英杰公司), 将实例2中描述的相应腺病毒载体基因组质粒(即, 分别为pAd26.HVRPtr1.luc、pAd26.HVRPtr12.luc、pAd26.HVRPtr13.luc、pAd26.HVR5, pAd26.HVR35和pAd26.HVR52) 转染到在T25烧瓶中培养的补充E1的PER.55K细胞(Vogels等人, *J. Virol.* [病毒学杂志]77:8263-71(2003))中, 生成了腺病毒载体Ad26HVRPtr1.Fluc、Ad26HVRPtr12.Fluc和Ad26HVRPtr13.Fluc以及对载体Ad26HVR5.Fluc、Ad26HVR35.Fluc和Ad26HVR52.Fluc。在转染之前, 将腺病毒载体基因组质粒用PacI消化, 以从质粒中释放相应的腺病毒载体基因组。每天监测转染的细胞培养物, 以记录第一个病毒斑形成的开始天数以及达到总细胞病变效应(CPE)的天数(表1)。在完全

CPE时,收集感染的细胞和培养基,并通过三个冻融循环释放病毒。在收获病毒拯救转染后,通过在补充E1的细胞培养物上的连续几轮感染而进一步扩增病毒。然后从粗病毒收获物中纯化病毒(通过两步氯化铯(CsCl)密度梯度超速离心程序),随后测定病毒颗粒(VP)和感染单位滴度(IU/mL),所有这些均通过前述标准方法进行(Alba R,Baker AH,Nicklin SA.Vector systems for prenatal gene therapy:principles of adenovirus design and production.[用于产前基因治疗的载体系统:腺病毒设计和生产原理]Methods Mol Biol[分子生物学方法]2012;891:55-84.:55-84)。

[0116] 表1:六邻体嵌合腺病毒载体所观察到的拯救效率、最终产量和VP/IU比。

载体	HVR 供体的 HAdV 种	病毒拯救效率			纯化的批次表征	
		形成病毒斑	第 1 个病毒斑 (p.t. 天数)	总 CPE (p.t. 天数)	25 个 T150 烧瓶中的总产量 (VP)	VP 与 IU 比
Ad26.FLuc	n.a.	是	3-5	7-8	1.10×10^{13}	337
Ad26HVR5.FLuc	C	是	5	11	1.05×10^{11}	4000
Ad26HVR35.FLuc	B	是	5	12	1.75×10^{12}	829
Ad26HVR52.FLuc	G	否	-	-	-	-
Ad26HVRPtr1.FLuc	E	是	3	9	3.78×10^{11}	1029
Ad26HVRPtr12.FLuc	E	是	4	8	2.16×10^{12}	272
Ad26HVRPtr13.FLuc	E	是	3	7	1.07×10^{13}	150

[0117] n.a., 不适用;p.t., 转染后

[0119] 在所测试的六个嵌合载体中,只有Ad26HVRPtr12.FLuc和Ad26HVRPtr13.FLuc给出的结果表明它们的衣壳修饰不会损害载体生产率和感染性(表1)。这两个载体的病毒拯救和生长效率,如斑形成的开始时间和达到完全CPE所需的时间(病毒DNA转染到补充E1的细胞中后)所反映的,均在亲本载体Ad26.FLuc所见的范围内。除Ad26HVRPtr1.FLuc外,其他测试的嵌合载体并非如此。此外,在所有测试的载体中,Ad26HVRPtr12.FLuc和Ad26HVRPtr13.FLuc在大规模生产和纯化时产生最高的病毒颗粒(VP)产量。最后,虽然其他嵌合载体都显示出高于亲本Ad26.FLuc的VP:IU比率,但是发现Ad26HVRPtr12.FLuc和Ad26HVRPtr13.FLuc具有不受影响的VP:IU比率。

[0120] 其他四个嵌合载体即Ad26HVR5.FLuc、Ad26HVR35.FLuc、Ad26HVR52.FLuc和Ad26HVRPtr1.FLuc显示出不同程度的受损的生产率和/或感染性。Ad26HVR52.FLuc根本不能存活(即,在病毒DNA转染后无法检测到病毒斑),而其他三个载体均成功获救。在这三个中,Ad26HVR5.FLuc和Ad26HVR35.FLuc清楚地显示出延迟的拯救和生长动力学,而Ad26HVRPtr1.FLuc似乎像亲本载体一样有效地拯救和生长。纯化的载体批次的表征揭示,Ad26HVR5.FLuc和Ad26HVRPtr1.FLuc的实际病毒颗粒产量尤其受到影响,而对所有这三个载体而言,颗粒感染性似乎都受到很大损害(如这些载体所见的较高VP:IU比率所示)。

[0121] 总之,作为包含腺病毒物种之间的六邻体序列交换的六邻体嵌合载体的Ad26HVRPtr12和Ad26HVRPtr13显示出良好的生长和生产特性,并因此被认为是用作新的疫苗载体的有希望的候选物(从可制造性的角度来看)。通过使用相同的嵌合六邻体设计但使用其他腺病毒作为六邻体序列供体而生成的其他四个六邻体嵌合载体显示出不太有利的

特性。

[0122] 实例4:腺病毒载体Ad26HVRPtr12.Fluc和Ad26HVRPtr13.Fluc的生成

[0123] 该实例描述在实例6、8和9中描述的免疫原性、血清阳性率、交叉中和和可制造性实验中使用的六邻体嵌合的编码Fluc的腺病毒载体的生成。

[0124] 通过将相应的腺病毒载体基因组质粒(即,分别为pAd26.HVRPtr12.luc和pAd26.HVRPtr13.luc)转染到补充E1的PER.C6细胞中,生成了分别包含腺病毒载体基因组序列SEQ ID NO:8和SEQ ID NO:9的腺病毒载体Ad26HVRPtr12.Fluc(也称为Ad26C4NVT005)和Ad26HVRPtr13.Fluc(也称为Ad26C3NVT005)。在转染到PER.C6细胞(这些细胞在补充了10%胎牛血清(FBS)和10mM MgCl₂的达尔伯克氏改良伊格尔培养基(DMEM)中作为贴壁细胞培养物生长)中之前,用PacI消化腺病毒载体基因组质粒以从质粒释放相应的腺病毒载体基因组。使用Lipofectamine转染试剂(加利福利亚州卡尔斯巴德的英杰公司(Invitrogen; Carlsbad, CA)),根据标准程序进行转染。在收获病毒拯救转染后,通过在PER.C6细胞培养物上的连续几轮感染而进一步扩增病毒。如前所述(Havenga等人,“Novel replication-incompetent adenoviral B-group vectors:high vector stability and yield in PER.C6 cells,”[新的无复制能力的腺病毒B组载体:在PER.C6细胞中的高载体稳定性和生产率]J.Gen.Virol.[普通病毒学杂志]87(8):2135-43(2006)),使用两步氯化铯(CsCl)密度梯度超速离心程序从粗病毒收获物中纯化病毒。病毒颗粒(VP)滴度通过先前描述的基于分光光度法的程序进行测量(Maizel等人,“The polypeptides of adenovirus:I.Evidence for multiple protein components in the virion and a comparison of types 2,7A, and 12,”[腺病毒的多肽:I.病毒体中多种蛋白组分的证据以及2、7A和12型的比较]Virology[病毒学],36(1):115-25(1968))。

[0125] 实例5:腺病毒载体Ad26HVRPtr12.RSVF-2A-GLuc和Ad26HVRPtr13.RSVF-2A-GLuc的生成

[0126] 该实例描述在实例7中描述的免疫原性实验中使用的六邻体嵌合的编码RSVF-2A-GLuc的腺病毒载体的生成。

[0127] 分别包含腺病毒载体基因组序列SEQ ID NO:10和SEQ ID NO:11的腺病毒载体Ad26HVRPtr12.RSVF-2A-GLuc(也称为Ad26C4NVT001)和Ad26HVRPtr13.RSVF-2A-GLuc(也称为Ad26C3NVT001)的生成涉及分别使用前述质粒pAd26.HVRPtr12.luc(SEQ ID NO:21;图2A)和pAd26.HVRPtr13.luc(SEQ ID NO:22;图2b)以及质粒pAdApt26.ApoAI.RSVF-2A-GLuc(SEQ ID NO:29;图3)。

[0128] pAdApt26.ApoAI.RSVF-2A-GLuc是带有先前描述(WO 2007104792A2;Abbink等人,2007)的E1缺失型基于HAdV-26的载体的左端基因组片段的质粒,其在腺病毒E1缺失位置处进一步包含上述编码“RSV-F_{A2}-2A-GLuc”的转基因表达盒(RSVF-2A-GLuc)。通过若干标准基因合成和分子克隆步骤构建了pAdApt26.ApoAI.RSVF-2A-GLuc,这些步骤一起产生所述RSVF-2A-GLuc盒并将其插入pAdApt26(先前描述(WO 2007104792A2;Abbink等人,2007)的带有所述左端腺病毒载体基因组片段的质粒)。

[0129] 如下生成腺病毒载体Ad26HVRPtr12.RSVF-2A-GLuc和Ad26HVRPtr13.RSVF-2A-GLuc。通过限制酶PacI和PsiI消化质粒pAd26.HVRPtr12.luc和pAd26.HVRPtr13.luc,以便从这些质粒中释放一定的28kb,即包含嵌合六邻体序列的左端缺失型腺病毒载体基因组片

段。将所得的相应消化产物各自分别用经PacI消化的pAdApt26.ApoAI.RSVF-2A-GLuc共转染到补充E1的PER.C6中,以便通过重叠的载体基因组限制片段之间的同源重组来拯救相应的六邻体嵌合的编码RSVF-2A-GLuc的病毒,如图4所示。在这种策略中,同源重组发生在pAdApt26.ApoAI.RSVF-2A-GLuc的6.7-kb PacI-PacI限制性片段(图4,顶部)与pAd26.HVRPtr12.luc或pAd26.HVRPtr13.luc的28-kb PsiI-PacI限制性片段(图4,底部)之间的重叠区域中的2.7-kb区域处。使用Lipofectamine转染试剂(加利福尼亚州卡尔斯巴德的英杰公司(Invitrogen;Carlsbad,CA)),根据标准程序进行转染。将两种拯救的病毒Ad26HVRPtr12.RSVF-2A-GLuc和Ad26HVRPtr13.RSVF-2A-GLuc的单个分离斑进一步在PER.C6细胞上繁殖,然后按照本文实例4中针对载体Ad26HVRPtr12.FLuc和Ad26HVRPtr13.FLuc所述进行纯化和滴定。

[0130] 由新型腺病毒载体诱导的细胞和体液免疫应答

[0131] 实例6和7描述了为了评估本文生成的新型Ad26HVRPtr12和Ad26HVRPtr13载体的免疫原性而进行的实验。在这些实验中,评估了新型载体在小鼠中肌肉免疫后诱导针对载体编码的(模型)抗原的体液和细胞免疫应答的能力。使用两种不同的抗原测试了载体:萤火虫萤光素酶(FLuc)和RSV-F_{A2}-2A-GLuc(RSVF-2A-GLuc)。RSVF-2A-GLuc是一种嵌合蛋白,由呼吸道合胞病毒株A2融合糖蛋白、口蹄疫病毒2A肽和高斯萤光素酶(GLuc)组成。将每个载体与基于携带相同的编码抗原的转基因盒的人26型腺病毒(HAdV-26,在本文中也称为Ad26)的基准载体并排比较。使用众所周知的免疫测定法,诸如酶联免疫斑点测定法(ELISPOT)、酶联免疫吸附测定法(ELISA)以及在RSVF-2A-GLuc抗原的情况下,呼吸道合胞病毒中和测定法(VNA),测量了针对相应抗原的免疫应答。

[0132] 实例6:由Ad26HVRPtr12.FLuc和Ad26HVRPtr13.FLuc诱导的细胞免疫应答

[0133] 为了评估新型腺病毒载体Ad26HVRPtr12和Ad26HVRPtr13的细胞免疫原性,用表达FLuc的Ad26.FLuc(阳性对照)、Ad26HVRPtr12和Ad26HVRPtr13载体(即,Ad26HVRPtr12.FLuc和Ad26HVRPtr13.FLuc)或用不编码FLuc的腺病毒载体Ad26空对Balb/C小鼠进行肌肉免疫。以每只小鼠 10^9 和 10^{10} 个病毒颗粒(vp)测试表达FLuc的载体,并以 10^{10} vp施用Ad26空载体。免疫后两周,处死小鼠并分离脾细胞(图5A)。通过离体ELISPOT试验测定了细胞免疫应答,该试验测量用15mer重叠FLuc肽库过夜刺激脾细胞后IFN- γ 分泌细胞的相对数量(图5B)。结果表明,在较高剂量免疫(10^{10})下,由Ad26HVRPtr12和Ad26HVRPtr13载体诱导的细胞免疫应答与Ad26.FLuc所见的在同一范围内或更高。

[0134] 总的来说,由本发明的表达FLuc的重组Ad26HVRPtr12和Ad26HVRPtr13腺病毒载体诱导的细胞免疫应答清楚地表明了这些载体在小鼠中的强有力的免疫原性。

[0135] 实例7:由Ad26HVRPtr12.RSVF-2A-GLuc和Ad26HVRPtr13.RSVF-2A-GLuc诱导的细胞和体液免疫应答

[0136] 使用RSV-F_{A2}-2A-GLuc(RSVF-2A-GLuc)作为载体编码的(模型)疫苗抗原,进一步评估了新型Ad26HVRPtr12和Ad26HVRPtr13腺病毒载体的免疫原性。用Ad26.RSVF-2A-GLuc(阳性对照)、Ad26HVRPtr12.RSVF-2A-GLuc或Ad26HVRPtr13.RSVF-2A-GLuc以三种不同的浓度(各自以每只小鼠 10^8 vp、 10^9 vp或 10^{10} vp)或者用Ad26.FLuc、Ad26HVRPtr12.FLuc或Ad26HVRPtr13.FLuc以每只小鼠 10^{10} vp对Balb/C小鼠进行肌肉免疫。免疫后八周,处死小鼠并收集血样和脾细胞(图6A)。如下所述评估不同的免疫参数。

[0137] 为了评估Ad26HVRPtr12.RSVF-2A-GLuc和Ad26HVRPtr13.RSVF-2A-GLuc引发呼吸道合胞病毒中和抗体的能力,进行了病毒中和试验(VNA)。图6B描绘了免疫后八周时收集的血清样品所测得的呼吸道合胞病毒株A2(RSV A2)VNA滴度。每个点代表一只小鼠;条代表组平均值,虚线对应于定量下限(LLOQ=6,88;线性样品的平均终点滴度)。结果表明,用Ad26HVRPtr12.RSVF-2A-GLuc和Ad26HVRPtr13.RSVF-2A-GLuc以 10^{10} vp剂量免疫所产生的RSV A2中和滴度与编码相同抗原的基准Ad26载体所见的中和滴度相似。主要在用于免疫的最高剂量 10^{10} vp下检测到由所有三个载体Ad26、编码RSVF-2A-GLuc的Ad26HVRPtr12和Ad26HVRPtr13所诱导的滴度。正如预期的那样,未检测到针对编码萤火虫萤光素酶的相应腺病毒载体的RSV A2特异性应答。

[0138] 通过RSV-F_{A2}特异性ELISPOT试验评估了针对载体编码的抗原的细胞免疫诱导。为此,在免疫后八周时,分离来自免疫小鼠的脾细胞,用跨越RSV-F_{A2}蛋白的15mer重叠肽刺激过夜,通过离体ELISPOT试验测定细胞免疫应答,该试验测量IFN- γ 分泌细胞的相对数量。数据显示,由编码RSVF-2A-GLuc的新型载体Ad26HVRPtr12和Ad26HVRPtr13引发的抗原特异性细胞免疫应答是剂量依赖性的,并且根据剂量,在大小上与基准载体Ad26.RSVF-2A-GLuc诱导的免疫应答分别更高和相似(图6C)。正如预期的那样,从用编码萤火虫萤光素酶的腺病毒载体免疫的小鼠的脾细胞中没有测量到RSVF-F_{A2}特异性应答。

[0139] 通过ELISA评估了表达RSVF-2A-GLuc的载体引发RSV-F_{A2}特异性IgG抗体的能力。在抗RSV F_{A2} IgG抗体ELISA中测试了从用表达RSVF-2A-GLuc转基因或萤火虫萤光素酶(对照)的Ad26(阳性对照)、Ad26HVRPtr12、Ad26HVRPtr13免疫的小鼠免疫后8周时收集的血清。具体而言,此ELISA检测能够结合重组稳定的融合前RSV-F_{A2}蛋白(前RSV-F)的IgG抗体。结果表明,Ad26HVRPtr12.RSVF-2A-GLuc和Ad26HVRPtr13.RSVF-2A-GLuc以剂量依赖性方式引发了与Ad26.RSVF-2A-GLuc诱导的相似的前RSV-F特异性IgG抗体滴度(图6D)。正如预期的那样,在仅用编码萤火虫萤光素酶的载体免疫的小鼠的血清中未检测到RSV-F_{A2}特异性抗体滴度。该图描绘以终点滴度(\log_{10})计算的IgG ELISA滴度。每个点代表一只小鼠;条代表组平均值,虚线代表计算为 $1,36\log_{10}$ 的定量下限(LLOQ)。

[0140] 总体而言,数据显示,新型Ad26HVRPtr12和Ad26HVRPtr13腺病毒载体诱导了针对所编码的抗原的强有力的细胞和体液免疫应答,在大小上与基于HAdV-26的基准载体所诱导的相似或更高。这些免疫应答清楚地表明了Ad26HVRPtr12和Ad26HVRPtr13腺病毒载体在小鼠中的强有力的免疫原性。

[0141] 实例8:对新型和现有腺病毒载体之间的血清交叉中和的评估

[0142] 由于它们作为新腺病毒疫苗载体的潜在用途,本文产生的新型Ad26HVRPtr12和Ad26HVRPtr13腺病毒载体优选地在血清学上不同于目前已经开发作为疫苗载体(诸如基于人腺病毒血清型HAdV-5和HAdV-35的载体)的现有腺病毒载体。因此,在新型Ad26HVRPtr12和Ad26HVRPtr13腺病毒载体以及基于HAdV-4、HAdV-5、HAdV-26和HAdV-35的几种现有载体之间进行了交叉中和测试。为此,在腺病毒中和试验中,针对每种不同的载体测试小鼠抗血清,每种抗血清针对这些腺病毒载体之一而产生。在将Balb/C小鼠用每只小鼠 10^{10} 个载体颗粒免疫后两周或八周时,从这些小鼠收集用于该试验的小鼠抗血清。如先前所述(Spangerson等人2003.J.Clin.Microbiol.[临床微生物学杂志]41:5046-5052)进行腺病毒中和试验。简而言之,从1:16稀释开始,将血清进行2倍系列稀释,然后与表达萤火虫萤光素酶(FLuc)

的腺病毒载体预混合,然后与A549细胞温育过夜(以每个细胞500个病毒颗粒的感染复数)。感染后24小时测得的被感染细胞裂解物中的萤光素酶活性水平代表载体感染效率。针对给定载体的中和滴度定义为能够使载体感染效率降低90%的最高血清稀释度。中和滴度可任意分为以下几类:<16(无中和)、16至200、200至2,000和>2,000。

[0143] 结果表明,在所测试的载体之间没有或只有极低水平的交叉中和(图7)。观察到Ad26HVRPtr12对Ad26和Ad26HVRPtr13载体以及Ad26HVRPtr13对Ad26和Ad26HVRPtr12载体的轻微交叉中和作用。对于这些载体观察到的相互交叉中和滴度明显低于对于这些相同载体所获得的相应的同源中和滴度。重要的是,除了Ad26观察到非常低水平的交叉中和外,新型Ad26HVRPtr12和Ad26HVRPtr13载体未显示出与测试组中的人腺病毒载体(即Ad35、Ad5和Ad4)的交叉中和。因此,这些新腺病毒载体Ad26HVRPtr12和Ad26HVRPtr13各自可以潜在地与一种或多种这些或其他不同的腺病毒载体联合用于顺序免疫,例如在异源初免-加强疫苗接种方案的情况下,或者,可替代地或另外,在一系列针对不同疾病或抗原的两个或更多个连续疫苗接种方案的情况下。

[0144] 实例9:新型腺病毒载体在人群中的血清阳性率

[0145] 对于它们作为有效疫苗载体的潜在用途而言重要的是,本文所述的新型腺病毒载体不受疫苗目标群体中高水平的预先存在的抗载体体液免疫的妨碍。因此,在200个来自成年人的人群血清样品中评价了Ad26HVRPtr12和Ad26HVRPtr13载体各自的血清阳性率,这些成年人年龄为18-55岁,生活在美国(US)和欧盟(EU)。通过进行如实例7中所开展的且如先前所述的(Spangers等人2003.J.Clin.Microbiol.[临床微生物学杂志]41:5046-5052)标准腺病毒中和试验,测试了这些载体被人血清样品中和的情况。简而言之,从1:16稀释开始,将血清进行2倍系列稀释,然后与表达萤火虫萤光素酶(FLuc)的腺病毒载体预混合,然后与A549细胞温育过夜(以每个细胞500个病毒颗粒的感染复数)。感染后24小时测得的被感染细胞裂解物中的萤光素酶活性水平代表载体感染效率。针对给定载体的中和滴度定义为能够使载体感染效率降低90%的最高血清稀释度。中和滴度可任意分为以下几类:<16(无中和)、16至300、300至1000、1000至4000和>4000。

[0146] 结果表明,在所研究的人类受试者中,腺病毒载体Ad26HVRPtr12和Ad26HVRPtr13的血清阳性率显著低于对照Ad5载体,并且在这些受试者中的血清阳性率与基准Ad26载体相似(图8)。此外,针对新型Ad26HVRPtr12和Ad26HVRPtr13载体的阳性中和滴度通常很低,大部分不高于300。相比之下,大多数针对Ad26和Ad5两者发现的阳性中和滴度高于300。

[0147] 总体而言,上述数据表明,可以认为在所评估的疫苗目标群体中,针对Ad26HVRPtr12和Ad26HVRPtr13载体的预先存在的体液抗载体免疫是较低的,这表明这些载体在这些群体中具有作为有效疫苗载体的潜力。

[0148] 实例10:在悬浮PER.C6细胞中的腺病毒载体生产率

[0149] 用于临床试验及其他方面的腺病毒载体需要在可扩展的无血清腺病毒生产平台中容易地生产至高滴度。悬浮-适应的PER.C6®细胞(本文也称为悬浮PER.C6细胞或sPER.C6)代表了这样的平台,因为它们已经显示出支持在生物反应器中大规模生产腺病毒载体,获得大量高滴度的临床级载体制备物,例如基于HAdV-26或HAdV-35的E1缺失型载体的制备物(EP 2536829B1、EP 2350268B1)。

[0150] 作为关于本文所述的新型载体是否适合基于sPER.C6细胞的生产工艺的初步评

估,对在摇瓶中培养的sPER.C6细胞进行了小规模载体生产率实验。这些生产率实验使用新型腺病毒载体Ad26HVRPtr12和Ad26HVRPtr13的Fluc编码形式(实例4中所述)进行。基于HAdV-26的载体Ad26.Fluc用作基准对照。将以 1×10^6 个细胞/ml的密度接种在摇瓶中的总体积为10ml的补充了4mM L-谷氨酰胺(龙沙集团(Lonza))的PERMEXCIS®培养基(可从龙沙集团获得)中的悬浮PER.C6细胞培养物用不同的载体以不同的病毒颗粒(VP)-细胞比感染,然后温育4天。用于感染的不同VP-细胞比是70、150和900。每天采集被感染的细胞培养物的样品,并通过基于定量PCR(qPCR)的方案测定这些样品中的VP滴度,该方案采用对CMV启动子(其存在于所有测试的载体中)特异的引物和探针。该方案需要在qPCR之前对测试样品进行DNA酶处理,以除去任何游离的载体DNA(即未包装到病毒颗粒中的载体基因组)。

[0151] 嵌合载体Ad26HVRPtr12.Fluc和Ad26HVRPtr13所得的生产率结果如图9所示。这两个嵌合载体产生的VP滴度等于亲本基准载体Ad26.Fluc获得的VP滴度。因此,这些结果证明了每种新型嵌合载体在基于sPER.C6的无血清悬浮细胞培养模型上的良好生产率。

[0152] 总之,如上所述,对本发明的新型重组腺病毒载体的体液和细胞免疫应答进行的研究清楚地表明这些载体在小鼠中的强有力的免疫原性。此外,这些载体被证明不诱导或诱导非常低的针对某些现有腺病毒疫苗载体候选物(例如Ad26和Ad35)的交叉中和抗体应答,反之亦然;以及仅诱导非常低的针对彼此的交叉中和抗体应答。此外,这些新载体在人类中显示出低血清阳性率。最后,这些新载体可以容易地以高产率产生。低血清阳性率、强有力的免疫原性和可生产性的组合表明本发明的新型腺病毒载体可用作针对多种病原体的新型疫苗载体候选物,并且可另外用于基因疗法和/或诊断。

[0153] 本领域技术人员将理解,在不偏离本发明的广泛发明构思的情况下,可以对上述实施例进行改变。因此,应当理解,本发明不限于所披露的特定实施例,而是旨在涵盖由本说明书限定的本发明的精神和范围内的修改。

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

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

1205	1210	1215
Gly Ala Thr Cys Gly Cys Cys Thr Gly Gly Ala Gly Ala Cys Gly		
1220	1225	1230
Cys Cys Ala Thr Cys Cys Ala Cys Gly Cys Thr Gly Thr Thr Thr		
1235	1240	1245
Thr Gly Ala Cys Cys Thr Cys Cys Ala Thr Ala Gly Ala Ala Gly		
1250	1255	1260
Ala Cys Ala Cys Cys Gly Gly Gly Ala Cys Cys Gly Ala Thr Cys		
1265	1270	1275
Cys Ala Gly Cys Cys Thr Cys Cys Gly Cys Gly Gly Cys Cys Gly		
1280	1285	1290
Gly Gly Ala Ala Cys Gly Gly Thr Gly Cys Ala Thr Thr Gly Gly		
1295	1300	1305
Ala Ala Gly Cys Thr Thr Gly Gly Cys Ala Thr Thr Cys Cys Gly		
1310	1315	1320
Gly Thr Ala Cys Thr Gly Thr Thr Gly Gly Thr Ala Ala Ala Gly		
1325	1330	1335
Cys Cys Ala Cys Cys Ala Thr Gly Gly Ala Ala Gly Ala Cys Gly		
1340	1345	1350
Cys Cys Ala Ala Ala Ala Ala Cys Ala Thr Ala Ala Ala Gly Ala		
1355	1360	1365
Ala Ala Gly Gly Cys Cys Cys Gly Gly Cys Gly Cys Cys Ala Thr		
1370	1375	1380
Thr Cys Thr Ala Thr Cys Cys Gly Cys Thr Gly Gly Ala Ala Gly		
1385	1390	1395
Ala Thr Gly Gly Ala Ala Cys Cys Gly Cys Thr Gly Gly Ala Gly		
1400	1405	1410
Ala Gly Cys Ala Ala Cys Thr Gly Cys Ala Thr Ala Ala Gly Gly		
1415	1420	1425
Cys Thr Ala Thr Gly Ala Ala Gly Ala Gly Ala Thr Ala Cys Gly		
1430	1435	1440
Cys Cys Cys Thr Gly Gly Thr Thr Cys Cys Thr Gly Gly Ala Ala		
1445	1450	1455
Cys Ala Ala Thr Thr Gly Cys Thr Thr Thr Thr Ala Cys Ala Gly		
1460	1465	1470
Ala Thr Gly Cys Ala Cys Ala Thr Ala Thr Cys Gly Ala Gly Gly		
1475	1480	1485
Thr Gly Gly Ala Cys Ala Thr Cys Ala Cys Thr Thr Ala Cys Gly		
1490	1495	1500

Cys Thr Gly Ala Gly Thr Ala Cys Thr Thr Cys Gly Ala Ala Ala	1505	1510	1515
Thr Gly Thr Cys Cys Gly Thr Thr Cys Gly Gly Thr Thr Gly Gly	1520	1525	1530
Cys Ala Gly Ala Ala Gly Cys Thr Ala Thr Gly Ala Ala Ala Cys	1535	1540	1545
Gly Ala Thr Ala Thr Gly Gly Gly Cys Thr Gly Ala Ala Thr Ala	1550	1555	1560
Cys Ala Ala Ala Thr Cys Ala Cys Ala Gly Ala Ala Thr Cys Gly	1565	1570	1575
Thr Cys Gly Thr Ala Thr Gly Cys Ala Gly Thr Gly Ala Ala Ala	1580	1585	1590
Ala Cys Thr Cys Thr Cys Thr Thr Cys Ala Ala Thr Thr Cys Thr	1595	1600	1605
Thr Thr Ala Thr Gly Cys Cys Gly Gly Thr Gly Thr Thr Gly Gly	1610	1615	1620
Gly Cys Gly Cys Gly Thr Thr Ala Thr Thr Thr Ala Thr Cys Gly	1625	1630	1635
Gly Ala Gly Thr Thr Gly Cys Ala Gly Thr Thr Gly Cys Gly Cys	1640	1645	1650
Cys Cys Gly Cys Gly Ala Ala Cys Gly Ala Cys Ala Thr Thr Thr	1655	1660	1665
Ala Thr Ala Ala Thr Gly Ala Ala Cys Gly Thr Gly Ala Ala Thr	1670	1675	1680
Thr Gly Cys Thr Cys Ala Ala Cys Ala Gly Thr Ala Thr Gly Gly	1685	1690	1695
Gly Cys Ala Thr Thr Thr Cys Gly Cys Ala Gly Cys Cys Thr Ala	1700	1705	1710
Cys Cys Gly Thr Gly Gly Thr Gly Thr Thr Cys Gly Thr Thr Thr	1715	1720	1725
Cys Cys Ala Ala Ala Ala Ala Gly Gly Gly Gly Thr Thr Gly Cys	1730	1735	1740
Ala Ala Ala Ala Ala Ala Thr Thr Thr Thr Gly Ala Ala Cys Gly	1745	1750	1755
Thr Gly Cys Ala Ala Ala Ala Ala Ala Ala Gly Cys Thr Cys Cys	1760	1765	1770
Cys Ala Ala Thr Cys Ala Thr Cys Cys Ala Ala Ala Ala Ala Ala	1775	1780	1785
Thr Thr Ala Thr Thr Ala Thr Cys Ala Thr Gly Gly Ala Thr Thr			

1790	1795	1800
Cys Thr Ala Ala Ala Ala	Cys Gly Gly Ala Thr	Thr Ala Cys Cys
1805	1810	1815
Ala Gly Gly Gly Ala Thr	Thr Thr Cys Ala Gly	Thr Cys Gly Ala
1820	1825	1830
Thr Gly Thr Ala Cys Ala	Cys Gly Thr Thr Cys	Gly Thr Cys Ala
1835	1840	1845
Cys Ala Thr Cys Thr Cys	Ala Thr Cys Thr Ala	Cys Cys Thr Cys
1850	1855	1860
Cys Cys Gly Gly Thr Thr	Thr Thr Ala Ala Thr	Gly Ala Ala Thr
1865	1870	1875
Ala Cys Gly Ala Thr Thr	Thr Thr Gly Thr Gly	Cys Cys Ala Gly
1880	1885	1890
Ala Gly Thr Cys Cys Thr	Thr Cys Gly Ala Thr	Ala Gly Gly Gly
1895	1900	1905
Ala Cys Ala Ala Gly Ala	Cys Ala Ala Thr Thr	Gly Cys Ala Cys
1910	1915	1920
Thr Gly Ala Thr Cys Ala	Thr Gly Ala Ala Cys	Thr Cys Cys Thr
1925	1930	1935
Cys Thr Gly Gly Ala Thr	Cys Thr Ala Cys Thr	Gly Gly Thr Cys
1940	1945	1950
Thr Gly Cys Cys Thr Ala	Ala Ala Gly Gly Thr	Gly Thr Cys Gly
1955	1960	1965
Cys Thr Cys Thr Gly Cys	Cys Thr Cys Ala Thr	Ala Gly Ala Ala
1970	1975	1980
Cys Thr Gly Cys Cys Thr	Gly Cys Gly Thr Gly	Ala Gly Ala Thr
1985	1990	1995
Thr Cys Thr Cys Gly Cys	Ala Thr Gly Cys Cys	Ala Gly Ala Gly
2000	2005	2010
Ala Thr Cys Cys Thr Ala	Thr Thr Thr Thr Thr	Gly Gly Cys Ala
2015	2020	2025
Ala Thr Cys Ala Ala Ala	Thr Cys Ala Thr Thr	Cys Cys Gly Gly
2030	2035	2040
Ala Thr Ala Cys Thr Gly	Cys Gly Ala Thr Thr	Thr Thr Ala Ala
2045	2050	2055
Gly Thr Gly Thr Thr Gly	Thr Thr Cys Cys Ala	Thr Thr Cys Cys
2060	2065	2070
Ala Thr Cys Ala Cys Gly	Gly Thr Thr Thr Thr	Gly Gly Ala Ala
2075	2080	2085

Thr Gly Thr Thr Thr Ala Cys Thr Ala Cys Ala Cys Thr Cys Gly	2090	2095	2100
Gly Ala Thr Ala Thr Thr Thr Gly Ala Thr Ala Thr Gly Thr Gly	2105	2110	2115
Gly Ala Thr Thr Thr Cys Gly Ala Gly Thr Cys Gly Thr Cys Thr	2120	2125	2130
Thr Ala Ala Thr Gly Thr Ala Thr Ala Gly Ala Thr Thr Thr Gly	2135	2140	2145
Ala Ala Gly Ala Ala Gly Ala Gly Cys Thr Gly Thr Thr Thr Cys	2150	2155	2160
Thr Gly Ala Gly Gly Ala Gly Cys Cys Thr Thr Cys Ala Gly Gly	2165	2170	2175
Ala Thr Thr Ala Cys Ala Ala Gly Ala Thr Thr Cys Ala Ala Ala	2180	2185	2190
Gly Thr Gly Cys Gly Cys Thr Gly Cys Thr Gly Gly Thr Gly Cys	2195	2200	2205
Cys Ala Ala Cys Cys Cys Thr Ala Thr Thr Cys Thr Cys Cys Thr	2210	2215	2220
Thr Cys Thr Thr Cys Gly Cys Cys Ala Ala Ala Ala Gly Cys Ala	2225	2230	2235
Cys Thr Cys Thr Gly Ala Thr Thr Gly Ala Cys Ala Ala Ala Thr	2240	2245	2250
Ala Cys Gly Ala Thr Thr Thr Ala Thr Cys Thr Ala Ala Thr Thr	2255	2260	2265
Thr Ala Cys Ala Cys Gly Ala Ala Ala Thr Thr Gly Cys Thr Thr	2270	2275	2280
Cys Thr Gly Gly Thr Gly Gly Cys Gly Cys Thr Cys Cys Cys Cys	2285	2290	2295
Thr Cys Thr Cys Thr Ala Ala Gly Gly Ala Ala Gly Thr Cys Gly	2300	2305	2310
Gly Gly Gly Ala Ala Gly Cys Gly Gly Thr Thr Gly Cys Cys Ala	2315	2320	2325
Ala Gly Ala Gly Gly Thr Thr Cys Cys Ala Thr Cys Thr Gly Cys	2330	2335	2340
Cys Ala Gly Gly Thr Ala Thr Cys Ala Gly Gly Cys Ala Ala Gly	2345	2350	2355
Gly Ala Thr Ala Thr Gly Gly Gly Cys Thr Cys Ala Cys Thr Gly	2360	2365	2370
Ala Gly Ala Cys Thr Ala Cys Ala Thr Cys Ala Gly Cys Thr Ala			

2375	2380	2385
Thr Thr Cys Thr Gly Ala	Thr Thr Ala Cys Ala	Cys Cys Cys Gly
2390	2395	2400
Ala Gly Gly Gly Gly Gly	Ala Thr Gly Ala Thr	Ala Ala Ala Cys
2405	2410	2415
Cys Gly Gly Gly Cys Gly	Cys Gly Gly Thr Cys	Gly Gly Thr Ala
2420	2425	2430
Ala Ala Gly Thr Thr Gly	Thr Thr Cys Cys Ala	Thr Thr Thr Thr
2435	2440	2445
Thr Thr Gly Ala Ala Gly	Cys Gly Ala Ala Gly	Gly Thr Thr Gly
2450	2455	2460
Thr Gly Gly Ala Thr Cys	Thr Gly Gly Ala Thr	Ala Cys Cys Gly
2465	2470	2475
Gly Gly Ala Ala Ala Ala	Cys Gly Cys Thr Gly	Gly Gly Cys Gly
2480	2485	2490
Thr Thr Ala Ala Thr Cys	Ala Ala Ala Gly Ala	Gly Gly Cys Gly
2495	2500	2505
Ala Ala Cys Thr Gly Thr	Gly Thr Gly Thr Gly	Ala Gly Ala Gly
2510	2515	2520
Gly Thr Cys Cys Thr Ala	Thr Gly Ala Thr Thr	Ala Thr Gly Thr
2525	2530	2535
Cys Cys Gly Gly Thr Thr	Ala Thr Gly Thr Ala	Ala Ala Cys Ala
2540	2545	2550
Ala Thr Cys Cys Gly Gly	Ala Ala Gly Cys Gly	Ala Cys Cys Ala
2555	2560	2565
Ala Cys Gly Cys Cys Thr	Thr Gly Ala Thr Thr	Gly Ala Cys Ala
2570	2575	2580
Ala Gly Gly Ala Thr Gly	Gly Ala Thr Gly Gly	Cys Thr Ala Cys
2585	2590	2595
Ala Thr Thr Cys Thr Gly	Gly Ala Gly Ala Cys	Ala Thr Ala Gly
2600	2605	2610
Cys Thr Thr Ala Cys Thr	Gly Gly Gly Ala Cys	Gly Ala Ala Gly
2615	2620	2625
Ala Cys Gly Ala Ala Cys	Ala Cys Thr Thr Cys	Thr Thr Cys Ala
2630	2635	2640
Thr Cys Gly Thr Thr Gly	Ala Cys Cys Gly Cys	Cys Thr Gly Ala
2645	2650	2655
Ala Gly Thr Cys Thr Cys	Thr Gly Ala Thr Thr	Ala Ala Gly Thr
2660	2665	2670

Ala Cys Ala Ala Ala Gly Gly Cys Thr Ala Thr Cys Ala Gly Gly	2675	2680	2685
Thr Gly Gly Cys Thr Cys Cys Cys Gly Cys Thr Gly Ala Ala Thr	2690	2695	2700
Thr Gly Gly Ala Ala Thr Cys Cys Ala Thr Cys Thr Thr Gly Cys	2705	2710	2715
Thr Cys Cys Ala Ala Cys Ala Cys Cys Cys Cys Ala Ala Cys Ala	2720	2725	2730
Thr Cys Thr Thr Cys Gly Ala Cys Gly Cys Ala Gly Gly Thr Gly	2735	2740	2745
Thr Cys Gly Cys Ala Gly Gly Thr Cys Thr Thr Cys Cys Cys Gly	2750	2755	2760
Ala Cys Gly Ala Thr Gly Ala Cys Gly Cys Cys Gly Gly Thr Gly	2765	2770	2775
Ala Ala Cys Thr Thr Cys Cys Cys Gly Cys Cys Gly Cys Cys Gly	2780	2785	2790
Thr Thr Gly Thr Thr Gly Thr Thr Thr Thr Gly Gly Ala Gly Cys	2795	2800	2805
Ala Cys Gly Gly Ala Ala Ala Gly Ala Cys Gly Ala Thr Gly Ala	2810	2815	2820
Cys Gly Gly Ala Ala Ala Ala Ala Gly Ala Gly Ala Thr Cys Gly	2825	2830	2835
Thr Gly Gly Ala Thr Thr Ala Cys Gly Thr Cys Gly Cys Cys Ala	2840	2845	2850
Gly Thr Cys Ala Ala Gly Thr Ala Ala Cys Ala Ala Cys Cys Gly	2855	2860	2865
Cys Gly Ala Ala Ala Ala Ala Gly Thr Thr Gly Cys Gly Cys Gly	2870	2875	2880
Gly Ala Gly Gly Ala Gly Thr Thr Gly Thr Gly Thr Thr Thr Gly	2885	2890	2895
Thr Gly Gly Ala Cys Gly Ala Ala Gly Thr Ala Cys Cys Gly Ala	2900	2905	2910
Ala Ala Gly Gly Thr Cys Thr Thr Ala Cys Cys Gly Gly Ala Ala	2915	2920	2925
Ala Ala Cys Thr Cys Gly Ala Cys Gly Cys Ala Ala Gly Ala Ala	2930	2935	2940
Ala Ala Ala Thr Cys Ala Gly Ala Gly Ala Gly Ala Thr Cys Cys	2945	2950	2955
Thr Cys Ala Thr Ala Ala Ala Gly Gly Cys Cys Ala Ala Gly Ala			

2960	2965	2970
Ala Gly Gly Gly Cys Gly	Gly Ala Ala Ala Gly	Ala Thr Cys Gly
2975	2980	2985
Cys Cys Gly Thr Gly Thr	Ala Ala Thr Thr Cys	Thr Ala Gly Ala
2990	2995	3000
Cys Gly Ala Gly Ala Thr	Cys Cys Gly Ala Ala	Cys Thr Thr Gly
3005	3010	3015
Thr Thr Thr Ala Thr Thr	Gly Cys Ala Gly Cys	Thr Thr Ala Thr
3020	3025	3030
Ala Ala Thr Gly Gly Thr	Thr Ala Cys Ala Ala	Ala Thr Ala Ala
3035	3040	3045
Ala Gly Cys Ala Ala Thr	Ala Gly Cys Ala Thr	Cys Ala Cys Ala
3050	3055	3060
Ala Ala Thr Thr Thr Cys	Ala Cys Ala Ala Ala	Thr Ala Ala Ala
3065	3070	3075
Gly Cys Ala Thr Thr Thr	Thr Thr Thr Thr Cys	Ala Cys Thr Gly
3080	3085	3090
Cys Ala Thr Thr Cys Thr	Ala Gly Thr Thr Gly	Thr Gly Gly Thr
3095	3100	3105
Thr Thr Gly Thr Cys Cys	Ala Ala Ala Cys Thr	Cys Ala Thr Cys
3110	3115	3120
Ala Ala Thr Gly Thr Ala	Thr Cys Thr Thr Ala	Thr Cys Ala Thr
3125	3130	3135
Gly Thr Cys Thr Ala Gly	Ala Thr Cys Cys Ala	Gly Gly Thr Ala
3140	3145	3150
Gly Gly Thr Thr Thr Gly	Ala Gly Thr Ala Gly	Thr Gly Gly Gly
3155	3160	3165
Cys Gly Thr Gly Gly Cys	Thr Ala Ala Gly Gly	Thr Gly Ala Cys
3170	3175	3180
Thr Ala Thr Ala Ala Ala	Gly Gly Cys Gly Gly	Gly Thr Gly Thr
3185	3190	3195
Cys Thr Thr Ala Cys Gly	Ala Gly Gly Gly Thr	Cys Thr Thr Thr
3200	3205	3210
Thr Thr Gly Cys Thr Thr	Thr Thr Cys Thr Gly	Cys Ala Gly Ala
3215	3220	3225
Cys Ala Thr Cys Ala Thr	Gly Ala Ala Cys Gly	Gly Gly Ala Cys
3230	3235	3240
Thr Gly Gly Cys Gly Gly	Gly Gly Cys Cys Thr	Thr Cys Gly Ala
3245	3250	3255

Ala Gly Gly Gly Gly Gly Gly Gly Cys Thr Thr Thr Thr Thr Ala Gly	3260	3265	3270
Cys Cys Cys Thr Thr Ala Thr Thr Thr Gly Ala Cys Ala Ala Cys	3275	3280	3285
Cys Cys Gly Cys Cys Thr Gly Cys Cys Gly Gly Gly Ala Thr Gly	3290	3295	3300
Gly Gly Cys Cys Gly Gly Ala Gly Thr Thr Cys Gly Thr Cys Ala	3305	3310	3315
Gly Ala Ala Thr Gly Thr Gly Ala Thr Gly Gly Gly Ala Thr Cys	3320	3325	3330
Gly Ala Cys Gly Gly Thr Gly Gly Ala Thr Gly Gly Gly Cys Gly	3335	3340	3345
Cys Cys Cys Ala Gly Thr Gly Cys Thr Thr Cys Cys Ala Gly Cys	3350	3355	3360
Ala Ala Ala Thr Thr Cys Cys Thr Cys Gly Ala Cys Cys Ala Thr	3365	3370	3375
Gly Ala Cys Cys Thr Ala Cys Gly Cys Gly Ala Cys Cys Gly Thr	3380	3385	3390
Gly Gly Gly Gly Ala Ala Cys Thr Cys Gly Thr Cys Gly Cys Thr	3395	3400	3405
Cys Gly Ala Cys Ala Gly Cys Ala Cys Cys Gly Cys Cys Gly Cys	3410	3415	3420
Ala Gly Cys Cys Gly Cys Gly Gly Cys Ala Gly Cys Cys Gly Cys	3425	3430	3435
Ala Gly Cys Cys Gly Cys Cys Ala Thr Gly Ala Cys Ala Gly Cys	3440	3445	3450
Gly Ala Cys Gly Ala Gly Ala Cys Thr Gly Gly Cys Cys Thr Cys	3455	3460	3465
Gly Ala Gly Cys Thr Ala Cys Ala Thr Gly Cys Cys Cys Ala Gly	3470	3475	3480
Cys Ala Gly Cys Gly Gly Thr Ala Gly Thr Ala Gly Cys Cys Cys	3485	3490	3495
Cys Thr Cys Thr Gly Thr Gly Cys Cys Cys Ala Gly Thr Thr Cys	3500	3505	3510
Cys Ala Thr Cys Ala Thr Cys Gly Cys Cys Gly Ala Gly Gly Ala	3515	3520	3525
Gly Ala Ala Ala Cys Thr Gly Cys Thr Gly Gly Cys Cys Cys Thr	3530	3535	3540
Gly Cys Thr Gly Gly Cys Cys Gly Ala Gly Cys Thr Gly Gly Ala			

3545	3550	3555
Ala Gly Cys Cys Cys Thr	Gly Ala Gly Cys Cys	Gly Cys Cys Ala
3560	3565	3570
Gly Cys Thr Gly Gly Cys	Cys Gly Cys Cys Cys	Thr Gly Ala Cys
3575	3580	3585
Cys Cys Ala Gly Cys Ala	Gly Gly Thr Gly Thr	Cys Cys Gly Ala
3590	3595	3600
Gly Cys Thr Cys Cys Gly	Cys Gly Ala Ala Cys	Ala Gly Cys Ala
3605	3610	3615
Gly Cys Ala Gly Cys Ala	Gly Cys Ala Ala Ala	Ala Thr Ala Ala
3620	3625	3630
Ala Thr Gly Ala Thr Thr	Cys Ala Ala Thr Ala	Ala Ala Cys Ala
3635	3640	3645
Cys Ala Gly Ala Thr Thr	Cys Thr Gly Ala Thr	Thr Cys Ala Ala
3650	3655	3660
Ala Cys Ala Gly Cys Ala	Ala Ala Gly Cys Ala	Thr Cys Thr Thr
3665	3670	3675
Thr Ala Thr Thr Ala Thr	Thr Thr Ala Thr Thr	Thr Thr Thr Thr
3680	3685	3690
Cys Gly Cys Gly Cys Gly	Cys Gly Gly Thr Ala	Gly Gly Cys Cys
3695	3700	3705
Cys Thr Gly Gly Thr Cys	Cys Ala Cys Cys Thr	Cys Thr Cys Cys
3710	3715	3720
Cys Gly Ala Thr Cys Ala	Thr Thr Gly Ala Gly	Ala Gly Thr Gly
3725	3730	3735
Cys Gly Gly Thr Gly Gly	Ala Thr Thr Thr Thr	Thr Thr Cys Cys
3740	3745	3750
Ala Gly Gly Ala Cys Cys	Cys Gly Gly Thr Ala	Gly Ala Gly Gly
3755	3760	3765
Thr Gly Gly Gly Ala Thr	Thr Gly Gly Ala Thr	Gly Thr Thr Gly
3770	3775	3780
Ala Gly Gly Thr Ala Cys	Ala Thr Gly Gly Gly	Cys Ala Thr Gly
3785	3790	3795
Ala Gly Cys Cys Cys Gly	Thr Cys Cys Cys Gly	Thr Gly Gly Gly
3800	3805	3810
Thr Gly Gly Ala Gly Gly	Thr Ala Gly Cys Ala	Cys Cys Ala Cys
3815	3820	3825
Thr Gly Cys Ala Thr Gly	Gly Cys Cys Thr Cys	Gly Thr Gly Cys
3830	3835	3840

Thr Cys Thr Gly Gly Gly Gly Thr Cys Gly Thr Gly Thr Thr Gly	3845	3850	3855
Thr Ala Gly Ala Thr Gly Ala Thr Cys Cys Ala Gly Thr Cys Ala	3860	3865	3870
Thr Ala Gly Cys Ala Gly Gly Gly Gly Cys Gly Cys Thr Gly Gly	3875	3880	3885
Gly Cys Gly Thr Gly Gly Thr Gly Cys Thr Gly Gly Ala Thr Gly	3890	3895	3900
Ala Thr Gly Thr Cys Cys Thr Thr Gly Ala Gly Gly Ala Gly Gly	3905	3910	3915
Ala Gly Ala Cys Thr Gly Ala Thr Gly Gly Cys Cys Ala Cys Gly	3920	3925	3930
Gly Gly Gly Ala Gly Cys Cys Cys Cys Thr Thr Gly Gly Thr Gly	3935	3940	3945
Thr Ala Gly Gly Thr Gly Thr Thr Gly Gly Cys Ala Ala Ala Ala	3950	3955	3960
Cys Gly Gly Thr Thr Gly Ala Gly Cys Thr Gly Gly Gly Ala Gly	3965	3970	3975
Gly Gly Ala Thr Gly Cys Ala Thr Gly Cys Gly Gly Gly Gly Gly	3980	3985	3990
Gly Ala Gly Ala Thr Gly Ala Thr Gly Thr Gly Cys Ala Gly Thr	3995	4000	4005
Thr Thr Gly Gly Cys Cys Thr Gly Gly Ala Thr Cys Thr Thr Gly	4010	4015	4020
Ala Gly Gly Thr Thr Gly Gly Cys Gly Ala Thr Gly Thr Thr Gly	4025	4030	4035
Cys Cys Ala Cys Cys Cys Ala Gly Ala Thr Cys Cys Cys Gly Cys	4040	4045	4050
Cys Gly Gly Gly Gly Gly Thr Thr Cys Ala Thr Gly Thr Thr Gly	4055	4060	4065
Thr Gly Cys Ala Gly Gly Ala Cys Cys Ala Cys Cys Ala Gly Ala	4070	4075	4080
Ala Cys Gly Gly Thr Gly Thr Ala Gly Cys Cys Cys Gly Thr Gly	4085	4090	4095
Cys Ala Cys Thr Thr Gly Gly Gly Gly Ala Ala Cys Thr Thr Gly	4100	4105	4110
Thr Cys Ala Thr Gly Cys Ala Ala Cys Thr Thr Gly Gly Ala Ala	4115	4120	4125
Gly Gly Gly Ala Ala Thr Gly Cys Gly Thr Gly Gly Ala Ala Gly			

4130	4135	4140
Ala Ala Thr Thr Thr Gly Gly Ala Gly Ala Cys Gly Cys Cys Cys		
4145	4150	4155
Thr Thr Gly Thr Gly Cys Cys Cys Gly Cys Cys Cys Ala Gly Gly		
4160	4165	4170
Thr Thr Thr Thr Cys Cys Ala Thr Gly Cys Ala Cys Thr Cys Ala		
4175	4180	4185
Thr Cys Cys Ala Thr Gly Ala Thr Gly Ala Thr Gly Gly Cys Ala		
4190	4195	4200
Ala Thr Gly Gly Gly Cys Cys Cys Gly Thr Gly Gly Gly Cys Thr		
4205	4210	4215
Gly Cys Gly Gly Cys Thr Thr Thr Gly Gly Cys Ala Ala Ala Gly		
4220	4225	4230
Ala Cys Gly Thr Thr Thr Cys Thr Gly Gly Gly Gly Thr Cys Ala		
4235	4240	4245
Gly Ala Gly Ala Cys Ala Thr Cys Gly Thr Ala Ala Thr Thr Ala		
4250	4255	4260
Thr Gly Cys Thr Cys Cys Thr Gly Gly Gly Thr Gly Ala Gly Ala		
4265	4270	4275
Thr Cys Ala Thr Cys Ala Thr Ala Ala Gly Ala Cys Ala Thr Thr		
4280	4285	4290
Thr Thr Ala Ala Thr Gly Ala Ala Thr Thr Thr Gly Gly Gly Gly		
4295	4300	4305
Cys Gly Gly Ala Gly Gly Gly Thr Gly Cys Cys Ala Gly Ala Thr		
4310	4315	4320
Thr Gly Gly Gly Gly Gly Ala Cys Gly Ala Thr Gly Gly Thr Thr		
4325	4330	4335
Cys Cys Cys Thr Cys Gly Gly Gly Cys Cys Cys Cys Gly Gly Gly		
4340	4345	4350
Gly Cys Gly Ala Ala Gly Thr Thr Cys Cys Cys Cys Thr Cys Gly		
4355	4360	4365
Cys Ala Gly Ala Thr Cys Thr Gly Cys Ala Thr Cys Thr Cys Cys		
4370	4375	4380
Cys Ala Gly Gly Cys Thr Thr Thr Cys Ala Thr Cys Thr Cys Gly		
4385	4390	4395
Gly Ala Gly Gly Gly Gly Gly Gly Gly Gly Ala Thr Cys Ala Thr Gly		
4400	4405	4410
Thr Cys Cys Ala Cys Cys Thr Gly Cys Gly Gly Gly Gly Cys Gly		
4415	4420	4425

Ala Thr Gly Ala Ala Ala Ala Ala Ala Ala Cys Gly Gly Thr Thr	4430	4435	4440
Thr Cys Cys Gly Gly Gly Gly Cys Gly Gly Gly Gly Gly Thr Gly	4445	4450	4455
Ala Thr Gly Ala Gly Cys Thr Gly Cys Gly Ala Gly Gly Ala Gly	4460	4465	4470
Ala Gly Cys Ala Gly Gly Thr Thr Thr Cys Thr Cys Ala Ala Cys	4475	4480	4485
Ala Gly Cys Thr Gly Gly Gly Ala Cys Thr Thr Gly Cys Cys Gly	4490	4495	4500
Cys Ala Cys Cys Cys Gly Gly Thr Cys Gly Gly Gly Cys Cys Gly	4505	4510	4515
Thr Ala Gly Ala Thr Gly Ala Cys Cys Cys Cys Gly Ala Thr Gly	4520	4525	4530
Ala Cys Gly Gly Gly Thr Thr Gly Cys Ala Gly Gly Thr Gly Gly	4535	4540	4545
Thr Ala Gly Thr Thr Cys Ala Ala Gly Gly Ala Cys Ala Thr Gly	4550	4555	4560
Cys Ala Gly Cys Thr Gly Cys Cys Gly Thr Cys Gly Thr Cys Cys	4565	4570	4575
Cys Gly Gly Ala Gly Gly Ala Gly Gly Gly Gly Gly Gly Cys Cys	4580	4585	4590
Ala Cys Cys Thr Cys Gly Thr Thr Gly Ala Gly Cys Thr Thr Gly	4595	4600	4605
Thr Cys Thr Cys Thr Gly Ala Cys Thr Thr Gly Gly Ala Gly Gly	4610	4615	4620
Thr Thr Thr Thr Cys Cys Cys Gly Gly Ala Cys Gly Ala Gly Cys	4625	4630	4635
Thr Cys Gly Cys Cys Gly Ala Gly Gly Ala Gly Gly Cys Gly Gly	4640	4645	4650
Thr Cys Cys Cys Cys Gly Cys Cys Cys Ala Gly Cys Gly Ala Gly	4655	4660	4665
Ala Gly Ala Ala Gly Cys Thr Cys Thr Thr Gly Cys Ala Gly Gly	4670	4675	4680
Gly Ala Ala Gly Cys Ala Ala Ala Gly Thr Thr Thr Thr Thr Cys	4685	4690	4695
Ala Gly Gly Gly Gly Cys Thr Thr Gly Ala Gly Cys Cys Cys Gly	4700	4705	4710
Thr Cys Gly Gly Cys Cys Ala Thr Gly Gly Gly Cys Ala Thr Cys			

4715	4720	4725
Thr Thr Gly Gly Cys Gly	Ala Gly Gly Gly Thr	Cys Thr Gly Cys
4730	4735	4740
Gly Ala Gly Ala Gly Gly	Ala Gly Cys Thr Cys	Cys Ala Gly Gly
4745	4750	4755
Cys Gly Gly Thr Cys Cys	Cys Ala Gly Ala Gly	Cys Thr Cys Gly
4760	4765	4770
Gly Thr Gly Ala Cys Gly	Thr Gly Cys Thr Cys	Thr Ala Cys Gly
4775	4780	4785
Gly Cys Ala Thr Cys Thr	Cys Gly Ala Thr Cys	Cys Ala Gly Cys
4790	4795	4800
Ala Gly Ala Cys Thr Thr	Cys Cys Thr Cys Gly	Thr Thr Thr Cys
4805	4810	4815
Gly Gly Gly Gly Gly Thr	Thr Gly Gly Gly Ala	Cys Gly Ala Cys
4820	4825	4830
Thr Gly Cys Gly Ala Cys	Thr Gly Thr Ala Gly	Gly Gly Cys Ala
4835	4840	4845
Cys Gly Ala Gly Ala Cys	Gly Ala Thr Gly Gly	Gly Cys Gly Thr
4850	4855	4860
Cys Cys Ala Gly Cys Gly	Cys Gly Gly Cys Cys	Ala Gly Cys Gly
4865	4870	4875
Thr Cys Ala Thr Gly Thr	Cys Cys Thr Thr Cys	Cys Ala Gly Gly
4880	4885	4890
Gly Thr Cys Thr Cys Ala	Gly Gly Gly Thr Cys	Cys Gly Cys Gly
4895	4900	4905
Thr Gly Ala Gly Gly Gly	Thr Gly Gly Thr Cys	Thr Cys Cys Gly
4910	4915	4920
Thr Cys Ala Cys Gly Gly	Thr Gly Ala Ala Gly	Gly Gly Gly Thr
4925	4930	4935
Gly Gly Gly Cys Cys Gly	Cys Gly Gly Gly Cys	Thr Gly Gly Gly
4940	4945	4950
Cys Gly Cys Thr Thr Gly	Cys Ala Ala Gly Gly	Gly Thr Gly Cys
4955	4960	4965
Gly Cys Thr Thr Gly Ala	Gly Ala Cys Thr Cys	Ala Thr Cys Cys
4970	4975	4980
Thr Gly Cys Thr Gly Gly	Thr Gly Cys Thr Gly	Ala Ala Ala Cys
4985	4990	4995
Gly Gly Gly Cys Ala Cys	Gly Gly Thr Cys Thr	Thr Cys Gly Cys
5000	5005	5010

Cys Cys Thr Gly Cys Gly Cys Gly Thr Cys Gly Gly Cys Gly Ala 5015	5020	5025
Gly Ala Thr Ala Gly Cys Ala Gly Thr Thr Gly Ala Cys Cys Ala 5030	5035	5040
Thr Gly Ala Gly Cys Thr Cys Gly Thr Ala Gly Thr Thr Gly Ala 5045	5050	5055
Gly Gly Gly Cys Cys Thr Cys Gly Gly Cys Gly Gly Cys Gly Thr 5060	5065	5070
Gly Gly Cys Cys Cys Thr Thr Gly Gly Cys Gly Cys Gly Gly Ala 5075	5080	5085
Gly Cys Thr Thr Gly Cys Cys Cys Thr Thr Gly Gly Ala Ala Gly 5090	5095	5100
Ala Gly Cys Gly Cys Cys Cys Gly Cys Ala Gly Gly Cys Gly Gly 5105	5110	5115
Gly Ala Cys Ala Gly Ala Gly Gly Ala Gly Gly Gly Ala Thr Thr 5120	5125	5130
Gly Cys Ala Gly Gly Gly Cys Gly Thr Ala Gly Ala Gly Cys Thr 5135	5140	5145
Thr Gly Gly Gly Cys Gly Cys Gly Ala Gly Ala Ala Ala Gly Ala 5150	5155	5160
Cys Gly Gly Ala Cys Thr Cys Gly Gly Gly Gly Gly Cys Gly Ala 5165	5170	5175
Ala Gly Gly Cys Gly Thr Cys Cys Gly Cys Thr Cys Cys Gly Cys 5180	5185	5190
Ala Gly Thr Gly Gly Gly Cys Gly Cys Ala Gly Ala Cys Gly Gly 5195	5200	5205
Thr Cys Thr Cys Gly Cys Ala Cys Thr Cys Gly Ala Cys Thr Ala 5210	5215	5220
Gly Cys Cys Ala Gly Gly Thr Gly Ala Gly Cys Thr Cys Gly Gly 5225	5230	5235
Gly Cys Thr Gly Cys Thr Cys Gly Gly Gly Gly Thr Cys Ala Ala 5240	5245	5250
Ala Ala Ala Cys Cys Ala Gly Thr Thr Thr Thr Cys Cys Cys Cys 5255	5260	5265
Cys Gly Thr Thr Cys Thr Thr Thr Thr Thr Gly Ala Thr Gly Cys 5270	5275	5280
Gly Cys Thr Thr Cys Thr Thr Ala Cys Cys Thr Cys Gly Cys Gly 5285	5290	5295
Thr Cys Thr Cys Cys Ala Thr Gly Ala Gly Thr Cys Thr Gly Thr		

5300	5305	5310
Gly Thr Cys Cys Gly Cys	Gly Cys Thr Cys Gly	Gly Thr Gly Ala
5315	5320	5325
Cys Ala Ala Ala Cys Ala	Gly Gly Cys Thr Gly	Thr Cys Thr Gly
5330	5335	5340
Thr Gly Thr Cys Cys Cys	Cys Gly Thr Ala Gly	Ala Cys Gly Gly
5345	5350	5355
Ala Cys Thr Thr Gly Ala	Thr Gly Gly Gly Cys	Cys Thr Gly Thr
5360	5365	5370
Cys Cys Thr Gly Cys Ala	Gly Gly Gly Gly Cys	Gly Thr Cys Cys
5375	5380	5385
Cys Gly Cys Gly Gly Thr	Cys Cys Thr Cys Cys	Thr Cys Gly Thr
5390	5395	5400
Ala Gly Ala Gly Ala Ala	Ala Cys Thr Cys Ala	Gly Ala Cys Cys
5405	5410	5415
Ala Cys Thr Cys Thr Gly	Ala Gly Ala Cys Gly	Ala Ala Gly Gly
5420	5425	5430
Cys Gly Cys Gly Cys Gly	Thr Cys Cys Ala Cys	Gly Cys Cys Ala
5435	5440	5445
Ala Gly Ala Cys Ala Ala	Ala Gly Gly Ala Gly	Gly Cys Cys Ala
5450	5455	5460
Cys Gly Thr Gly Cys Gly	Ala Gly Gly Gly Gly	Thr Ala Gly Cys
5465	5470	5475
Gly Gly Thr Cys Gly Thr	Thr Gly Thr Cys Cys	Ala Cys Cys Ala
5480	5485	5490
Gly Gly Gly Gly Gly Thr	Cys Cys Ala Cys Cys	Thr Thr Thr Thr
5495	5500	5505
Cys Cys Ala Cys Gly Gly	Thr Ala Thr Gly Cys	Ala Gly Gly Cys
5510	5515	5520
Ala Cys Ala Thr Gly Thr	Cys Cys Cys Cys Cys	Thr Cys Cys Thr
5525	5530	5535
Cys Cys Gly Cys Ala Thr	Cys Cys Ala Ala Gly	Ala Ala Gly Gly
5540	5545	5550
Thr Gly Ala Thr Thr Gly	Gly Cys Thr Thr Gly	Thr Ala Gly Gly
5555	5560	5565
Thr Gly Thr Ala Gly Gly	Cys Cys Ala Cys Gly	Thr Gly Ala Cys
5570	5575	5580
Cys Thr Gly Gly Gly Gly	Thr Thr Cys Cys Cys	Gly Ala Cys Gly
5585	5590	5595

Gly Gly Gly Gly Gly Gly Thr Ala Thr Ala Ala Ala Ala Gly Gly	5600	5605	5610
Gly Gly Gly Cys Gly Gly Gly Thr Cys Thr Gly Thr Gly Cys Thr	5615	5620	5625
Cys Gly Thr Cys Cys Thr Cys Ala Cys Thr Cys Thr Cys Thr Thr	5630	5635	5640
Cys Cys Gly Cys Gly Thr Cys Gly Cys Thr Gly Thr Cys Cys Ala	5645	5650	5655
Cys Gly Ala Gly Cys Gly Cys Cys Ala Gly Cys Thr Gly Thr Thr	5660	5665	5670
Gly Gly Gly Gly Thr Ala Gly Gly Thr Ala Thr Thr Cys Cys Cys	5675	5680	5685
Thr Cys Thr Cys Ala Ala Gly Ala Gly Cys Gly Gly Gly Cys Ala	5690	5695	5700
Thr Gly Ala Cys Cys Thr Cys Gly Gly Cys Ala Cys Thr Cys Ala	5705	5710	5715
Gly Gly Thr Thr Gly Thr Cys Ala Gly Thr Thr Thr Cys Thr Ala	5720	5725	5730
Gly Ala Ala Ala Cys Gly Ala Gly Gly Ala Gly Gly Ala Thr Thr	5735	5740	5745
Thr Gly Ala Thr Gly Thr Gly Gly Gly Cys Cys Thr Gly Cys Cys	5750	5755	5760
Cys Thr Gly Cys Cys Gly Cys Gly Ala Thr Gly Cys Thr Thr Thr	5765	5770	5775
Thr Thr Ala Gly Gly Ala Gly Ala Cys Thr Thr Thr Cys Ala Thr	5780	5785	5790
Cys Cys Ala Thr Cys Thr Gly Gly Thr Cys Ala Gly Ala Ala Ala	5795	5800	5805
Ala Gly Ala Cys Thr Ala Thr Thr Thr Thr Thr Thr Thr Ala Thr	5810	5815	5820
Thr Gly Thr Cys Ala Ala Gly Cys Thr Thr Gly Gly Thr Gly Gly	5825	5830	5835
Cys Gly Ala Ala Gly Gly Ala Gly Cys Cys Ala Thr Ala Gly Ala	5840	5845	5850
Gly Gly Gly Cys Gly Thr Thr Thr Gly Ala Gly Ala Gly Ala Ala	5855	5860	5865
Gly Cys Thr Thr Gly Gly Cys Gly Ala Thr Gly Gly Ala Thr Cys	5870	5875	5880
Thr Cys Ala Thr Gly Gly Thr Cys Thr Gly Ala Thr Thr Thr Thr			

5885	5890	5895
Thr Gly Thr Cys Ala Cys Gly Gly Thr Cys Gly Gly Cys Gly Cys		
5900	5905	5910
Gly Cys Thr Cys Cys Thr Thr Gly Gly Cys Cys Gly Cys Gly Ala		
5915	5920	5925
Thr Gly Thr Thr Gly Ala Gly Cys Thr Gly Gly Ala Cys Ala Thr		
5930	5935	5940
Ala Thr Thr Cys Gly Cys Gly Cys Gly Cys Gly Ala Cys Ala Cys		
5945	5950	5955
Ala Cys Thr Thr Cys Cys Ala Thr Thr Cys Gly Gly Gly Gly Ala		
5960	5965	5970
Ala Gly Ala Cys Gly Gly Thr Gly Gly Thr Gly Cys Gly Cys Thr		
5975	5980	5985
Cys Gly Thr Cys Gly Gly Gly Cys Ala Cys Gly Ala Thr Cys Cys		
5990	5995	6000
Thr Gly Ala Cys Gly Cys Gly Cys Cys Ala Gly Cys Cys Gly Cys		
6005	6010	6015
Gly Gly Thr Thr Ala Thr Gly Cys Ala Gly Gly Gly Thr Gly Ala		
6020	6025	6030
Cys Cys Ala Gly Gly Thr Cys Cys Ala Cys Gly Cys Thr Gly Gly		
6035	6040	6045
Thr Gly Gly Cys Cys Ala Cys Cys Thr Cys Gly Cys Cys Gly Cys		
6050	6055	6060
Gly Cys Ala Gly Gly Gly Gly Cys Thr Cys Gly Thr Thr Gly Gly		
6065	6070	6075
Thr Cys Cys Ala Gly Cys Ala Gly Ala Gly Thr Cys Thr Gly Cys		
6080	6085	6090
Cys Gly Cys Cys Cys Thr Thr Gly Cys Gly Cys Gly Ala Gly Cys		
6095	6100	6105
Ala Gly Ala Ala Cys Gly Gly Gly Gly Gly Cys Ala Gly Cys Ala		
6110	6115	6120
Cys Ala Thr Cys Ala Ala Gly Cys Ala Gly Ala Thr Gly Cys Thr		
6125	6130	6135
Cys Gly Thr Cys Ala Gly Gly Gly Gly Gly Thr Cys Cys Gly		
6140	6145	6150
Cys Ala Thr Cys Gly Ala Thr Gly Gly Thr Gly Ala Ala Gly Ala		
6155	6160	6165
Thr Gly Cys Cys Cys Gly Gly Ala Cys Ala Gly Ala Gly Thr Thr		
6170	6175	6180

Cys Cys Thr Thr Gly Thr Cys Ala Ala Ala Ala Thr Ala Ala Thr	6185	6190	6195
Cys Gly Ala Thr Thr Thr Thr Thr Gly Ala Gly Gly Ala Thr Gly	6200	6205	6210
Cys Ala Thr Cys Gly Thr Cys Cys Ala Ala Gly Gly Cys Cys Ala	6215	6220	6225
Thr Cys Thr Gly Cys Cys Ala Cys Thr Cys Gly Cys Gly Gly Gly	6230	6235	6240
Cys Gly Gly Cys Cys Ala Gly Cys Gly Cys Thr Cys Gly Cys Thr	6245	6250	6255
Cys Gly Thr Ala Gly Gly Gly Gly Thr Thr Gly Ala Gly Gly Gly	6260	6265	6270
Gly Cys Gly Gly Ala Cys Cys Cys Cys Ala Ala Gly Gly Cys Ala	6275	6280	6285
Thr Gly Gly Gly Ala Thr Gly Cys Gly Thr Gly Ala Gly Gly Gly	6290	6295	6300
Cys Gly Gly Ala Gly Gly Cys Gly Thr Ala Cys Ala Thr Gly Cys	6305	6310	6315
Cys Gly Cys Ala Gly Ala Thr Gly Thr Cys Ala Thr Ala Gly Ala	6320	6325	6330
Cys Ala Thr Ala Gly Ala Thr Gly Gly Gly Cys Thr Cys Cys Gly	6335	6340	6345
Ala Gly Ala Gly Gly Ala Thr Gly Cys Cys Gly Ala Thr Gly Thr	6350	6355	6360
Ala Gly Gly Thr Gly Gly Gly Ala Thr Ala Gly Cys Ala Gly Cys	6365	6370	6375
Gly Cys Cys Cys Cys Cys Cys Gly Cys Gly Gly Ala Thr Gly Cys	6380	6385	6390
Thr Thr Gly Cys Gly Cys Gly Cys Ala Cys Gly Thr Ala Gly Thr	6395	6400	6405
Cys Ala Thr Ala Cys Ala Ala Cys Thr Cys Gly Thr Gly Cys Gly	6410	6415	6420
Ala Gly Gly Gly Gly Gly Cys Cys Ala Ala Gly Ala Ala Gly Gly	6425	6430	6435
Cys Gly Gly Gly Gly Cys Cys Gly Ala Gly Ala Thr Thr Gly Gly	6440	6445	6450
Thr Gly Cys Gly Cys Thr Gly Gly Gly Gly Cys Thr Gly Cys Thr	6455	6460	6465
Cys Gly Gly Cys Gly Cys Gly Gly Ala Ala Gly Ala Cys Gly Ala			

6470	6475	6480
Thr Cys Thr Gly Gly Cys	Gly Ala Ala Ala Gly	Ala Thr Gly Gly
6485	6490	6495
Cys Gly Thr Gly Cys Gly	Ala Gly Thr Thr Gly	Gly Ala Gly Gly
6500	6505	6510
Ala Gly Ala Thr Gly Gly	Thr Gly Gly Gly Cys	Cys Gly Thr Thr
6515	6520	6525
Gly Gly Ala Ala Gly Ala	Thr Gly Thr Thr Ala	Ala Ala Gly Thr
6530	6535	6540
Gly Gly Gly Cys Gly Thr	Gly Ala Gly Gly Cys	Ala Gly Gly Cys
6545	6550	6555
Gly Gly Ala Cys Cys Gly	Ala Gly Thr Cys Gly	Cys Gly Gly Ala
6560	6565	6570
Thr Gly Ala Ala Gly Thr	Gly Cys Gly Cys Gly	Thr Ala Gly Gly
6575	6580	6585
Ala Gly Thr Cys Thr Thr	Gly Cys Ala Gly Cys	Thr Thr Gly Gly
6590	6595	6600
Cys Gly Ala Cys Gly Ala	Gly Cys Thr Cys Gly	Gly Cys Gly Gly
6605	6610	6615
Thr Gly Ala Cys Gly Ala	Gly Gly Ala Cys Gly	Thr Cys Cys Ala
6620	6625	6630
Thr Gly Gly Cys Gly Cys	Ala Gly Thr Ala Gly	Thr Cys Cys Ala
6635	6640	6645
Gly Cys Gly Thr Thr Thr	Cys Gly Cys Gly Gly	Ala Thr Gly Ala
6650	6655	6660
Thr Gly Thr Cys Ala Thr	Ala Ala Cys Thr Cys	Gly Cys Cys Thr
6665	6670	6675
Cys Thr Cys Cys Thr Thr	Thr Cys Thr Thr Cys	Thr Cys Cys Cys
6680	6685	6690
Ala Cys Ala Gly Cys Thr	Cys Gly Cys Gly Gly	Thr Thr Gly Ala
6695	6700	6705
Gly Gly Gly Cys Gly Thr	Ala Thr Thr Cys Cys	Thr Cys Gly Thr
6710	6715	6720
Cys Ala Thr Cys Cys Thr	Thr Cys Cys Ala Gly	Thr Ala Cys Thr
6725	6730	6735
Cys Cys Cys Gly Gly Ala	Gly Cys Gly Gly Gly	Ala Ala Thr Cys
6740	6745	6750
Cys Thr Cys Gly Ala Thr	Cys Gly Thr Cys Cys	Gly Cys Ala Cys
6755	6760	6765

Gly Gly Thr Ala Ala Gly Ala Gly Cys Cys Cys Ala Gly Cys Ala 6770	6775	6780
Thr Gly Thr Ala Gly Ala Ala Ala Thr Gly Gly Thr Thr Cys Ala 6785	6790	6795
Cys Gly Gly Cys Cys Thr Thr Gly Thr Ala Gly Gly Gly Ala Cys 6800	6805	6810
Ala Gly Cys Ala Gly Cys Cys Cys Thr Thr Cys Thr Cys Cys Ala 6815	6820	6825
Cys Gly Gly Gly Gly Ala Gly Gly Gly Cys Gly Thr Ala Ala Gly 6830	6835	6840
Cys Thr Thr Gly Ala Gly Cys Gly Gly Cys Cys Thr Thr Gly Cys 6845	6850	6855
Gly Gly Ala Gly Cys Gly Ala Gly Gly Thr Gly Thr Gly Cys Gly 6860	6865	6870
Thr Cys Ala Gly Gly Gly Cys Ala Ala Ala Gly Gly Thr Gly Thr 6875	6880	6885
Cys Cys Cys Thr Gly Ala Cys Cys Ala Thr Gly Ala Cys Thr Thr 6890	6895	6900
Thr Cys Ala Ala Gly Ala Ala Cys Thr Gly Gly Thr Ala Cys Thr 6905	6910	6915
Thr Gly Ala Ala Gly Thr Cys Cys Gly Ala Gly Thr Cys Gly Thr 6920	6925	6930
Cys Gly Cys Ala Gly Cys Cys Gly Cys Cys Gly Thr Gly Cys Thr 6935	6940	6945
Cys Cys Cys Ala Gly Ala Gly Cys Thr Cys Gly Ala Ala Ala Thr 6950	6955	6960
Cys Gly Gly Thr Gly Cys Gly Cys Thr Thr Cys Thr Thr Cys Gly 6965	6970	6975
Ala Gly Ala Gly Gly Gly Gly Gly Gly Thr Thr Ala Gly Gly Cys Ala 6980	6985	6990
Gly Ala Gly Cys Gly Ala Ala Ala Gly Thr Gly Ala Cys Gly Thr 6995	7000	7005
Cys Ala Thr Thr Gly Ala Ala Gly Ala Gly Ala Ala Thr Cys Thr 7010	7015	7020
Thr Gly Cys Cys Thr Gly Cys Cys Cys Gly Cys Gly Gly Cys Ala 7025	7030	7035
Thr Gly Ala Ala Ala Thr Thr Gly Cys Gly Gly Gly Thr Gly Ala 7040	7045	7050
Thr Gly Cys Gly Gly Ala Ala Ala Gly Gly Gly Cys Cys Cys Gly 7055	7060	7065

7055	7060	7065
Gly Gly Ala Cys Gly Gly	Ala Gly Gly Cys Thr	Cys Gly Gly Thr
7070	7075	7080
Thr Gly Thr Thr Gly Ala	Thr Gly Ala Cys Cys	Thr Gly Gly Gly
7085	7090	7095
Cys Gly Gly Cys Gly Ala	Gly Gly Ala Cys Gly	Ala Thr Cys Thr
7100	7105	7110
Cys Gly Thr Cys Ala Ala	Ala Gly Cys Cys Gly	Thr Thr Gly Ala
7115	7120	7125
Thr Gly Thr Thr Gly Thr	Gly Cys Cys Cys Gly	Ala Cys Gly Ala
7130	7135	7140
Thr Gly Thr Ala Gly Ala	Gly Thr Thr Cys Cys	Ala Thr Gly Ala
7145	7150	7155
Ala Thr Cys Gly Cys Gly	Gly Gly Cys Gly Gly	Cys Cys Thr Thr
7160	7165	7170
Thr Gly Ala Thr Gly Thr	Gly Cys Gly Gly Cys	Ala Gly Cys Thr
7175	7180	7185
Thr Thr Thr Thr Gly Ala	Gly Cys Thr Cys Cys	Thr Cys Gly Thr
7190	7195	7200
Ala Gly Gly Thr Gly Ala	Gly Gly Thr Cys Cys	Thr Cys Gly Gly
7205	7210	7215
Gly Gly Cys Ala Thr Thr	Gly Cys Ala Gly Gly	Cys Cys Gly Thr
7220	7225	7230
Gly Cys Thr Gly Cys Thr	Cys Gly Ala Gly Cys	Gly Cys Cys Cys
7235	7240	7245
Ala Cys Thr Cys Cys Thr	Gly Gly Ala Gly Ala	Thr Gly Thr Gly
7250	7255	7260
Gly Gly Thr Thr Gly Gly	Cys Thr Thr Gly Cys	Ala Thr Gly Ala
7265	7270	7275
Ala Gly Gly Ala Ala Gly	Cys Cys Cys Ala Gly	Ala Gly Cys Thr
7280	7285	7290
Cys Gly Cys Gly Gly Gly	Cys Cys Ala Thr Gly	Ala Gly Gly Gly
7295	7300	7305
Thr Cys Thr Gly Gly Ala	Gly Cys Thr Cys Gly	Thr Cys Gly Cys
7310	7315	7320
Gly Ala Ala Ala Gly Ala	Gly Gly Cys Gly Gly	Ala Ala Cys Thr
7325	7330	7335
Gly Cys Thr Gly Gly Cys	Cys Cys Ala Cys Gly	Gly Gly Cys Cys Ala
7340	7345	7350

Thr Cys Thr Thr Thr Thr Thr Cys Thr Gly Gly Gly Gly Thr Gly Ala 7355	7360	7365
Cys Gly Cys Ala Gly Thr Ala Gly Ala Ala Gly Gly Thr Gly Ala 7370	7375	7380
Gly Gly Gly Gly Gly Thr Cys Cys Cys Gly Cys Thr Cys Cys Cys 7385	7390	7395
Ala Gly Cys Gly Ala Thr Cys Cys Cys Ala Gly Cys Gly Thr Ala 7400	7405	7410
Ala Ala Cys Gly Cys Ala Cys Gly Gly Cys Gly Ala Gly Ala Thr 7415	7420	7425
Cys Gly Cys Gly Ala Gly Cys Gly Ala Gly Gly Gly Cys Gly Ala 7430	7435	7440
Cys Cys Ala Gly Cys Thr Cys Thr Gly Gly Gly Thr Cys Cys Cys 7445	7450	7455
Cys Gly Gly Ala Gly Ala Ala Thr Thr Thr Cys Ala Thr Gly Ala 7460	7465	7470
Cys Cys Ala Gly Cys Ala Thr Gly Ala Ala Gly Gly Gly Gly Ala 7475	7480	7485
Cys Gly Ala Gly Cys Thr Gly Cys Thr Thr Gly Cys Cys Gly Ala 7490	7495	7500
Ala Gly Gly Ala Cys Cys Cys Cys Ala Thr Cys Cys Ala Gly Gly 7505	7510	7515
Thr Gly Thr Ala Gly Gly Thr Thr Thr Cys Thr Ala Cys Ala Thr 7520	7525	7530
Cys Gly Thr Ala Gly Gly Thr Gly Ala Cys Ala Ala Ala Gly Ala 7535	7540	7545
Gly Cys Cys Gly Cys Thr Cys Cys Gly Thr Gly Cys Gly Ala Gly 7550	7555	7560
Gly Ala Thr Gly Ala Gly Ala Gly Cys Cys Gly Ala Thr Thr Gly 7565	7570	7575
Gly Gly Ala Ala Gly Ala Ala Cys Thr Gly Gly Ala Thr Thr Thr 7580	7585	7590
Cys Cys Thr Gly Cys Cys Ala Cys Cys Ala Gly Thr Thr Gly Gly 7595	7600	7605
Ala Cys Gly Ala Gly Thr Gly Gly Cys Thr Gly Thr Thr Gly Ala 7610	7615	7620
Thr Gly Thr Gly Ala Thr Gly Ala Ala Ala Gly Thr Ala Gly Ala 7625	7630	7635
Ala Ala Thr Cys Cys Cys Gly Cys Cys Gly Gly Cys Gly Ala Ala		

7640	7645	7650
Cys Cys Gly Ala Gly Cys	Ala Cys Thr Cys Gly	Thr Gly Cys Thr
7655	7660	7665
Gly Ala Thr Gly Cys Thr	Thr Gly Thr Ala Ala	Ala Ala Gly Cys
7670	7675	7680
Gly Thr Cys Cys Gly Cys	Ala Gly Thr Ala Cys	Thr Cys Gly Cys
7685	7690	7695
Ala Gly Cys Gly Cys Thr	Gly Cys Ala Cys Gly	Gly Gly Cys Thr
7700	7705	7710
Gly Thr Ala Cys Cys Thr	Cys Ala Thr Cys Cys	Ala Cys Gly Ala
7715	7720	7725
Gly Ala Thr Ala Cys Ala	Cys Ala Gly Cys Gly	Cys Gly Thr Cys
7730	7735	7740
Cys Cys Thr Thr Gly Ala	Gly Gly Ala Gly Gly	Ala Ala Cys Thr
7745	7750	7755
Thr Cys Ala Gly Gly Ala	Gly Thr Gly Gly Cys	Gly Gly Cys Cys
7760	7765	7770
Cys Thr Gly Gly Cys Thr	Gly Gly Thr Gly Gly	Thr Thr Thr Thr
7775	7780	7785
Cys Ala Thr Gly Thr Thr	Cys Gly Cys Cys Thr	Gly Cys Gly Thr
7790	7795	7800
Gly Gly Gly Ala Cys Thr	Cys Ala Cys Cys Cys	Thr Gly Gly Gly
7805	7810	7815
Gly Cys Thr Cys Cys Thr	Cys Gly Ala Gly Gly	Ala Cys Gly Gly
7820	7825	7830
Ala Gly Ala Gly Gly Cys	Thr Gly Ala Cys Gly	Ala Gly Cys Cys
7835	7840	7845
Cys Gly Cys Gly Cys Gly	Gly Gly Ala Gly Cys	Cys Ala Gly Gly
7850	7855	7860
Thr Cys Cys Ala Gly Ala	Thr Cys Thr Cys Gly	Gly Cys Gly Cys
7865	7870	7875
Gly Gly Cys Gly Gly Gly	Gly Gly Cys Gly Gly	Ala Gly Ala Gly
7880	7885	7890
Cys Gly Ala Ala Gly Ala	Cys Gly Ala Gly Gly	Gly Cys Gly Cys
7895	7900	7905
Gly Cys Ala Gly Thr Thr	Gly Gly Gly Ala Gly	Cys Thr Gly Thr
7910	7915	7920
Cys Cys Ala Thr Gly Gly	Thr Gly Thr Cys Gly	Cys Gly Gly Ala
7925	7930	7935

Gly Ala Thr Cys Cys Ala Gly Gly Thr Cys Cys Gly Gly Gly Gly 7940	Gly Gly Thr Cys Cys Gly Gly Thr Cys Cys Gly Gly Gly Gly 7945	Gly Gly Gly Gly 7950
Gly Cys Ala Gly Gly Gly Thr Thr Cys Thr Gly Ala Gly Gly Thr 7955	Gly Thr Thr Cys Thr Gly Ala Gly Gly Thr 7960	Gly Thr Thr Cys Thr Gly Ala Gly Gly Thr 7965
Thr Gly Ala Cys Cys Thr Cys Gly Thr Ala Gly Ala Gly Gly Cys 7970	Thr Cys Gly Thr Ala Gly Ala Gly Gly Cys 7975	Thr Ala Gly Ala Gly Gly Cys 7980
Gly Gly Gly Thr Gly Ala Gly Gly Gly Cys Gly Thr Gly Cys Thr 7985	Gly Gly Gly Cys Gly Thr Gly Cys Thr 7990	Gly Thr Gly Cys Thr 7995
Thr Gly Ala Gly Ala Thr Gly Cys Ala Gly Ala Thr Gly Gly Thr 8000	Thr Gly Cys Ala Gly Ala Thr Gly Gly Thr 8005	Thr Gly Gly Thr 8010
Ala Cys Thr Thr Gly Ala Thr Thr Thr Cys Thr Ala Cys Gly Gly 8015	Thr Thr Thr Cys Thr Ala Cys Gly Gly 8020	Thr Ala Cys Gly Gly 8025
Gly Thr Gly Ala Gly Thr Thr Gly Gly Thr Gly Gly Thr Cys Gly 8030	Thr Gly Gly Thr Gly Gly Thr Gly Gly Thr Cys Gly 8035	Gly Thr Cys Gly 8040
Thr Gly Thr Cys Cys Ala Cys Gly Cys Ala Thr Thr Gly Cys Ala 8045	Thr Cys Gly Cys Ala Thr Thr Gly Cys Ala 8050	Thr Thr Gly Cys Ala 8055
Thr Gly Ala Gly Cys Cys Cys Gly Thr Ala Gly Cys Thr Gly Cys 8060	Thr Gly Cys Thr Ala Gly Cys Thr Gly Cys 8065	Thr Ala Gly Cys Thr Gly Cys 8070
Gly Cys Gly Gly Gly Gly Cys Cys Ala Cys Gly Ala Cys Cys Gly 8075	Gly Cys Cys Ala Cys Gly Ala Cys Cys Gly 8080	Gly Ala Cys Cys Gly 8085
Thr Gly Cys Cys Gly Cys Gly Gly Thr Gly Cys Gly Cys Thr Thr 8090	Thr Gly Cys Gly Gly Thr Gly Cys Gly Cys Thr Thr 8095	Gly Cys Thr Thr 8100
Thr Thr Ala Gly Ala Ala Gly Cys Gly Gly Thr Gly Thr Cys Gly 8105	Thr Thr Ala Gly Ala Ala Gly Cys Gly Gly Thr Gly Thr Cys Gly 8110	Gly Thr Cys Gly 8115
Cys Gly Gly Ala Cys Gly Cys Gly Cys Thr Cys Cys Cys Gly Gly 8120	Cys Gly Cys Thr Cys Cys Cys Gly Gly 8125	Cys Cys Gly Gly 8130
Cys Gly Gly Cys Ala Gly Cys Gly Gly Cys Gly Gly Thr Thr Cys 8135	Cys Gly Cys Ala Gly Cys Gly Gly Cys Gly Gly Thr Thr Cys 8140	Gly Thr Thr Cys 8145
Cys Gly Gly Cys Cys Cys Cys Gly Cys Gly Gly Gly Cys Ala Gly 8150	Cys Gly Cys Gly Gly Gly Cys Ala Gly 8155	Gly Cys Ala Gly 8160
Gly Gly Gly Cys Gly Gly Cys Ala Gly Ala Gly Gly Cys Ala Cys 8165	Gly Gly Thr Cys Cys Cys Gly Gly Thr Cys Ala Cys 8170	Gly Gly Thr Gly 8175
Gly Thr Cys Gly Gly Cys Gly Thr Gly Gly Cys Gly Cys Thr Cys 8180	Gly Thr Gly Gly Cys Gly Thr Gly Gly Cys Gly Cys Thr Cys 8185	Gly Cys Thr Cys 8190
Gly Gly Gly Cys Ala Gly Gly Thr Cys Cys Cys Gly Gly Thr Gly 8195	Gly Thr Cys Cys Cys Gly Gly Thr Cys Cys Cys Gly Gly Thr Gly 8200	Gly Gly Thr Gly 8205
Cys Thr Gly Cys Gly Cys Cys Cys Thr Gly Ala Gly Ala Gly Cys 8210	Cys Cys Thr Gly Ala Gly Ala Gly Cys 8215	Gly Ala Gly Cys 8220
Gly Cys Thr Gly Gly Cys Gly Thr Gly Cys Gly Cys Gly Ala Cys 8225	Gly Thr Gly Cys Gly Cys Gly Ala Cys 8230	Gly Cys Gly Ala Cys 8235

8225	8230	8235
Gly Ala Cys Gly Cys Gly Gly Cys Gly Gly Thr Thr Gly Ala Cys		
8240	8245	8250
Ala Thr Cys Cys Thr Gly Gly Ala Thr Cys Thr Gly Cys Cys Gly		
8255	8260	8265
Cys Cys Thr Cys Thr Gly Cys Gly Thr Gly Ala Ala Gly Ala Cys		
8270	8275	8280
Cys Ala Cys Gly Gly Gly Cys Cys Cys Cys Gly Thr Gly Ala Cys		
8285	8290	8295
Thr Thr Thr Gly Ala Ala Cys Cys Thr Gly Ala Ala Ala Gly Ala		
8300	8305	8310
Cys Ala Gly Thr Thr Cys Ala Ala Cys Ala Gly Ala Ala Thr Cys		
8315	8320	8325
Ala Ala Thr Cys Thr Cys Thr Gly Cys Gly Thr Cys Ala Thr Thr		
8330	8335	8340
Gly Ala Cys Gly Gly Cys Gly Gly Cys Cys Thr Gly Ala Cys Gly		
8345	8350	8355
Cys Ala Gly Gly Ala Thr Cys Thr Cys Thr Thr Gly Cys Ala Cys		
8360	8365	8370
Gly Thr Cys Gly Cys Cys Cys Gly Ala Gly Thr Thr Gly Thr Cys		
8375	8380	8385
Cys Thr Gly Gly Thr Ala Gly Gly Cys Gly Ala Thr Cys Thr Cys		
8390	8395	8400
Gly Gly Ala Cys Ala Thr Gly Ala Ala Cys Thr Gly Thr Thr Cys		
8405	8410	8415
Gly Ala Thr Cys Thr Cys Cys Thr Cys Cys Thr Cys Cys Thr Gly		
8420	8425	8430
Gly Ala Gly Ala Thr Cys Gly Cys Cys Gly Cys Gly Gly Cys Cys		
8435	8440	8445
Cys Gly Cys Gly Cys Gly Cys Thr Cys Cys Ala Cys Gly Gly Thr		
8450	8455	8460
Gly Gly Cys Gly Gly Cys Gly Ala Gly Gly Thr Cys Ala Thr Thr		
8465	8470	8475
Gly Gly Ala Gly Ala Thr Gly Cys Gly Ala Cys Cys Cys Ala Thr		
8480	8485	8490
Gly Ala Gly Cys Thr Gly Cys Gly Ala Gly Ala Ala Gly Gly Cys		
8495	8500	8505
Gly Cys Cys Cys Ala Gly Gly Cys Cys Gly Cys Thr Cys Thr Cys		
8510	8515	8520

Gly Thr Thr Cys Cys Ala Gly Ala Cys Gly Cys Gly Gly Cys Thr 8525	8530	8535
Gly Thr Ala Gly Ala Cys Cys Ala Cys Gly Thr Cys Cys Cys Cys 8540	8545	8550
Gly Thr Cys Gly Gly Cys Gly Thr Cys Gly Cys Gly Cys Gly Cys 8555	8560	8565
Gly Cys Gly Cys Ala Thr Gly Ala Cys Cys Ala Cys Cys Thr Gly 8570	8575	8580
Cys Gly Cys Gly Ala Gly Gly Thr Thr Gly Ala Gly Cys Thr Cys 8585	8590	8595
Cys Ala Cys Gly Thr Gly Cys Cys Gly Cys Gly Cys Ala Ala Ala 8600	8605	8610
Gly Ala Cys Gly Gly Cys Gly Thr Ala Gly Thr Thr Gly Cys Gly 8615	8620	8625
Cys Ala Gly Gly Cys Gly Cys Thr Gly Gly Ala Ala Gly Ala Gly 8630	8635	8640
Gly Thr Ala Gly Thr Thr Gly Ala Gly Gly Gly Thr Gly Gly Thr 8645	8650	8655
Gly Gly Cys Gly Ala Thr Gly Thr Gly Cys Thr Cys Gly Gly Thr 8660	8665	8670
Gly Ala Cys Gly Ala Ala Gly Ala Ala Gly Thr Ala Cys Ala Thr 8675	8680	8685
Gly Ala Thr Cys Cys Ala Gly Cys Gly Gly Cys Gly Cys Ala Gly 8690	8695	8700
Gly Gly Gly Cys Ala Thr Cys Thr Cys Gly Cys Thr Gly Ala Thr 8705	8710	8715
Gly Thr Cys Gly Cys Cys Gly Ala Thr Gly Gly Cys Thr Thr Cys 8720	8725	8730
Cys Ala Gly Cys Cys Thr Thr Thr Cys Cys Ala Thr Gly Gly Cys 8735	8740	8745
Cys Thr Cys Gly Thr Ala Gly Ala Ala Gly Thr Cys Cys Ala Cys 8750	8755	8760
Gly Gly Cys Gly Ala Ala Gly Thr Thr Gly Ala Ala Ala Ala Ala 8765	8770	8775
Cys Thr Gly Gly Gly Cys Gly Thr Thr Gly Cys Gly Gly Gly Cys 8780	8785	8790
Cys Gly Ala Gly Ala Cys Cys Gly Thr Gly Ala Gly Cys Thr Cys 8795	8800	8805
Gly Thr Cys Thr Thr Cys Cys Ala Gly Gly Ala Gly Cys Cys Gly 8810	8815	8820

8810	8815	8820
Gly Ala Thr Gly Ala Gly Thr Thr Cys Gly Gly Cys Gly Ala Thr		
8825	8830	8835
Gly Gly Thr Gly Gly Cys Gly Cys Gly Cys Ala Cys Cys Thr Cys		
8840	8845	8850
Gly Cys Gly Cys Thr Cys Gly Ala Ala Ala Thr Cys Cys Cys Cys		
8855	8860	8865
Gly Gly Gly Gly Gly Cys Cys Thr Cys Cys Thr Cys Cys Thr Cys		
8870	8875	8880
Thr Thr Cys Cys Thr Cys Thr Thr Cys Thr Thr Cys Cys Ala Thr		
8885	8890	8895
Gly Ala Cys Gly Ala Cys Cys Thr Cys Thr Thr Cys Thr Thr Cys		
8900	8905	8910
Thr Ala Thr Thr Thr Cys Thr Thr Cys Cys Thr Cys Thr Gly Gly		
8915	8920	8925
Gly Gly Gly Cys Gly Gly Thr Gly Gly Thr Gly Gly Thr Gly Gly		
8930	8935	8940
Cys Gly Gly Gly Gly Gly Cys Cys Gly Ala Cys Gly Ala Cys Gly		
8945	8950	8955
Ala Cys Gly Gly Cys Gly Ala Cys Gly Cys Ala Cys Cys Gly Gly		
8960	8965	8970
Gly Ala Gly Ala Cys Gly Gly Thr Cys Gly Ala Cys Gly Ala Ala		
8975	8980	8985
Gly Cys Gly Cys Thr Cys Gly Ala Thr Cys Ala Thr Cys Thr Cys		
8990	8995	9000
Cys Cys Cys Gly Cys Gly Gly Cys Gly Gly Cys Gly Ala Cys Gly		
9005	9010	9015
Cys Ala Thr Gly Gly Thr Thr Thr Cys Gly Gly Thr Gly Ala Cys		
9020	9025	9030
Gly Gly Cys Gly Cys Gly Ala Cys Cys Cys Cys Gly Thr Thr Cys		
9035	9040	9045
Gly Cys Gly Ala Gly Gly Ala Cys Gly Cys Ala Gly Cys Gly Thr		
9050	9055	9060
Gly Ala Ala Gly Ala Cys Gly Cys Cys Gly Cys Cys Gly Gly Thr		
9065	9070	9075
Cys Ala Thr Cys Thr Cys Cys Cys Gly Gly Thr Ala Ala Thr Gly		
9080	9085	9090
Gly Gly Gly Cys Gly Gly Gly Thr Cys Cys Cys Cys Ala Thr Thr		
9095	9100	9105

Gly Gly Gly Cys Ala Gly Cys Gly Ala Thr Ala Gly Gly Gly Cys 9110	9115	9120
Gly Cys Thr Gly Ala Cys Gly Ala Thr Gly Cys Ala Thr Cys Thr 9125	9130	9135
Thr Ala Thr Cys Ala Ala Thr Thr Gly Cys Gly Gly Thr Gly Thr 9140	9145	9150
Ala Gly Gly Gly Gly Ala Cys Gly Thr Gly Ala Gly Cys Gly Cys 9155	9160	9165
Gly Thr Cys Gly Ala Gly Ala Thr Cys Gly Ala Cys Cys Gly Gly 9170	9175	9180
Ala Thr Cys Gly Gly Ala Gly Ala Ala Thr Cys Thr Thr Thr Cys 9185	9190	9195
Gly Ala Gly Gly Ala Ala Ala Gly Cys Gly Thr Cys Thr Ala Gly 9200	9205	9210
Cys Cys Ala Ala Thr Cys Gly Cys Ala Gly Thr Cys Gly Cys Ala 9215	9220	9225
Ala Gly Gly Thr Ala Ala Gly Cys Thr Cys Ala Ala Ala Cys Ala 9230	9235	9240
Cys Gly Thr Ala Gly Cys Ala Gly Cys Cys Cys Thr Gly Cys Gly 9245	9250	9255
Gly Ala Cys Gly Cys Thr Gly Thr Thr Ala Gly Ala Ala Thr Thr 9260	9265	9270
Gly Cys Gly Gly Thr Thr Gly Cys Thr Gly Ala Thr Gly Ala Thr 9275	9280	9285
Gly Thr Ala Ala Thr Thr Gly Ala Ala Gly Thr Ala Gly Gly Cys 9290	9295	9300
Gly Thr Thr Thr Thr Thr Gly Ala Gly Gly Cys Gly Gly Cys Gly 9305	9310	9315
Gly Ala Thr Gly Gly Thr Gly Gly Cys Gly Ala Gly Gly Ala Gly 9320	9325	9330
Gly Ala Cys Cys Ala Gly Gly Thr Cys Cys Thr Thr Gly Gly Gly 9335	9340	9345
Thr Cys Cys Ala Gly Cys Thr Thr Gly Cys Thr Gly Gly Ala Thr 9350	9355	9360
Gly Cys Gly Gly Ala Gly Cys Cys Gly Cys Thr Cys Gly Gly Cys 9365	9370	9375
Cys Ala Thr Gly Cys Cys Cys Cys Ala Gly Gly Cys Cys Thr Gly 9380	9385	9390
Gly Cys Cys Cys Thr Gly Ala Cys Ala Cys Cys Gly Gly Cys Thr		

9395	9400	9405
Cys Ala Gly Gly Thr Thr	Cys Thr Thr Gly Thr	Ala Gly Thr Ala
9410	9415	9420
Gly Thr Cys Ala Thr Gly	Cys Ala Thr Gly Ala	Gly Cys Cys Thr
9425	9430	9435
Cys Thr Cys Ala Ala Thr	Gly Thr Cys Ala Thr	Cys Ala Cys Thr
9440	9445	9450
Gly Gly Cys Thr Gly Ala	Gly Gly Cys Gly Gly	Ala Gly Thr Cys
9455	9460	9465
Thr Thr Cys Cys Ala Thr	Gly Cys Gly Gly Gly	Thr Gly Ala Cys
9470	9475	9480
Cys Cys Cys Gly Ala Cys	Gly Cys Cys Cys Cys	Thr Gly Ala Gly
9485	9490	9495
Cys Gly Gly Cys Thr Gly	Cys Ala Cys Gly Ala	Gly Cys Gly Cys
9500	9505	9510
Cys Ala Gly Gly Thr Cys	Gly Gly Cys Gly Ala	Cys Gly Ala Cys
9515	9520	9525
Gly Cys Gly Cys Thr Cys	Gly Gly Cys Gly Ala	Gly Gly Ala Thr
9530	9535	9540
Gly Gly Cys Cys Thr Gly	Thr Thr Gly Cys Ala	Cys Gly Cys Gly
9545	9550	9555
Gly Gly Thr Gly Ala Gly	Gly Gly Thr Gly Thr	Cys Cys Thr Gly
9560	9565	9570
Gly Ala Ala Gly Thr Cys	Gly Thr Cys Cys Ala	Thr Gly Thr Cys
9575	9580	9585
Gly Ala Cys Gly Ala Ala	Gly Cys Gly Gly Thr	Gly Ala Thr Ala
9590	9595	9600
Gly Gly Cys Cys Cys Cys	Gly Gly Thr Gly Thr	Thr Gly Ala Thr
9605	9610	9615
Gly Gly Thr Gly Thr Ala	Gly Gly Thr Gly Cys	Ala Gly Thr Thr
9620	9625	9630
Gly Gly Cys Cys Ala Thr	Gly Ala Gly Cys Gly	Ala Cys Cys Ala
9635	9640	9645
Gly Thr Thr Gly Ala Cys	Gly Gly Thr Cys Thr	Gly Cys Ala Gly
9650	9655	9660
Gly Cys Cys Thr Gly Gly	Cys Thr Gly Cys Ala	Cys Gly Ala Cys
9665	9670	9675
Cys Thr Cys Gly Gly Ala	Gly Thr Ala Cys Cys	Thr Gly Ala Gly
9680	9685	9690

Cys Cys Gly Cys Gly Ala Gly Ala Ala Gly Gly Cys Gly Cys Gly	9695	9700	9705
Cys Gly Ala Gly Thr Cys Gly Ala Ala Gly Ala Cys Gly Thr Ala	9710	9715	9720
Gly Thr Cys Gly Thr Thr Gly Cys Ala Gly Gly Thr Gly Cys Gly	9725	9730	9735
Cys Ala Cys Gly Ala Gly Gly Thr Ala Cys Thr Gly Gly Thr Ala	9740	9745	9750
Thr Cys Cys Gly Ala Cys Thr Ala Gly Gly Ala Ala Gly Thr Gly	9755	9760	9765
Cys Gly Gly Cys Gly Gly Cys Gly Gly Cys Thr Gly Gly Cys Gly	9770	9775	9780
Gly Thr Ala Gly Ala Gly Cys Gly Gly Cys Cys Ala Gly Cys Gly	9785	9790	9795
Cys Thr Gly Gly Gly Thr Gly Gly Cys Cys Gly Gly Cys Gly Cys	9800	9805	9810
Gly Cys Cys Cys Gly Gly Gly Gly Cys Cys Ala Gly Gly Thr Cys	9815	9820	9825
Cys Thr Cys Gly Ala Gly Cys Ala Thr Gly Ala Gly Gly Cys Gly	9830	9835	9840
Gly Thr Gly Gly Thr Ala Gly Cys Cys Gly Thr Ala Gly Ala Gly	9845	9850	9855
Gly Thr Ala Gly Cys Gly Gly Gly Ala Cys Ala Thr Cys Cys Ala	9860	9865	9870
Gly Gly Thr Gly Ala Thr Gly Cys Cys Gly Gly Cys Gly Gly Cys	9875	9880	9885
Gly Gly Thr Gly Gly Thr Gly Gly Ala Gly Gly Cys Gly Cys Gly	9890	9895	9900
Cys Gly Gly Gly Ala Ala Cys Thr Cys Gly Cys Gly Gly Ala Cys	9905	9910	9915
Gly Cys Gly Gly Thr Thr Cys Cys Ala Gly Ala Thr Gly Thr Thr	9920	9925	9930
Gly Cys Gly Cys Ala Gly Cys Gly Gly Cys Ala Gly Gly Ala Ala	9935	9940	9945
Ala Thr Ala Gly Thr Cys Cys Ala Thr Gly Gly Thr Cys Gly Gly	9950	9955	9960
Cys Ala Cys Gly Gly Thr Cys Thr Gly Gly Cys Cys Gly Gly Thr	9965	9970	9975
Gly Ala Gly Ala Cys Gly Cys Gly Cys Gly Cys Ala Gly Thr Cys			

9980	9985	9990
Ala Thr Thr Gly Ala Cys	Gly Cys Thr Cys Thr	Ala Gly Ala Gly
9995	10000	10005
Gly Cys Ala Ala Ala Ala	Ala Cys Gly Ala Ala	Ala Gly Cys Gly
10010	10015	10020
Gly Thr Thr Gly Ala Gly	Cys Gly Gly Gly Cys	Thr Cys Thr Thr
10025	10030	10035
Cys Cys Thr Cys Cys Gly	Thr Ala Gly Cys Cys	Thr Gly Gly Cys
10040	10045	10050
Gly Gly Ala Ala Cys Gly	Cys Ala Ala Ala Cys	Gly Gly Gly Thr
10055	10060	10065
Thr Ala Gly Gly Cys Cys	Gly Cys Gly Thr Gly	Thr Gly Thr Ala
10070	10075	10080
Cys Cys Cys Cys Gly Gly	Thr Thr Cys Gly Ala	Gly Thr Cys Cys
10085	10090	10095
Cys Cys Thr Cys Gly Ala	Ala Thr Cys Ala Gly	Gly Cys Thr Gly
10100	10105	10110
Gly Ala Gly Cys Cys Gly	Cys Gly Ala Cys Thr	Ala Ala Cys Gly
10115	10120	10125
Thr Gly Gly Thr Ala Thr	Thr Gly Gly Cys Ala	Cys Thr Cys Cys
10130	10135	10140
Cys Gly Thr Cys Thr Cys	Gly Ala Cys Cys Cys	Gly Ala Gly Cys
10145	10150	10155
Cys Cys Gly Ala Thr Ala	Gly Cys Cys Gly Cys	Cys Ala Gly Gly
10160	10165	10170
Ala Thr Ala Cys Gly Gly	Cys Gly Gly Ala Gly	Ala Gly Cys Cys
10175	10180	10185
Cys Thr Thr Thr Thr Thr	Gly Cys Cys Gly Gly	Cys Cys Gly Ala
10190	10195	10200
Gly Thr Gly Gly Gly Gly	Thr Cys Gly Cys Thr	Ala Gly Ala Cys
10205	10210	10215
Thr Thr Gly Ala Ala Ala	Gly Cys Gly Ala Cys	Cys Gly Ala Ala
10220	10225	10230
Ala Ala Cys Cys Cys Thr	Gly Cys Cys Gly Gly	Gly Thr Ala Gly
10235	10240	10245
Thr Gly Gly Cys Thr Cys	Gly Cys Gly Cys Cys	Cys Gly Thr Ala
10250	10255	10260
Gly Thr Cys Thr Gly Gly	Ala Gly Ala Ala Gly	Cys Ala Thr Cys
10265	10270	10275

Gly Cys Cys Ala Gly Gly Gly Thr Thr Gly Ala Gly Thr Cys Gly	10280	10285	10290
Cys Gly Gly Cys Ala Gly Ala Ala Cys Cys Cys Gly Gly Thr Thr	10295	10300	10305
Cys Gly Ala Gly Gly Ala Cys Gly Gly Cys Cys Gly Cys Gly Gly	10310	10315	10320
Cys Gly Ala Gly Cys Gly Gly Gly Ala Cys Thr Thr Gly Gly Thr	10325	10330	10335
Cys Ala Cys Cys Cys Cys Gly Cys Cys Gly Ala Thr Ala Thr Ala	10340	10345	10350
Ala Ala Gly Ala Cys Cys Cys Ala Cys Ala Gly Cys Cys Ala Gly	10355	10360	10365
Cys Cys Gly Ala Cys Thr Thr Cys Thr Cys Cys Ala Gly Thr Thr	10370	10375	10380
Ala Cys Gly Gly Gly Ala Gly Cys Gly Ala Gly Cys Cys Cys Cys	10385	10390	10395
Cys Thr Thr Thr Thr Thr Thr Cys Thr Thr Thr Thr Thr Gly Cys	10400	10405	10410
Cys Ala Gly Ala Thr Gly Cys Ala Thr Cys Cys Cys Gly Thr Cys	10415	10420	10425
Cys Thr Gly Cys Gly Cys Cys Ala Ala Ala Thr Gly Cys Gly Thr	10430	10435	10440
Cys Cys Cys Ala Cys Cys Cys Cys Cys Cys Cys Gly Gly Cys Gly	10445	10450	10455
Ala Cys Cys Ala Cys Cys Gly Cys Gly Ala Cys Cys Gly Cys Gly	10460	10465	10470
Gly Cys Cys Gly Thr Ala Gly Cys Ala Gly Gly Cys Gly Cys Cys	10475	10480	10485
Gly Gly Cys Gly Cys Thr Ala Gly Cys Cys Ala Gly Cys Cys Ala	10490	10495	10500
Cys Cys Ala Cys Ala Gly Ala Cys Ala Gly Ala Gly Ala Thr Gly	10505	10510	10515
Gly Ala Cys Thr Thr Gly Gly Ala Ala Gly Ala Gly Gly Gly Cys	10520	10525	10530
Gly Ala Ala Gly Gly Gly Cys Thr Gly Gly Cys Ala Ala Gly Ala	10535	10540	10545
Cys Thr Gly Gly Gly Gly Gly Cys Gly Cys Cys Gly Thr Cys Cys	10550	10555	10560
Cys Cys Gly Gly Ala Gly Cys Gly Ala Cys Ala Thr Cys Cys Cys			

10565	10570	10575
Cys Gly Cys Gly Thr Gly	Cys Ala Gly Cys Thr Gly	Cys Ala Gly
10580	10585	10590
Ala Ala Gly Gly Ala Cys	Gly Thr Gly Cys Gly	Cys Cys Cys Gly
10595	10600	10605
Gly Cys Gly Thr Ala Cys	Gly Thr Gly Cys Cys	Thr Ala Cys Gly
10610	10615	10620
Cys Ala Gly Ala Ala Cys	Cys Thr Gly Thr Thr	Cys Ala Gly Gly
10625	10630	10635
Gly Ala Cys Cys Gly Cys	Ala Gly Cys Gly Gly	Gly Gly Ala Gly
10640	10645	10650
Gly Ala Gly Cys Cys Cys	Gly Ala Gly Gly Ala	Gly Ala Thr Gly
10655	10660	10665
Cys Gly Cys Gly Ala Cys	Thr Gly Cys Cys Gly	Gly Thr Thr Thr
10670	10675	10680
Cys Gly Gly Gly Cys Gly	Gly Gly Cys Ala Gly	Gly Gly Ala Gly
10685	10690	10695
Cys Thr Gly Cys Gly Cys	Gly Ala Gly Gly Gly	Cys Cys Thr Gly
10700	10705	10710
Gly Ala Cys Cys Gly Cys	Cys Ala Gly Cys Gly	Cys Gly Thr Gly
10715	10720	10725
Cys Thr Gly Cys Gly Cys	Gly Ala Cys Gly Ala	Gly Gly Ala Thr
10730	10735	10740
Thr Thr Cys Gly Ala Gly	Cys Cys Gly Ala Ala	Cys Gly Ala Gly
10745	10750	10755
Cys Ala Gly Ala Cys Gly	Gly Gly Gly Ala Thr	Cys Ala Gly Cys
10760	10765	10770
Cys Cys Cys Gly Cys Ala	Cys Gly Cys Gly Cys	Gly Cys Ala Cys
10775	10780	10785
Gly Thr Gly Gly Cys Gly	Gly Cys Ala Gly Cys	Cys Ala Ala Cys
10790	10795	10800
Cys Thr Gly Gly Thr Gly	Ala Cys Gly Gly Cys	Cys Thr Ala Cys
10805	10810	10815
Gly Ala Gly Cys Ala Gly	Ala Cys Gly Gly Thr	Gly Ala Ala Gly
10820	10825	10830
Cys Ala Gly Gly Ala Gly	Cys Gly Cys Ala Ala	Cys Thr Thr Cys
10835	10840	10845
Cys Ala Ala Ala Ala Gly	Ala Gly Thr Thr Thr	Cys Ala Ala Cys
10850	10855	10860

Ala Ala Cys Cys Ala Cys Gly Thr Gly Cys Gly Cys Ala Cys Cys 10865	10870	10875
Cys Thr Gly Ala Thr Cys Gly Cys Gly Cys Gly Cys Gly Ala Gly 10880	10885	10890
Gly Ala Gly Gly Thr Gly Gly Cys Cys Cys Thr Gly Gly Gly Cys 10895	10900	10905
Cys Thr Gly Ala Thr Gly Cys Ala Cys Cys Thr Gly Thr Gly Gly 10910	10915	10920
Gly Ala Cys Cys Thr Gly Gly Cys Gly Gly Ala Gly Gly Cys Cys 10925	10930	10935
Ala Thr Cys Gly Thr Gly Cys Ala Gly Ala Ala Cys Cys Cys Gly 10940	10945	10950
Gly Ala Cys Ala Gly Cys Ala Ala Gly Cys Cys Thr Cys Thr Gly 10955	10960	10965
Ala Cys Gly Gly Cys Gly Cys Ala Gly Cys Thr Gly Thr Thr Cys 10970	10975	10980
Cys Thr Gly Gly Thr Gly Gly Thr Gly Cys Ala Gly Cys Ala Cys 10985	10990	10995
Ala Gly Cys Ala Gly Gly Gly Ala Cys Ala Ala Cys Gly Ala Gly 11000	11005	11010
Gly Cys Gly Thr Thr Cys Ala Gly Gly Gly Ala Gly Gly Cys Gly 11015	11020	11025
Cys Thr Gly Cys Thr Gly Ala Ala Cys Ala Thr Cys Gly Cys Cys 11030	11035	11040
Gly Ala Gly Cys Cys Cys Gly Ala Gly Gly Gly Thr Cys Gly Cys 11045	11050	11055
Thr Gly Gly Cys Thr Gly Cys Thr Gly Gly Ala Gly Cys Thr Gly 11060	11065	11070
Ala Thr Thr Ala Ala Cys Ala Thr Cys Thr Thr Gly Cys Ala Gly 11075	11080	11085
Ala Gly Cys Ala Thr Cys Gly Thr Ala Gly Thr Gly Cys Ala Gly 11090	11095	11100
Gly Ala Gly Cys Gly Cys Ala Gly Cys Cys Thr Gly Ala Gly Cys 11105	11110	11115
Cys Thr Gly Gly Cys Cys Gly Ala Gly Ala Ala Gly Gly Thr Gly 11120	11125	11130
Gly Cys Gly Gly Cys Gly Ala Thr Cys Ala Ala Cys Thr Ala Cys 11135	11140	11145
Thr Cys Gly Gly Thr Gly Cys Thr Gly Ala Gly Cys Cys Thr Gly		

11150	11155	11160
Gly Gly Cys Ala Ala Gly Thr Thr Thr Thr Ala Cys Gly Cys Gly		
11165	11170	11175
Cys Gly Cys Ala Ala Gly Ala Thr Thr Thr Ala Cys Ala Ala Gly		
11180	11185	11190
Ala Cys Gly Cys Cys Gly Thr Ala Cys Gly Thr Gly Cys Cys Cys		
11195	11200	11205
Ala Thr Ala Gly Ala Cys Ala Ala Gly Gly Ala Gly Gly Thr Gly		
11210	11215	11220
Ala Ala Gly Ala Thr Ala Gly Ala Cys Ala Gly Cys Thr Thr Thr		
11225	11230	11235
Thr Ala Cys Ala Thr Gly Cys Gly Cys Ala Thr Gly Gly Cys Gly		
11240	11245	11250
Cys Thr Cys Ala Ala Gly Gly Thr Gly Cys Thr Gly Ala Cys Gly		
11255	11260	11265
Cys Thr Gly Ala Gly Cys Gly Ala Cys Gly Ala Cys Cys Thr Gly		
11270	11275	11280
Gly Gly Cys Gly Thr Gly Thr Ala Cys Cys Gly Cys Ala Ala Cys		
11285	11290	11295
Gly Ala Cys Cys Gly Cys Ala Thr Cys Cys Ala Cys Ala Ala Gly		
11300	11305	11310
Gly Cys Cys Gly Thr Gly Ala Gly Cys Ala Cys Gly Ala Gly Cys		
11315	11320	11325
Cys Gly Gly Cys Gly Gly Cys Gly Cys Gly Ala Gly Cys Thr Gly		
11330	11335	11340
Ala Gly Cys Gly Ala Cys Cys Gly Cys Gly Ala Gly Cys Thr Gly		
11345	11350	11355
Ala Thr Gly Cys Thr Gly Ala Gly Thr Cys Thr Gly Cys Gly Cys		
11360	11365	11370
Cys Gly Gly Gly Cys Gly Cys Thr Gly Gly Thr Ala Gly Gly Gly		
11375	11380	11385
Gly Gly Cys Gly Cys Cys Gly Cys Cys Gly Gly Cys Gly Gly Cys		
11390	11395	11400
Gly Ala Gly Gly Ala Gly Thr Cys Cys Thr Ala Cys Thr Thr Cys		
11405	11410	11415
Gly Ala Cys Ala Thr Gly Gly Gly Thr Gly Cys Gly Gly Ala Cys		
11420	11425	11430
Cys Thr Gly Cys Ala Thr Thr Gly Gly Cys Ala Gly Cys Cys Gly		
11435	11440	11445

Ala Gly Cys Cys Gly Gly Cys Gly Cys Gly Cys Cys Thr Thr Gly	11450	11455	11460
Gly Ala Gly Gly Cys Cys Gly Cys Cys Thr Ala Cys Gly Gly Thr	11465	11470	11475
Thr Cys Ala Gly Ala Gly Gly Ala Cys Thr Thr Gly Gly Ala Thr	11480	11485	11490
Gly Ala Gly Gly Ala Ala Gly Ala Gly Gly Ala Ala Gly Ala Gly	11495	11500	11505
Gly Ala Gly Gly Ala Gly Gly Ala Thr Gly Cys Ala Cys Cys Cys	11510	11515	11520
Gly Cys Thr Gly Cys Gly Gly Gly Gly Thr Ala Cys Thr Gly Ala	11525	11530	11535
Cys Gly Cys Cys Thr Cys Cys Gly Thr Gly Ala Thr Gly Thr Gly	11540	11545	11550
Thr Thr Thr Thr Thr Ala Gly Ala Thr Gly Thr Cys Cys Cys Ala	11555	11560	11565
Gly Cys Ala Ala Gly Cys Cys Cys Cys Gly Gly Ala Cys Cys Cys	11570	11575	11580
Cys Gly Cys Cys Ala Thr Ala Ala Gly Gly Gly Cys Gly Gly Cys	11585	11590	11595
Gly Cys Thr Gly Cys Ala Ala Ala Gly Cys Cys Ala Gly Cys Cys	11600	11605	11610
Gly Thr Cys Cys Gly Gly Thr Cys Thr Ala Gly Cys Ala Thr Cys	11615	11620	11625
Gly Gly Ala Cys Gly Ala Cys Thr Gly Gly Gly Ala Gly Gly Cys	11630	11635	11640
Cys Gly Cys Gly Ala Thr Gly Cys Ala Ala Cys Gly Cys Ala Thr	11645	11650	11655
Cys Ala Thr Gly Gly Cys Cys Cys Thr Gly Ala Cys Gly Ala Cys	11660	11665	11670
Cys Cys Gly Cys Ala Ala Cys Cys Cys Cys Gly Ala Gly Thr Cys	11675	11680	11685
Cys Thr Thr Thr Ala Gly Ala Cys Ala Ala Cys Ala Gly Cys Cys	11690	11695	11700
Gly Cys Ala Gly Gly Cys Cys Ala Ala Cys Ala Gly Ala Cys Thr	11705	11710	11715
Cys Thr Cys Gly Gly Cys Cys Ala Thr Thr Cys Thr Gly Gly Ala	11720	11725	11730
Gly Gly Cys Gly Gly Thr Gly Gly Thr Cys Cys Cys Cys Thr Cys			

11735	11740	11745
Thr Cys Gly Gly Ala Cys	Cys Ala Ala Cys Cys	Cys Cys Ala Cys
11750	11755	11760
Gly Cys Ala Cys Gly Ala	Gly Ala Ala Gly Gly	Thr Gly Cys Thr
11765	11770	11775
Gly Gly Cys Gly Ala Thr	Cys Gly Thr Gly Ala	Ala Cys Gly Cys
11780	11785	11790
Gly Cys Thr Gly Gly Cys	Gly Gly Ala Gly Ala	Ala Cys Ala Ala
11795	11800	11805
Gly Gly Cys Cys Ala Thr	Cys Cys Gly Thr Cys	Cys Cys Gly Ala
11810	11815	11820
Cys Gly Ala Gly Gly Cys	Cys Gly Gly Gly Cys	Thr Gly Gly Thr
11825	11830	11835
Gly Thr Ala Cys Ala Ala	Cys Gly Cys Cys Cys	Thr Gly Cys Thr
11840	11845	11850
Gly Gly Ala Gly Cys Gly	Cys Gly Thr Gly Gly	Gly Cys Cys Gly
11855	11860	11865
Cys Thr Ala Cys Ala Ala	Cys Ala Gly Cys Ala	Cys Gly Ala Ala
11870	11875	11880
Cys Gly Thr Gly Cys Ala	Gly Thr Cys Cys Ala	Ala Cys Cys Thr
11885	11890	11895
Gly Gly Ala Thr Cys Gly	Gly Cys Thr Gly Gly	Thr Gly Ala Cys
11900	11905	11910
Gly Gly Ala Cys Gly Thr	Gly Cys Gly Cys Gly	Ala Gly Gly Cys
11915	11920	11925
Cys Gly Thr Gly Gly Cys	Gly Cys Ala Gly Cys	Gly Cys Gly Ala
11930	11935	11940
Gly Cys Gly Gly Thr Thr	Cys Ala Ala Gly Ala	Ala Cys Gly Ala
11945	11950	11955
Gly Gly Gly Cys Cys Thr	Gly Gly Gly Cys Thr	Cys Gly Cys Thr
11960	11965	11970
Gly Gly Thr Gly Gly Cys	Gly Cys Thr Gly Ala	Ala Cys Gly Cys
11975	11980	11985
Cys Thr Thr Cys Cys Thr	Gly Gly Cys Gly Ala	Cys Gly Cys Ala
11990	11995	12000
Gly Cys Cys Gly Gly Cys	Gly Ala Ala Cys Gly	Thr Gly Cys Cys
12005	12010	12015
Gly Cys Gly Cys Gly Gly	Gly Cys Ala Gly Gly	Ala Cys Gly Ala
12020	12025	12030

Thr Thr Ala Cys Ala Cys Cys Ala Ala Cys Thr Thr Thr Ala Thr 12035	12040	12045
Cys Ala Gly Cys Gly Cys Gly Cys Thr Gly Cys Gly Gly Cys Thr 12050	12055	12060
Gly Ala Thr Gly Gly Thr Gly Ala Cys Cys Gly Ala Gly Gly Thr 12065	12070	12075
Gly Cys Cys Cys Cys Ala Gly Ala Gly Cys Gly Ala Gly Gly Thr 12080	12085	12090
Gly Thr Ala Cys Cys Ala Gly Thr Cys Thr Gly Gly Cys Cys Cys 12095	12100	12105
Gly Gly Ala Cys Thr Ala Cys Thr Thr Thr Thr Thr Cys Cys Ala 12110	12115	12120
Gly Ala Cys Gly Ala Gly Cys Cys Gly Gly Cys Ala Gly Gly Gly 12125	12130	12135
Cys Thr Thr Gly Cys Ala Gly Ala Cys Gly Gly Thr Gly Ala Ala 12140	12145	12150
Cys Cys Thr Gly Ala Gly Cys Cys Ala Gly Gly Cys Thr Thr Thr 12155	12160	12165
Cys Ala Ala Gly Ala Ala Thr Cys Thr Gly Cys Gly Cys Gly Gly 12170	12175	12180
Gly Cys Thr Gly Thr Gly Gly Gly Gly Cys Gly Thr Gly Cys Ala 12185	12190	12195
Gly Gly Cys Gly Cys Cys Cys Gly Thr Gly Gly Gly Cys Gly Ala 12200	12205	12210
Cys Cys Gly Gly Thr Cys Ala Ala Cys Gly Gly Thr Gly Ala Gly 12215	12220	12225
Cys Ala Gly Cys Thr Thr Gly Cys Thr Gly Ala Cys Gly Cys Cys 12230	12235	12240
Cys Ala Ala Cys Thr Cys Gly Cys Gly Gly Cys Thr Gly Cys Thr 12245	12250	12255
Gly Cys Thr Gly Cys Thr Gly Cys Thr Gly Ala Thr Cys Gly Cys 12260	12265	12270
Gly Cys Cys Cys Thr Thr Cys Ala Cys Cys Gly Ala Cys Ala Gly 12275	12280	12285
Cys Gly Gly Cys Ala Gly Cys Gly Thr Gly Ala Ala Cys Cys Gly 12290	12295	12300
Cys Ala Ala Cys Thr Cys Gly Thr Ala Cys Cys Thr Gly Gly Gly 12305	12310	12315
Cys Cys Ala Thr Cys Thr Gly Cys Thr Gly Ala Cys Gly Cys Thr		

12320	12325	12330
Gly Thr Ala Cys Cys Gly Cys Gly Ala Gly Gly Cys Cys Ala Thr		
12335	12340	12345
Ala Gly Gly Cys Cys Ala Gly Gly Cys Gly Cys Ala Gly Gly Thr		
12350	12355	12360
Gly Gly Ala Cys Gly Ala Gly Cys Ala Gly Ala Cys Cys Thr Thr		
12365	12370	12375
Cys Cys Ala Gly Gly Ala Gly Ala Thr Cys Ala Cys Thr Ala Gly		
12380	12385	12390
Cys Gly Thr Gly Ala Gly Cys Cys Gly Cys Gly Cys Gly Cys Thr		
12395	12400	12405
Gly Gly Gly Gly Cys Ala Gly Ala Ala Cys Gly Ala Cys Ala Cys		
12410	12415	12420
Cys Gly Ala Cys Ala Gly Thr Cys Thr Gly Ala Gly Gly Gly Cys		
12425	12430	12435
Cys Ala Cys Cys Cys Thr Gly Ala Ala Cys Thr Thr Thr Thr Thr		
12440	12445	12450
Gly Cys Thr Gly Ala Cys Cys Ala Ala Thr Ala Gly Ala Cys Ala		
12455	12460	12465
Gly Cys Ala Gly Ala Ala Gly Ala Thr Cys Cys Cys Gly Gly Cys		
12470	12475	12480
Gly Cys Ala Gly Thr Ala Cys Gly Cys Ala Cys Thr Gly Thr Cys		
12485	12490	12495
Gly Gly Cys Cys Gly Ala Gly Gly Ala Gly Gly Ala Ala Ala Gly		
12500	12505	12510
Gly Ala Thr Thr Cys Thr Gly Ala Gly Ala Thr Ala Thr Gly Thr		
12515	12520	12525
Gly Cys Ala Gly Cys Ala Gly Ala Gly Cys Gly Thr Ala Gly Gly		
12530	12535	12540
Gly Cys Thr Gly Thr Thr Cys Cys Thr Gly Ala Thr Gly Cys Ala		
12545	12550	12555
Gly Gly Ala Gly Gly Gly Thr Gly Cys Cys Ala Cys Cys Cys Cys		
12560	12565	12570
Cys Ala Gly Cys Gly Cys Cys Gly Cys Gly Cys Thr Gly Gly Ala		
12575	12580	12585
Cys Ala Thr Gly Ala Cys Cys Gly Cys Gly Cys Gly Cys Ala Ala		
12590	12595	12600
Cys Ala Thr Gly Gly Ala Ala Cys Cys Thr Ala Gly Cys Ala Thr		
12605	12610	12615

Gly Thr Ala Cys Gly Cys Cys Gly Cys Cys Ala Ala Cys Cys Gly 12620	Cys Gly Cys Cys Gly Cys Cys Cys Gly Cys Cys Ala Ala Cys Cys Gly 12625	Ala Cys Cys Gly 12630
Gly Cys Cys Gly Thr Thr Cys Ala Thr Cys Ala Ala Thr Ala Ala 12635	Cys Ala Thr Cys Ala Ala Thr Ala Ala 12640	Ala Thr Ala Ala 12645
Gly Cys Thr Gly Ala Thr Gly Gly Ala Cys Thr Ala Cys Thr Thr 12650	Gly Gly Ala Cys Thr Ala Cys Thr Thr 12655	Ala Cys Thr Thr 12660
Gly Cys Ala Cys Cys Gly Cys Gly Cys Gly Gly Cys Gly Gly Cys 12665	Cys Gly Cys Gly Gly Cys Gly Gly Cys 12670	Gly Gly Cys 12675
Cys Ala Thr Gly Ala Ala Cys Ala Cys Gly Gly Ala Cys Thr Ala 12680	Cys Ala Cys Gly Gly Ala Cys Thr Ala 12685	Ala Cys Thr Ala 12690
Cys Thr Thr Thr Ala Cys Cys Ala Ala Cys Gly Cys Cys Ala Thr 12695	Cys Ala Ala Cys Gly Cys Cys Ala Thr 12700	Cys Cys Ala Thr 12705
Cys Cys Thr Gly Ala Ala Cys Cys Cys Gly Cys Ala Cys Thr Gly 12710	Cys Cys Cys Gly Cys Ala Cys Thr Gly 12715	Ala Cys Thr Gly 12720
Gly Cys Thr Cys Cys Cys Gly Cys Cys Gly Cys Cys Gly Gly Gly 12725	Cys Cys Gly Cys Cys Gly Cys Cys Gly 12730	Cys Gly Gly Gly 12735
Gly Thr Thr Cys Thr Ala Cys Ala Cys Gly Gly Gly Cys Gly Ala 12740	Cys Ala Cys Gly Gly Gly Cys Gly Ala 12745	Gly Cys Gly Ala 12750
Gly Thr Ala Cys Gly Ala Cys Ala Thr Gly Cys Cys Cys Gly Ala 12755	Cys Ala Thr Gly Cys Cys Cys Gly Ala 12760	Cys Cys Gly Ala 12765
Cys Cys Cys Cys Ala Ala Cys Gly Ala Cys Gly Gly Gly Thr Thr 12770	Cys Gly Ala Cys Gly Gly Gly Thr Thr 12775	Gly Gly Thr Thr 12780
Cys Cys Thr Gly Thr Gly Gly Gly Ala Cys Gly Ala Cys Gly Thr 12785	Gly Gly Ala Cys Gly Ala Cys Gly Thr 12790	Ala Cys Gly Thr 12795
Gly Gly Ala Cys Ala Gly Cys Gly Cys Gly Gly Thr Gly Thr Thr 12800	Cys Gly Cys Gly Gly Thr Gly Thr Thr 12805	Gly Thr Thr Thr 12810
Cys Thr Cys Gly Cys Cys Gly Ala Cys Cys Thr Thr Thr Cys Ala 12815	Gly Ala Cys Cys Thr Thr Thr Cys Ala 12820	Thr Thr Cys Ala 12825
Ala Ala Ala Gly Cys Gly Cys Cys Ala Gly Gly Ala Gly Gly Cys 12830	Gly Cys Cys Ala Gly Gly Ala Gly Gly Cys 12835	Ala Gly Gly Cys 12840
Gly Cys Cys Gly Cys Cys Gly Ala Gly Cys Gly Ala Gly Gly Gly 12845	Cys Ala Gly Cys Gly Ala Gly Gly Gly 12850	Ala Gly Gly Gly 12855
Cys Gly Cys Gly Gly Thr Gly Gly Gly Gly Ala Gly Gly Ala Gly 12860	Gly Gly Gly Gly Ala Gly Gly Ala Gly 12865	Gly Gly Ala Gly 12870
Cys Cys Cys Cys Thr Thr Thr Cys Cys Thr Ala Gly Cys Thr Thr 12875	Cys Cys Thr Ala Gly Cys Thr Thr 12880	Ala Gly Cys Thr Thr 12885
Ala Gly Gly Gly Ala Gly Thr Thr Thr Gly Cys Ala Thr Ala Gly 12890	Gly Thr Thr Thr Gly Cys Ala Thr Ala Gly 12895	Ala Thr Ala Gly 12900
Cys Thr Thr Gly Cys Cys Gly Gly Gly Cys Thr Cys Gly Gly Thr 12905	Gly Gly Gly Cys Thr Cys Gly Gly Thr 12910	Cys Gly Gly Thr 12915

12905	12910	12915
Gly Ala Ala Cys Ala Gly Cys Gly Gly Cys Ala Gly Gly Gly Thr		
12920	12925	12930
Gly Ala Gly Cys Cys Gly Gly Cys Cys Gly Cys Gly Cys Thr Thr		
12935	12940	12945
Gly Cys Thr Gly Gly Gly Cys Gly Ala Gly Gly Ala Cys Gly Ala		
12950	12955	12960
Gly Thr Ala Cys Cys Thr Gly Ala Ala Cys Gly Ala Cys Thr Cys		
12965	12970	12975
Gly Cys Thr Gly Cys Thr Gly Cys Ala Gly Cys Cys Gly Cys Cys		
12980	12985	12990
Gly Cys Gly Gly Gly Cys Cys Ala Ala Gly Ala Ala Cys Gly Cys		
12995	13000	13005
Cys Ala Thr Gly Gly Cys Cys Ala Ala Thr Ala Ala Cys Gly Gly		
13010	13015	13020
Gly Ala Thr Ala Gly Ala Gly Ala Gly Thr Cys Thr Gly Gly Thr		
13025	13030	13035
Gly Gly Ala Cys Ala Ala Ala Cys Thr Gly Ala Ala Cys Cys Gly		
13040	13045	13050
Cys Thr Gly Gly Ala Ala Gly Ala Cys Cys Thr Ala Cys Gly Cys		
13055	13060	13065
Thr Cys Ala Gly Gly Ala Cys Cys Ala Thr Ala Gly Gly Gly Ala		
13070	13075	13080
Cys Gly Cys Gly Cys Cys Cys Gly Cys Gly Cys Cys Gly Cys Gly		
13085	13090	13095
Gly Cys Gly Ala Cys Ala Gly Cys Gly Cys Cys Ala Cys Gly Ala		
13100	13105	13110
Cys Cys Gly Gly Cys Ala Gly Cys Gly Gly Gly Gly Cys Cys Thr		
13115	13120	13125
Gly Gly Thr Gly Thr Gly Gly Gly Ala Cys Gly Ala Cys Gly Ala		
13130	13135	13140
Gly Gly Ala Cys Thr Cys Gly Gly Cys Cys Gly Ala Cys Gly Ala		
13145	13150	13155
Thr Ala Gly Cys Ala Gly Cys Gly Thr Gly Thr Thr Gly Gly Ala		
13160	13165	13170
Cys Thr Thr Gly Gly Gly Cys Gly Gly Gly Ala Gly Cys Gly Gly		
13175	13180	13185
Thr Gly Gly Gly Gly Thr Cys Ala Ala Cys Cys Cys Gly Thr Thr		
13190	13195	13200

Cys Gly Cys Gly Cys Ala Thr Cys Thr Gly Cys Ala Gly Cys Cys 13205	13210	13215
Cys Ala Ala Ala Cys Thr Gly Gly Gly Gly Cys Gly Ala Cys Gly 13220	13225	13230
Gly Ala Thr Gly Thr Thr Thr Thr Gly Ala Ala Thr Gly Ala Ala 13235	13240	13245
Ala Thr Ala Ala Ala Ala Cys Thr Cys Ala Cys Cys Ala Ala Gly 13250	13255	13260
Gly Cys Cys Ala Thr Ala Gly Cys Gly Thr Gly Cys Gly Thr Thr 13265	13270	13275
Cys Thr Cys Thr Thr Cys Cys Thr Thr Gly Thr Thr Ala Gly Ala 13280	13285	13290
Gly Ala Thr Gly Ala Gly Gly Cys Gly Cys Gly Cys Gly Gly Thr 13295	13300	13305
Gly Gly Thr Gly Thr Cys Thr Thr Cys Cys Thr Cys Thr Cys Cys 13310	13315	13320
Thr Cys Cys Thr Cys Cys Cys Thr Cys Gly Thr Ala Cys Gly Ala 13325	13330	13335
Gly Ala Gly Cys Gly Thr Gly Ala Thr Gly Gly Cys Gly Cys Ala 13340	13345	13350
Gly Gly Cys Gly Ala Cys Cys Cys Thr Gly Gly Ala Gly Gly Thr 13355	13360	13365
Thr Cys Cys Gly Thr Thr Thr Gly Thr Gly Cys Cys Thr Cys Cys 13370	13375	13380
Gly Cys Gly Gly Thr Ala Thr Ala Thr Gly Gly Cys Thr Cys Cys 13385	13390	13395
Thr Ala Cys Gly Gly Ala Gly Gly Gly Cys Ala Gly Ala Ala Ala 13400	13405	13410
Cys Ala Gly Cys Ala Thr Thr Cys Gly Thr Thr Ala Cys Thr Cys 13415	13420	13425
Gly Gly Ala Gly Cys Thr Gly Gly Cys Thr Cys Cys Gly Cys Ala 13430	13435	13440
Gly Thr Ala Cys Gly Ala Cys Ala Cys Cys Ala Cys Thr Cys Gly 13445	13450	13455
Cys Gly Thr Gly Thr Ala Cys Thr Thr Gly Gly Thr Gly Gly Ala 13460	13465	13470
Cys Ala Ala Cys Ala Ala Gly Thr Cys Gly Gly Cys Gly Gly Ala 13475	13480	13485
Cys Ala Thr Cys Gly Cys Thr Thr Cys Cys Cys Thr Gly Ala Ala 13490	13495	13500

13490	13495	13500
Cys Thr Ala Cys Cys Ala	Ala Ala Ala Cys Gly	Ala Cys Cys Ala
13505	13510	13515
Cys Ala Gly Cys Ala Ala	Cys Thr Thr Cys Cys	Thr Gly Ala Cys
13520	13525	13530
Cys Ala Cys Gly Gly Thr	Gly Gly Thr Gly Cys	Ala Gly Ala Ala
13535	13540	13545
Cys Ala Ala Cys Gly Ala	Thr Thr Thr Cys Ala	Cys Cys Cys Cys
13550	13555	13560
Cys Gly Cys Cys Gly Ala	Gly Gly Cys Cys Ala	Gly Cys Ala Cys
13565	13570	13575
Gly Cys Ala Gly Ala Cys	Gly Ala Thr Ala Ala	Ala Thr Thr Thr
13580	13585	13590
Thr Gly Ala Cys Gly Ala	Gly Cys Gly Gly Thr	Cys Gly Cys Gly
13595	13600	13605
Gly Thr Gly Gly Gly Gly	Cys Gly Gly Thr Gly	Ala Thr Cys Thr
13610	13615	13620
Gly Ala Ala Gly Ala Cys	Cys Ala Thr Thr Cys	Thr Gly Cys Ala
13625	13630	13635
Cys Ala Cys Thr Ala Ala	Cys Ala Thr Gly Cys	Cys Cys Ala Ala
13640	13645	13650
Thr Gly Thr Gly Ala Ala	Cys Gly Ala Gly Thr	Ala Cys Ala Thr
13655	13660	13665
Gly Thr Thr Cys Ala Cys	Cys Ala Gly Cys Ala	Ala Gly Thr Thr
13670	13675	13680
Thr Ala Ala Gly Gly Cys	Gly Cys Gly Gly Gly	Thr Gly Ala Thr
13685	13690	13695
Gly Gly Thr Gly Thr Cys	Thr Ala Gly Gly Ala	Ala Gly Cys Ala
13700	13705	13710
Thr Cys Cys Ala Gly Ala	Gly Gly Gly Gly Gly	Thr Ala Gly Thr
13715	13720	13725
Thr Gly Ala Ala Ala Cys	Ala Gly Ala Thr Thr	Thr Gly Ala Gly
13730	13735	13740
Thr Cys Ala Gly Gly Ala	Thr Ala Ala Gly Cys	Thr Thr Gly Ala
13745	13750	13755
Ala Thr Ala Thr Gly Ala	Gly Thr Gly Gly Thr	Thr Thr Gly Ala
13760	13765	13770
Gly Thr Thr Thr Ala Cys	Cys Cys Thr Gly Cys	Cys Cys Gly Ala
13775	13780	13785

Gly Gly Gly Ala Ala Ala Cys Thr Thr Thr Thr Cys Cys Gly Ala	13790	13795	13800
Gly Ala Cys Cys Ala Thr Gly Ala Cys Cys Ala Thr Ala Gly Ala	13805	13810	13815
Cys Cys Thr Gly Ala Thr Gly Ala Ala Cys Ala Ala Cys Gly Cys	13820	13825	13830
Cys Ala Thr Cys Thr Thr Gly Gly Ala Ala Ala Ala Cys Thr Ala	13835	13840	13845
Cys Thr Thr Gly Cys Ala Ala Gly Thr Gly Gly Gly Gly Cys Gly	13850	13855	13860
Gly Cys Ala Gly Ala Ala Thr Gly Gly Cys Gly Thr Gly Cys Thr	13865	13870	13875
Gly Gly Ala Gly Ala Gly Cys Gly Ala Thr Ala Thr Cys Gly Gly	13880	13885	13890
Ala Gly Thr Cys Ala Ala Gly Thr Thr Thr Gly Ala Cys Ala Gly	13895	13900	13905
Cys Ala Gly Ala Ala Ala Thr Thr Thr Cys Ala Ala Gly Cys Thr	13910	13915	13920
Gly Gly Gly Cys Thr Gly Gly Gly Ala Cys Cys Cys Gly Gly Thr	13925	13930	13935
Gly Ala Cys Cys Ala Ala Gly Cys Thr Gly Gly Thr Gly Ala Thr	13940	13945	13950
Gly Cys Cys Ala Gly Gly Gly Gly Thr Cys Thr Ala Cys Ala Cys	13955	13960	13965
Cys Thr Ala Cys Gly Ala Gly Gly Cys Cys Thr Thr Cys Cys Ala	13970	13975	13980
Cys Cys Cys Gly Gly Ala Cys Gly Thr Gly Gly Thr Gly Cys Thr	13985	13990	13995
Gly Cys Thr Gly Cys Cys Gly Gly Gly Cys Thr Gly Cys Gly Gly	14000	14005	14010
Gly Gly Thr Gly Gly Ala Cys Thr Thr Cys Ala Cys Cys Gly Ala	14015	14020	14025
Gly Ala Gly Cys Cys Gly Cys Cys Thr Gly Ala Gly Cys Ala Ala	14030	14035	14040
Cys Cys Thr Cys Cys Thr Gly Gly Gly Cys Ala Thr Thr Cys Gly	14045	14050	14055
Cys Ala Ala Gly Ala Ala Gly Cys Ala Ala Cys Cys Thr Thr Thr	14060	14065	14070
Cys Cys Ala Ala Gly Ala Gly Gly Gly Cys Thr Thr Cys Ala Gly			

14075	14080	14085
Ala Ala Thr Cys Ala Thr Gly Thr Ala Thr Gly Ala Gly Gly Ala		
14090	14095	14100
Thr Cys Thr Ala Gly Ala Ala Gly Gly Thr Gly Gly Cys Ala Ala		
14105	14110	14115
Cys Ala Thr Cys Cys Cys Cys Gly Cys Cys Cys Thr Cys Cys Thr		
14120	14125	14130
Thr Gly Ala Thr Gly Thr Gly Cys Cys Cys Ala Ala Gly Thr Ala		
14135	14140	14145
Cys Thr Thr Gly Gly Ala Ala Ala Gly Cys Ala Ala Gly Ala Ala		
14150	14155	14160
Gly Ala Ala Ala Gly Thr Thr Gly Ala Ala Gly Ala Cys Gly Ala		
14165	14170	14175
Ala Ala Cys Thr Ala Ala Ala Ala Ala Thr Gly Cys Ala Gly Cys		
14180	14185	14190
Thr Gly Cys Gly Gly Cys Cys Ala Cys Ala Gly Cys Cys Gly Ala		
14195	14200	14205
Thr Ala Cys Ala Ala Cys Cys Ala Cys Thr Ala Gly Gly Gly Gly		
14210	14215	14220
Thr Gly Ala Thr Ala Cys Ala Thr Thr Thr Gly Cys Ala Ala Cys		
14225	14230	14235
Thr Cys Cys Ala Gly Cys Gly Cys Ala Ala Gly Ala Gly Ala Cys		
14240	14245	14250
Ala Gly Cys Ala Gly Cys Thr Gly Ala Thr Ala Ala Gly Ala Ala		
14255	14260	14265
Gly Gly Thr Ala Gly Ala Ala Gly Thr Cys Thr Thr Gly Cys Cys		
14270	14275	14280
Cys Ala Thr Thr Gly Ala Ala Ala Ala Gly Gly Ala Thr Gly Ala		
14285	14290	14295
Gly Ala Gly Thr Gly Gly Thr Ala Gly Ala Ala Gly Thr Thr Ala		
14300	14305	14310
Cys Ala Ala Cys Cys Thr Gly Ala Thr Cys Cys Ala Gly Gly Gly		
14315	14320	14325
Gly Ala Cys Cys Cys Ala Cys Gly Ala Cys Ala Cys Gly Cys Thr		
14330	14335	14340
Gly Thr Ala Cys Cys Gly Cys Ala Gly Thr Thr Gly Gly Thr Ala		
14345	14350	14355
Cys Cys Thr Gly Thr Cys Cys Thr Ala Thr Ala Cys Cys Thr Ala		
14360	14365	14370

Cys Gly Gly Gly Gly Ala Cys Cys Cys Cys Gly Ala Gly Ala Ala	14375	14380	14385
Gly Gly Gly Gly Gly Thr Gly Cys Ala Gly Thr Cys Gly Thr Gly	14390	14395	14400
Gly Ala Cys Gly Cys Thr Gly Cys Thr Cys Ala Cys Cys Ala Cys	14405	14410	14415
Cys Cys Cys Gly Gly Ala Cys Gly Thr Thr Ala Cys Cys Thr Gly	14420	14425	14430
Cys Gly Gly Cys Gly Cys Gly Gly Ala Gly Cys Ala Ala Gly Thr	14435	14440	14445
Cys Thr Ala Cys Thr Gly Gly Thr Cys Ala Cys Thr Gly Cys Cys	14450	14455	14460
Gly Gly Ala Cys Cys Thr Cys Ala Thr Gly Cys Ala Ala Gly Ala	14465	14470	14475
Cys Cys Cys Cys Gly Thr Cys Ala Cys Cys Thr Thr Cys Cys Gly	14480	14485	14490
Cys Thr Cys Cys Ala Cys Cys Cys Ala Gly Cys Ala Ala Gly Thr	14495	14500	14505
Cys Ala Gly Cys Ala Ala Cys Thr Ala Cys Cys Cys Cys Gly Thr	14510	14515	14520
Gly Gly Thr Cys Gly Gly Cys Gly Cys Cys Gly Ala Gly Cys Thr	14525	14530	14535
Cys Ala Thr Gly Cys Cys Cys Thr Thr Cys Cys Gly Cys Gly Cys	14540	14545	14550
Cys Ala Ala Gly Ala Gly Cys Thr Thr Thr Thr Ala Cys Ala Ala	14555	14560	14565
Cys Gly Ala Cys Cys Thr Cys Gly Cys Cys Gly Thr Cys Thr Ala	14570	14575	14580
Cys Thr Cys Cys Cys Ala Gly Cys Thr Cys Ala Thr Cys Cys Gly	14585	14590	14595
Cys Ala Gly Cys Thr Ala Cys Ala Cys Cys Thr Cys Cys Cys Thr	14600	14605	14610
Cys Ala Cys Cys Cys Ala Cys Gly Thr Cys Thr Thr Cys Ala Ala	14615	14620	14625
Cys Cys Gly Cys Thr Thr Cys Cys Cys Cys Gly Ala Cys Ala Ala	14630	14635	14640
Cys Cys Ala Gly Ala Thr Cys Cys Thr Cys Thr Gly Cys Cys Gly	14645	14650	14655
Cys Cys Cys Gly Cys Cys Cys Gly Cys Gly Cys Cys Cys Ala Cys			

14660	14665	14670
Cys Ala Thr Cys Ala Cys	Cys Ala Cys Cys Gly	Thr Cys Ala Gly
14675	14680	14685
Thr Gly Ala Ala Ala Ala	Cys Gly Thr Gly Cys	Cys Thr Gly Cys
14690	14695	14700
Thr Cys Thr Cys Ala Cys	Ala Gly Ala Thr Cys	Ala Cys Gly Gly
14705	14710	14715
Gly Ala Cys Gly Cys Thr	Ala Cys Cys Gly Cys	Thr Gly Cys Gly
14720	14725	14730
Cys Ala Gly Cys Ala Gly	Thr Ala Thr Cys Cys	Gly Cys Gly Gly
14735	14740	14745
Ala Gly Thr Cys Cys Ala	Gly Cys Gly Ala Gly	Thr Gly Ala Cys
14750	14755	14760
Cys Gly Thr Cys Ala Cys	Thr Gly Ala Cys Gly	Cys Cys Cys Gly
14765	14770	14775
Thr Cys Gly Cys Cys Gly	Cys Ala Cys Cys Thr	Gly Thr Cys Cys
14780	14785	14790
Cys Thr Ala Cys Gly Thr	Cys Thr Ala Cys Ala	Ala Gly Gly Cys
14795	14800	14805
Cys Cys Thr Gly Gly Gly	Cys Ala Thr Ala Gly	Thr Cys Gly Cys
14810	14815	14820
Gly Cys Cys Gly Cys Gly	Cys Gly Thr Gly Cys	Thr Thr Thr Cys
14825	14830	14835
Cys Ala Gly Thr Cys Gly	Cys Ala Cys Cys Thr	Thr Cys Thr Ala
14840	14845	14850
Ala Ala Ala Ala Ala Ala	Thr Gly Thr Cys Thr	Ala Thr Thr Cys
14855	14860	14865
Thr Cys Ala Thr Cys Thr	Cys Gly Cys Cys Cys	Ala Gly Cys Ala
14870	14875	14880
Ala Thr Ala Ala Cys Ala	Cys Cys Gly Gly Cys	Thr Gly Gly Gly
14885	14890	14895
Gly Thr Cys Thr Thr Ala	Cys Thr Ala Gly Ala	Cys Cys Cys Ala
14900	14905	14910
Gly Cys Ala Cys Cys Ala	Thr Gly Thr Ala Cys	Gly Gly Ala Gly
14915	14920	14925
Gly Ala Gly Cys Cys Ala	Ala Gly Ala Ala Gly	Cys Gly Cys Thr
14930	14935	14940
Cys Cys Cys Ala Gly Cys	Ala Gly Cys Ala Cys	Cys Cys Cys Gly
14945	14950	14955

Thr Cys Cys Gly Cys Gly	Thr Cys Cys Gly Cys Gly Gly Cys Cys	14960	14965	14970
Ala Cys Thr Thr Cys Cys	Gly Cys Gly Cys Thr Cys Cys Cys Thr	14975	14980	14985
Gly Gly Gly Gly Cys Gly	Cys Ala Thr Ala Cys Ala Ala Gly Cys	14990	14995	15000
Gly Cys Gly Gly Gly Cys	Gly Gly Ala Cys Thr Thr Cys Cys Ala	15005	15010	15015
Cys Cys Gly Cys Cys Gly	Cys Cys Gly Thr Gly Cys Gly Cys Ala	15020	15025	15030
Cys Cys Ala Cys Cys Gly	Thr Cys Gly Ala Cys Gly Ala Cys Gly	15035	15040	15045
Thr Cys Ala Thr Cys Gly	Ala Cys Thr Cys Gly Gly Thr Gly Gly	15050	15055	15060
Thr Cys Gly Cys Cys Gly	Ala Cys Gly Cys Gly Cys Gly Cys Ala	15065	15070	15075
Ala Cys Thr Ala Thr Ala	Cys Cys Cys Cys Cys Gly Cys Cys Cys	15080	15085	15090
Cys Cys Thr Cys Cys Ala	Cys Cys Gly Thr Gly Gly Ala Cys Gly	15095	15100	15105
Cys Gly Gly Thr Cys Ala	Thr Cys Gly Ala Cys Ala Gly Cys Gly	15110	15115	15120
Thr Gly Gly Thr Gly Gly	Cys Cys Gly Ala Cys Gly Cys Gly Cys	15125	15130	15135
Gly Cys Gly Ala Cys Thr	Ala Thr Gly Cys Cys Ala Gly Ala Cys	15140	15145	15150
Gly Cys Ala Ala Gly Ala	Gly Cys Cys Gly Gly Cys Gly Gly Cys	15155	15160	15165
Gly Ala Cys Gly Gly Ala	Thr Cys Gly Cys Cys Ala Gly Gly Cys	15170	15175	15180
Gly Cys Cys Ala Cys Cys	Gly Gly Ala Gly Cys Ala Cys Gly Cys	15185	15190	15195
Cys Cys Gly Cys Cys Ala	Thr Gly Cys Gly Cys Gly Cys Cys Gly	15200	15205	15210
Cys Cys Cys Gly Gly Gly	Cys Thr Cys Thr Gly Cys Thr Gly Cys	15215	15220	15225
Gly Cys Cys Gly Cys Gly	Cys Cys Ala Gly Ala Cys Gly Cys Ala	15230	15235	15240
Cys Gly Gly Gly Cys Cys	Gly Cys Cys Gly Gly Gly Cys Cys Ala			

15245	15250	15255
Thr Gly Ala Thr Gly Cys Gly Ala Gly Cys Cys Gly Cys Gly Cys		
15260	15265	15270
Gly Cys Cys Gly Cys Gly Cys Thr Gly Cys Cys Ala Cys Thr Gly		
15275	15280	15285
Cys Ala Cys Cys Cys Ala Cys Cys Cys Cys Cys Gly Cys Ala Gly		
15290	15295	15300
Gly Cys Ala Gly Gly Ala Cys Thr Cys Gly Cys Ala Gly Ala Cys		
15305	15310	15315
Gly Ala Gly Cys Gly Gly Cys Cys Gly Cys Cys Gly Cys Cys Gly		
15320	15325	15330
Cys Cys Gly Cys Thr Gly Cys Gly Gly Cys Cys Ala Thr Cys Thr		
15335	15340	15345
Cys Thr Ala Gly Cys Ala Thr Gly Ala Cys Cys Ala Gly Ala Cys		
15350	15355	15360
Cys Cys Ala Gly Gly Cys Gly Cys Gly Gly Ala Ala Ala Cys Gly		
15365	15370	15375
Thr Gly Thr Ala Cys Thr Gly Gly Gly Thr Gly Cys Gly Cys Gly		
15380	15385	15390
Ala Cys Thr Cys Cys Gly Thr Cys Ala Cys Gly Gly Gly Cys Gly		
15395	15400	15405
Thr Gly Cys Gly Cys Gly Thr Gly Cys Cys Cys Gly Thr Gly Cys		
15410	15415	15420
Gly Cys Ala Cys Cys Cys Gly Thr Cys Cys Thr Cys Cys Thr Cys		
15425	15430	15435
Gly Thr Cys Cys Cys Thr Gly Ala Thr Cys Thr Ala Ala Thr Gly		
15440	15445	15450
Cys Thr Thr Gly Thr Gly Thr Cys Cys Thr Cys Cys Cys Cys		
15455	15460	15465
Gly Cys Ala Ala Gly Cys Gly Ala Cys Gly Ala Thr Gly Thr Cys		
15470	15475	15480
Ala Ala Ala Gly Cys Gly Cys Ala Ala Ala Ala Thr Cys Ala Ala		
15485	15490	15495
Gly Gly Ala Gly Gly Ala Gly Ala Thr Gly Cys Thr Cys Cys Ala		
15500	15505	15510
Gly Gly Thr Cys Gly Thr Cys Gly Cys Cys Cys Cys Gly Gly Ala		
15515	15520	15525
Gly Ala Thr Thr Thr Ala Cys Gly Gly Ala Cys Cys Ala Cys Cys		
15530	15535	15540

Cys Cys Ala Gly Gly Cys Gly Gly Ala Cys Cys Ala Gly Ala Ala	15545	15550	15555
Ala Cys Cys Cys Cys Gly Cys Ala Ala Ala Ala Thr Cys Ala Ala	15560	15565	15570
Gly Cys Gly Gly Gly Thr Thr Ala Ala Ala Ala Ala Ala Ala Ala	15575	15580	15585
Gly Gly Ala Thr Gly Ala Gly Gly Thr Gly Gly Ala Cys Gly Ala	15590	15595	15600
Gly Gly Gly Gly Gly Cys Ala Gly Thr Ala Gly Ala Gly Thr Thr	15605	15610	15615
Thr Gly Thr Gly Cys Gly Cys Gly Ala Gly Thr Thr Cys Gly Cys	15620	15625	15630
Thr Cys Cys Gly Cys Gly Gly Cys Gly Gly Cys Gly Cys Gly Thr	15635	15640	15645
Ala Ala Ala Thr Thr Gly Gly Ala Ala Gly Gly Gly Gly Cys Gly	15650	15655	15660
Cys Ala Gly Gly Gly Thr Gly Cys Ala Gly Cys Gly Cys Gly Thr	15665	15670	15675
Gly Thr Thr Gly Cys Gly Gly Cys Cys Cys Gly Gly Cys Ala Cys	15680	15685	15690
Gly Gly Cys Gly Gly Thr Gly Gly Thr Gly Thr Thr Cys Ala Cys	15695	15700	15705
Gly Cys Cys Cys Gly Gly Cys Gly Ala Gly Cys Gly Gly Thr Cys	15710	15715	15720
Cys Thr Cys Gly Gly Thr Cys Ala Gly Gly Ala Gly Cys Ala Ala	15725	15730	15735
Gly Cys Gly Thr Ala Gly Cys Thr Ala Thr Gly Ala Cys Gly Ala	15740	15745	15750
Gly Gly Thr Gly Thr Ala Cys Gly Gly Cys Gly Ala Cys Gly Ala	15755	15760	15765
Cys Gly Ala Cys Ala Thr Cys Cys Thr Gly Gly Ala Cys Cys Ala	15770	15775	15780
Gly Gly Cys Gly Gly Cys Gly Gly Ala Gly Cys Gly Gly Gly Cys	15785	15790	15795
Gly Gly Gly Cys Gly Ala Gly Thr Thr Cys Gly Cys Cys Thr Ala	15800	15805	15810
Cys Gly Gly Gly Ala Ala Gly Cys Gly Gly Thr Cys Gly Cys Gly	15815	15820	15825
Cys Gly Ala Ala Gly Ala Gly Gly Ala Gly Cys Thr Gly Ala Thr			

15830	15835	15840
Cys Thr Cys Gly Cys Thr	Gly Cys Cys Gly Cys	Thr Gly Gly Ala
15845	15850	15855
Cys Gly Ala Ala Ala Gly	Cys Ala Ala Cys Cys	Cys Cys Ala Cys
15860	15865	15870
Gly Cys Cys Gly Ala Gly	Cys Cys Thr Gly Ala	Ala Gly Cys Cys
15875	15880	15885
Cys Gly Thr Gly Ala Cys	Cys Cys Thr Gly Cys	Ala Gly Cys Ala
15890	15895	15900
Gly Gly Thr Gly Cys Thr	Gly Cys Cys Cys Cys	Ala Gly Gly Cys
15905	15910	15915
Gly Gly Thr Gly Cys Thr	Gly Cys Thr Gly Cys	Cys Gly Ala Gly
15920	15925	15930
Cys Cys Gly Cys Gly Gly	Gly Gly Thr Cys Ala	Ala Gly Cys Gly
15935	15940	15945
Cys Gly Ala Gly Gly Gly	Cys Gly Ala Gly Ala	Gly Cys Ala Thr
15950	15955	15960
Gly Thr Ala Cys Cys Cys	Gly Ala Cys Cys Ala	Thr Gly Cys Ala
15965	15970	15975
Gly Ala Thr Cys Ala Thr	Gly Gly Thr Gly Cys	Cys Cys Ala Ala
15980	15985	15990
Gly Cys Gly Cys Cys Gly	Gly Cys Gly Cys Gly	Thr Gly Gly Ala
15995	16000	16005
Gly Gly Ala Cys Gly Thr	Gly Cys Thr Gly Gly	Ala Cys Ala Cys
16010	16015	16020
Cys Gly Thr Gly Ala Ala	Ala Ala Thr Gly Gly	Ala Thr Gly Thr
16025	16030	16035
Gly Gly Ala Gly Cys Cys	Cys Gly Ala Gly Gly	Thr Cys Ala Ala
16040	16045	16050
Gly Gly Thr Gly Cys Gly	Cys Cys Cys Cys Ala	Thr Cys Ala Ala
16055	16060	16065
Gly Cys Ala Gly Gly Thr	Gly Gly Cys Gly Cys	Cys Gly Gly Gly
16070	16075	16080
Cys Cys Thr Gly Gly Gly	Cys Gly Thr Gly Cys	Ala Ala Ala Cys
16085	16090	16095
Cys Gly Thr Gly Gly Ala	Cys Ala Thr Thr Cys	Ala Gly Ala Thr
16100	16105	16110
Cys Cys Cys Cys Ala Cys	Cys Gly Ala Cys Ala	Thr Gly Gly Ala
16115	16120	16125

Thr Gly Thr Cys Gly Ala Cys Ala Ala Ala Ala Ala Ala Cys Cys	16130	16135	16140
Cys Thr Cys Gly Ala Cys Cys Ala Gly Cys Ala Thr Cys Gly Ala	16145	16150	16155
Gly Gly Thr Gly Cys Ala Ala Ala Cys Cys Gly Ala Cys Cys Cys	16160	16165	16170
Cys Thr Gly Gly Cys Thr Cys Cys Cys Ala Gly Cys Cys Thr Cys	16175	16180	16185
Cys Ala Cys Cys Gly Cys Thr Ala Cys Cys Gly Thr Cys Thr Cys	16190	16195	16200
Cys Ala Cys Thr Thr Cys Thr Ala Cys Cys Gly Cys Cys Gly Cys	16205	16210	16215
Cys Ala Cys Gly Gly Cys Thr Ala Cys Cys Gly Ala Gly Cys Cys	16220	16225	16230
Thr Cys Cys Cys Ala Gly Gly Ala Gly Gly Cys Gly Ala Ala Gly	16235	16240	16245
Ala Thr Gly Gly Gly Gly Cys Gly Cys Cys Gly Cys Cys Ala Gly	16250	16255	16260
Cys Cys Gly Gly Cys Thr Gly Ala Thr Gly Cys Cys Cys Ala Ala	16265	16270	16275
Cys Thr Ala Cys Gly Thr Gly Thr Thr Gly Cys Ala Thr Cys Cys	16280	16285	16290
Thr Thr Cys Cys Ala Thr Cys Ala Thr Cys Cys Cys Gly Ala Cys	16295	16300	16305
Gly Cys Cys Gly Gly Gly Cys Thr Ala Cys Cys Gly Cys Gly Gly	16310	16315	16320
Cys Ala Cys Cys Cys Gly Gly Thr Ala Cys Thr Ala Cys Gly Cys	16325	16330	16335
Cys Ala Gly Cys Cys Gly Cys Cys Gly Gly Cys Gly Cys Cys Cys	16340	16345	16350
Ala Gly Cys Cys Ala Gly Cys Ala Ala Ala Cys Gly Cys Cys Gly	16355	16360	16365
Cys Cys Gly Cys Cys Gly Cys Ala Cys Cys Gly Cys Cys Ala Cys	16370	16375	16380
Cys Cys Gly Cys Cys Gly Cys Cys Gly Thr Cys Thr Gly Gly Cys	16385	16390	16395
Cys Cys Cys Cys Gly Cys Cys Cys Gly Cys Gly Thr Gly Cys Gly	16400	16405	16410
Cys Cys Gly Cys Gly Thr Gly Ala Cys Cys Ala Cys Gly Cys Gly			

16415	16420	16425
Cys Cys Gly Gly Gly Gly Cys Cys Gly Cys Thr Cys Gly Cys Thr		
16430	16435	16440
Cys Gly Thr Thr Cys Thr Gly Cys Cys Cys Ala Cys Cys Gly Thr		
16445	16450	16455
Gly Cys Gly Cys Thr Ala Cys Cys Ala Cys Cys Cys Cys Ala Gly		
16460	16465	16470
Cys Ala Thr Cys Cys Thr Thr Thr Ala Ala Thr Cys Cys Gly Thr		
16475	16480	16485
Gly Thr Gly Cys Thr Gly Thr Gly Ala Thr Ala Cys Thr Gly Thr		
16490	16495	16500
Thr Gly Cys Ala Gly Ala Gly Ala Gly Ala Thr Gly Gly Cys Thr		
16505	16510	16515
Cys Thr Cys Ala Cys Thr Thr Gly Cys Cys Gly Cys Cys Thr Gly		
16520	16525	16530
Cys Gly Cys Ala Thr Cys Cys Cys Cys Gly Thr Cys Cys Cys Gly		
16535	16540	16545
Ala Ala Thr Thr Ala Cys Cys Gly Ala Gly Gly Ala Ala Gly Ala		
16550	16555	16560
Thr Cys Cys Cys Gly Cys Cys Gly Cys Ala Gly Gly Ala Gly Ala		
16565	16570	16575
Gly Gly Cys Ala Thr Gly Gly Cys Ala Gly Gly Cys Ala Gly Cys		
16580	16585	16590
Gly Gly Cys Cys Thr Gly Ala Ala Cys Cys Gly Cys Cys Gly Cys		
16595	16600	16605
Cys Gly Gly Cys Gly Gly Cys Gly Gly Gly Cys Cys Ala Thr Gly		
16610	16615	16620
Cys Gly Cys Ala Gly Gly Cys Gly Cys Cys Thr Gly Ala Gly Thr		
16625	16630	16635
Gly Gly Cys Gly Gly Cys Thr Thr Thr Cys Thr Gly Cys Cys Cys		
16640	16645	16650
Gly Cys Gly Cys Thr Cys Ala Thr Cys Cys Cys Cys Ala Thr Ala		
16655	16660	16665
Ala Thr Cys Gly Cys Cys Gly Cys Gly Gly Cys Cys Ala Thr Thr		
16670	16675	16680
Gly Gly Cys Ala Cys Gly Ala Thr Cys Cys Cys Gly Gly Gly Cys		
16685	16690	16695
Ala Thr Ala Gly Cys Thr Thr Cys Cys Gly Thr Thr Gly Cys Gly		
16700	16705	16710

Cys Thr Gly Cys Ala Gly Gly Cys Gly Thr Cys Gly Cys Ala Gly 16715	Gly Gly Cys Gly Thr Cys Thr Gly Ala Thr Gly Thr Gly Cys Gly 16720	Gly Cys Ala Gly 16725
Cys Gly Cys Cys Gly Thr Thr Gly Ala Thr Gly Thr Gly Cys Gly 16730	Gly Thr Thr Gly Ala Thr Gly Thr Gly Cys Gly 16735	Gly Thr Thr Thr Ala 16740
Ala Ala Thr Ala Ala Ala Gly Cys Cys Thr Cys Thr Thr Thr Ala 16745	Gly Cys Cys Thr Cys Thr Thr Thr Thr Ala 16750	Gly Thr Thr Thr Thr 16755
Gly Ala Cys Thr Cys Thr Gly Ala Cys Ala Cys Ala Cys Cys Thr 16760	Gly Thr Ala Thr Ala Thr Thr Thr Thr 16765	Gly Thr Thr Thr Thr 16770
Gly Gly Thr Cys Cys Thr Gly Thr Ala Thr Ala Thr Thr Thr Thr 16775	Gly Thr Ala Thr Ala Thr Thr Thr Thr 16780	Gly Thr Thr Thr Thr 16785
Thr Ala Gly Ala Ala Thr Gly Gly Ala Ala Gly Ala Cys Ala Thr 16790	Gly Gly Ala Ala Gly Ala Cys Ala Thr 16795	Gly Thr Thr Thr Thr 16800
Cys Ala Ala Thr Thr Thr Thr Gly Cys Gly Thr Cys Cys Cys Thr 16805	Gly Cys Gly Thr Cys Cys Cys Thr 16810	Gly Thr Thr Thr Thr 16815
Gly Gly Cys Thr Cys Cys Gly Cys Gly Gly Cys Ala Cys Gly Gly 16820	Gly Cys Gly Gly Cys Ala Cys Gly Gly 16825	Gly Thr Thr Thr Thr 16830
Cys Ala Cys Gly Cys Gly Gly Cys Cys Gly Thr Thr Cys Ala Thr 16835	Gly Cys Cys Gly Thr Thr Thr Thr 16840	Gly Thr Thr Thr Thr 16845
Gly Gly Gly Cys Ala Cys Cys Thr Gly Gly Ala Ala Cys Gly Ala 16850	Gly Gly Ala Ala Cys Gly Ala 16855	Gly Thr Thr Thr Thr 16860
Gly Ala Thr Cys Gly Gly Cys Ala Cys Cys Ala Gly Cys Cys Ala 16865	Gly Cys Ala Cys Cys Ala Gly Cys Cys Ala 16870	Gly Thr Thr Thr Thr 16875
Gly Cys Thr Gly Ala Ala Cys Gly Gly Gly Gly Gly Cys Gly Cys 16880	Gly Gly Gly Gly Gly Gly Gly Cys Gly Cys 16885	Gly Thr Thr Thr Thr 16890
Cys Thr Thr Cys Ala Ala Thr Thr Gly Gly Ala Gly Cys Ala Gly 16895	Gly Gly Ala Gly Cys Gly Gly Gly Cys Thr 16900	Gly Thr Thr Thr Thr 16905
Thr Gly Thr Cys Thr Gly Gly Ala Gly Cys Gly Gly Gly Cys Thr 16910	Gly Thr Thr Thr Thr Thr Thr Thr Thr 16915	Gly Thr Thr Thr Thr 16920
Thr Ala Ala Ala Ala Ala Thr Thr Thr Cys Gly Gly Cys Thr Cys 16925	Gly Thr Thr Thr Thr Thr Thr Thr Thr 16930	Gly Thr Thr Thr Thr 16935
Gly Ala Cys Gly Cys Thr Cys Cys Gly Gly Ala Cys Cys Thr Ala 16940	Gly Gly Ala Gly Gly Ala Cys Cys Thr Ala 16945	Gly Thr Thr Thr Thr 16950
Thr Gly Gly Gly Ala Ala Cys Ala Ala Gly Gly Cys Cys Thr Gly 16955	Gly Thr Thr Thr Thr Thr Thr Thr Thr 16960	Gly Thr Thr Thr Thr 16965
Gly Ala Ala Thr Ala Gly Thr Ala Gly Cys Ala Cys Gly Gly Gly 16970	Gly Thr Thr Thr Thr Thr Thr Thr Thr 16975	Gly Thr Thr Thr Thr 16980
Gly Cys Ala Gly Thr Thr Gly Thr Thr Gly Ala Gly Gly Gly Ala 16985	Gly Thr Thr Thr Thr Thr Thr Thr Thr 16990	Gly Thr Thr Thr Thr 16995
Ala Ala Ala Gly Cys Thr Cys Ala Ala Ala Gly Ala Cys Cys Ala		

17000	17005	17010
Gly Ala Ala Cys Thr Thr	Cys Cys Ala Gly Cys	Ala Gly Ala Ala
17015	17020	17025
Gly Gly Thr Gly Gly Thr	Gly Gly Ala Cys Gly	Gly Gly Cys Thr
17030	17035	17040
Gly Gly Cys Cys Thr Cys	Gly Gly Gly Cys Ala	Thr Thr Ala Ala
17045	17050	17055
Cys Gly Gly Gly Gly Thr	Gly Gly Thr Gly Gly	Ala Cys Ala Thr
17060	17065	17070
Cys Gly Cys Gly Ala Ala	Cys Cys Ala Gly Gly	Cys Cys Gly Thr
17075	17080	17085
Gly Cys Ala Gly Cys Gly	Cys Gly Ala Gly Ala	Thr Ala Ala Ala
17090	17095	17100
Cys Ala Gly Cys Cys Gly	Cys Cys Thr Gly Gly	Ala Cys Cys Cys
17105	17110	17115
Gly Cys Gly Ala Cys Cys	Gly Cys Cys Cys Ala	Cys Gly Gly Thr
17120	17125	17130
Gly Gly Thr Gly Gly Ala	Gly Ala Thr Gly Gly	Ala Ala Gly Ala
17135	17140	17145
Thr Gly Cys Ala Ala Cys	Thr Cys Thr Thr Cys	Cys Gly Cys Cys
17150	17155	17160
Gly Cys Cys Cys Ala Ala	Gly Gly Gly Cys Gly	Ala Gly Ala Ala
17165	17170	17175
Gly Cys Gly Gly Cys Cys	Gly Cys Gly Gly Cys	Cys Cys Gly Ala
17180	17185	17190
Cys Gly Cys Gly Gly Ala	Gly Gly Ala Gly Ala	Cys Gly Ala Thr
17195	17200	17205
Cys Cys Thr Gly Cys Ala	Gly Gly Thr Gly Gly	Ala Cys Gly Ala
17210	17215	17220
Gly Cys Cys Gly Cys Cys	Cys Thr Cys Gly Thr	Ala Cys Gly Ala
17225	17230	17235
Gly Gly Ala Gly Gly Cys	Cys Gly Thr Cys Ala	Ala Gly Gly Cys
17240	17245	17250
Cys Gly Gly Cys Ala Thr	Gly Cys Cys Cys Ala	Cys Cys Ala Cys
17255	17260	17265
Gly Cys Gly Cys Ala Thr	Cys Ala Thr Cys Gly	Cys Gly Cys Cys
17270	17275	17280
Gly Cys Thr Gly Gly Cys	Cys Ala Cys Gly Gly	Gly Thr Gly Thr
17285	17290	17295

Ala Ala Thr Gly Ala Ala Ala Cys Cys Cys Gly Cys Cys Ala Cys	17300	17305	17310
Cys Cys Thr Thr Gly Ala Cys Cys Thr Gly Cys Cys Thr Cys Cys	17315	17320	17325
Ala Cys Cys Ala Cys Cys Cys Gly Cys Gly Cys Cys Cys Gly Cys	17330	17335	17340
Thr Cys Cys Ala Cys Cys Gly Ala Ala Gly Gly Cys Ala Ala Cys	17345	17350	17355
Thr Cys Cys Gly Gly Thr Thr Gly Thr Gly Cys Ala Gly Gly Cys	17360	17365	17370
Cys Cys Cys Cys Cys Cys Gly Gly Thr Gly Gly Cys Gly Ala Cys	17375	17380	17385
Cys Gly Cys Cys Gly Thr Gly Cys Gly Cys Cys Gly Cys Gly Thr	17390	17395	17400
Cys Cys Cys Cys Gly Cys Cys Cys Gly Cys Cys Gly Cys Cys Ala	17405	17410	17415
Gly Gly Cys Cys Cys Ala Gly Ala Ala Cys Thr Gly Gly Cys Ala	17420	17425	17430
Gly Ala Gly Cys Ala Cys Gly Cys Thr Gly Cys Ala Cys Ala Gly	17435	17440	17445
Thr Ala Thr Cys Gly Thr Gly Gly Gly Cys Cys Thr Gly Gly Gly	17450	17455	17460
Ala Gly Thr Gly Ala Ala Ala Ala Gly Thr Cys Thr Gly Ala Ala	17465	17470	17475
Gly Cys Gly Cys Cys Gly Cys Cys Gly Ala Thr Gly Cys Thr Ala	17480	17485	17490
Thr Thr Gly Ala Gly Ala Gly Ala Gly Ala Gly Gly Ala Ala Ala	17495	17500	17505
Gly Ala Gly Gly Ala Cys Ala Cys Thr Ala Ala Ala Gly Gly Gly	17510	17515	17520
Ala Gly Ala Gly Cys Thr Thr Ala Ala Cys Thr Thr Gly Thr Ala	17525	17530	17535
Thr Gly Thr Gly Cys Cys Thr Thr Ala Cys Cys Gly Cys Cys Ala	17540	17545	17550
Gly Ala Gly Ala Ala Cys Gly Cys Gly Cys Gly Ala Ala Gly Ala	17555	17560	17565
Thr Gly Gly Cys Cys Ala Cys Cys Cys Cys Cys Thr Cys Gly Ala	17570	17575	17580
Thr Gly Ala Thr Gly Cys Cys Gly Cys Ala Gly Thr Gly Gly Gly			

17585	17590	17595
Cys Gly Thr Ala Cys Ala	Thr Gly Cys Ala Cys Ala	Thr Cys Gly
17600	17605	17610
Cys Cys Gly Gly Gly Cys	Ala Gly Gly Ala Cys Gly	Cys Cys Thr
17615	17620	17625
Cys Gly Gly Ala Gly Thr	Ala Cys Cys Thr Gly Ala	Gly Cys Cys
17630	17635	17640
Cys Gly Gly Gly Thr Cys	Thr Gly Gly Thr Gly Cys	Ala Gly Thr
17645	17650	17655
Thr Thr Gly Cys Cys Cys	Gly Cys Gly Cys Cys Ala	Cys Cys Gly
17660	17665	17670
Ala Cys Ala Cys Gly Thr	Ala Cys Thr Thr Cys Ala	Gly Cys Cys
17675	17680	17685
Thr Gly Gly Gly Cys Ala	Ala Cys Ala Ala Gly Thr	Thr Thr Ala
17690	17695	17700
Gly Gly Ala Ala Cys Cys	Cys Cys Ala Cys Gly Gly	Thr Gly Gly
17705	17710	17715
Cys Cys Cys Cys Gly Ala	Cys Cys Cys Ala Cys Gly	Ala Thr Gly
17720	17725	17730
Thr Gly Ala Cys Cys Ala	Cys Gly Gly Ala Cys Cys	Gly Gly Thr
17735	17740	17745
Cys Cys Cys Ala Gly Cys	Gly Thr Cys Thr Gly Ala	Cys Gly Cys
17750	17755	17760
Thr Gly Cys Gly Cys Thr	Thr Cys Gly Thr Gly Cys	Cys Cys Gly
17765	17770	17775
Thr Gly Gly Ala Thr Cys	Gly Cys Gly Ala Gly Gly	Ala Cys Ala
17780	17785	17790
Cys Cys Ala Cys Gly Thr	Ala Cys Thr Cys Gly Thr	Ala Cys Ala
17795	17800	17805
Ala Gly Gly Cys Gly Cys	Gly Cys Thr Thr Cys Ala	Cys Thr Cys
17810	17815	17820
Thr Gly Gly Cys Cys Gly	Thr Gly Gly Gly Cys Gly	Ala Cys Ala
17825	17830	17835
Ala Cys Cys Gly Gly Gly	Thr Gly Cys Thr Ala Gly	Ala Cys Ala
17840	17845	17850
Thr Gly Gly Cys Cys Ala	Gly Cys Ala Cys Thr Thr	Ala Cys Thr
17855	17860	17865
Thr Thr Gly Ala Cys Ala	Thr Cys Cys Gly Cys Gly	Gly Cys Gly
17870	17875	17880

Thr Cys Cys Thr Gly Gly Ala Cys Cys Gly Cys Gly Gly Thr Cys 17885	17890	17895
Cys Cys Ala Gly Cys Thr Thr Cys Ala Ala Ala Cys Cys Cys Thr 17900	17905	17910
Ala Cys Thr Cys Gly Gly Gly Cys Ala Cys Gly Gly Cys Cys Thr 17915	17920	17925
Ala Cys Ala Ala Cys Ala Gly Cys Cys Thr Gly Gly Cys Thr Cys 17930	17935	17940
Cys Cys Ala Ala Gly Gly Gly Thr Gly Cys Cys Cys Cys Cys Ala 17945	17950	17955
Ala Thr Cys Cys Cys Ala Gly Cys Cys Ala Gly Thr Gly Gly Gly 17960	17965	17970
Ala Gly Cys Ala Ala Ala Ala Thr Gly Ala Ala Ala Cys Cys Ala 17975	17980	17985
Ala Thr Gly Thr Thr Ala Ala Thr Ala Ala Ala Ala Cys Ala Cys 17990	17995	18000
Ala Cys Ala Cys Cys Thr Thr Thr Gly Gly Gly Ala Thr Gly Gly 18005	18010	18015
Cys Ala Gly Cys Cys Ala Thr Gly Ala Ala Ala Gly Gly Ala Gly 18020	18025	18030
Ala Ala Gly Cys Thr Ala Thr Thr Gly Ala Cys Ala Ala Ala Ala 18035	18040	18045
Ala Thr Gly Gly Thr Cys Thr Gly Cys Ala Ala Ala Thr Thr Gly 18050	18055	18060
Gly Ala Ala Cys Thr Gly Ala Cys Gly Cys Gly Gly Cys Gly Gly 18065	18070	18075
Ala Thr Cys Ala Gly Gly Ala Thr Ala Ala Ala Cys Cys Ala Ala 18080	18085	18090
Thr Thr Thr Ala Thr Gly Cys Ala Gly Ala Thr Ala Ala Ala Ala 18095	18100	18105
Cys Thr Thr Thr Cys Cys Ala Gly Cys Cys Ala Gly Ala Ala Cys 18110	18115	18120
Cys Thr Cys Ala Ala Gly Thr Ala Gly Gly Ala Gly Ala Gly Gly 18125	18130	18135
Ala Ala Gly Ala Cys Thr Gly Gly Ala Thr Thr Gly Ala Thr Ala 18140	18145	18150
Ala Ala Gly Cys Ala Gly Ala Thr Thr Thr Cys Thr Ala Thr Gly 18155	18160	18165
Gly Cys Gly Gly Ala Ala Gly Ala Gly Cys Thr Cys Thr Thr Ala		

18170	18175	18180
Ala Ala Ala Ala Ala Gly	Ala Cys Ala Cys Thr	Ala Ala Ala Ala
18185	18190	18195
Thr Gly Ala Ala Ala Cys	Cys Ala Thr Gly Cys	Thr Ala Thr Gly
18200	18205	18210
Gly Ala Thr Cys Thr Thr	Thr Thr Gly Cys Thr	Ala Gly Ala Cys
18215	18220	18225
Cys Thr Ala Cys Thr Ala	Ala Thr Gly Ala Gly	Ala Ala Ala Gly
18230	18235	18240
Gly Ala Gly Gly Thr Cys	Ala Gly Gly Cys Ala	Ala Ala Gly Thr
18245	18250	18255
Thr Cys Ala Ala Ala Cys	Cys Ala Gly Thr Thr	Ala Ala Thr Gly
18260	18265	18270
Ala Ala Gly Gly Ala Gly	Ala Ala Cys Ala Ala	Cys Cys Thr Ala
18275	18280	18285
Ala Ala Gly Ala Thr Cys	Thr Gly Gly Ala Thr	Ala Thr Ala Gly
18290	18295	18300
Ala Thr Ala Thr Gly Ala	Ala Cys Thr Thr Cys	Thr Thr Thr Gly
18305	18310	18315
Ala Cys Cys Cys Ala Ala	Cys Cys Ala Cys Thr	Ala Thr Thr Ala
18320	18325	18330
Ala Cys Ala Cys Ala Cys	Cys Ala Gly Ala Thr	Gly Thr Ala Gly
18335	18340	18345
Thr Gly Cys Thr Gly Thr	Ala Cys Ala Cys Thr	Gly Ala Ala Ala
18350	18355	18360
Ala Thr Gly Thr Thr Ala	Ala Thr Cys Thr Thr	Gly Ala Ala Ala
18365	18370	18375
Cys Ala Cys Cys Ala Gly	Ala Cys Ala Cys Thr	Cys Ala Thr Gly
18380	18385	18390
Thr Gly Gly Thr Thr Thr	Ala Cys Ala Ala Gly	Gly Cys Ala Gly
18395	18400	18405
Gly Ala Ala Cys Thr Thr	Cys Ala Gly Ala Thr	Gly Ala Cys Ala
18410	18415	18420
Gly Thr Thr Cys Thr Gly	Ala Gly Gly Thr Cys	Ala Ala Thr Thr
18425	18430	18435
Thr Gly Gly Cys Thr Cys	Ala Gly Cys Ala Gly	Thr Cys Cys Ala
18440	18445	18450
Thr Gly Cys Cys Ala Ala	Ala Cys Ala Gly Ala	Cys Cys Cys Ala
18455	18460	18465

Ala Cys Thr Ala Cys Ala Thr Thr Gly Gly Cys Thr Thr Thr Ala	18470	18475	18480
Gly Gly Gly Ala Cys Ala Ala Cys Thr Thr Thr Gly Thr Ala Gly	18485	18490	18495
Gly Thr Cys Thr Cys Ala Thr Gly Thr Ala Thr Thr Ala Cys Ala	18500	18505	18510
Ala Cys Ala Gly Cys Ala Cys Cys Gly Gly Ala Ala Ala Thr Ala	18515	18520	18525
Thr Gly Gly Gly Thr Gly Thr Gly Cys Thr Gly Gly Cys Thr Gly	18530	18535	18540
Gly Thr Cys Ala Gly Gly Cys Thr Thr Cys Thr Cys Ala Gly Thr	18545	18550	18555
Thr Gly Ala Ala Cys Gly Cys Thr Gly Thr Gly Gly Thr Cys Gly	18560	18565	18570
Ala Cys Thr Thr Gly Cys Ala Ala Gly Ala Cys Ala Gly Ala Ala	18575	18580	18585
Ala Cys Ala Cys Cys Gly Ala Gly Thr Thr Ala Thr Cys Thr Thr	18590	18595	18600
Ala Cys Cys Ala Gly Cys Thr Ala Thr Thr Gly Cys Thr Ala Gly	18605	18610	18615
Ala Thr Thr Cys Thr Cys Thr Gly Gly Gly Thr Gly Ala Cys Ala	18620	18625	18630
Gly Ala Ala Cys Cys Ala Gly Ala Thr Ala Cys Thr Thr Thr Ala	18635	18640	18645
Gly Cys Ala Thr Gly Thr Gly Gly Ala Ala Cys Thr Cys Thr Gly	18650	18655	18660
Cys Gly Gly Thr Gly Gly Ala Cys Ala Gly Thr Thr Ala Cys Gly	18665	18670	18675
Ala Thr Cys Cys Ala Gly Ala Thr Gly Thr Cys Ala Gly Gly Ala	18680	18685	18690
Thr Cys Ala Thr Thr Gly Ala Ala Ala Ala Thr Cys Ala Cys Gly	18695	18700	18705
Gly Thr Gly Thr Gly Gly Ala Ala Gly Ala Thr Gly Ala Ala Cys	18710	18715	18720
Thr Thr Cys Cys Ala Ala Ala Cys Thr Ala Thr Thr Gly Cys Thr	18725	18730	18735
Thr Cys Cys Cys Ala Thr Thr Gly Gly Ala Thr Gly Gly Thr Gly	18740	18745	18750
Thr Gly Gly Gly Cys Ala Cys Thr Ala Ala Thr Ala Cys Thr Gly			

18755	18760	18765
Cys Ala Thr Ala Cys Cys	Ala Ala Gly Gly Cys Gly Thr Thr Ala	
18770	18775	18780
Ala Ala Gly Thr Thr Ala	Ala Ala Gly Ala Cys Ala Ala Cys Thr Ala	
18785	18790	18795
Ala Thr Gly Gly Ala Ala	Ala Cys Gly Ala Cys Ala Cys Gly Thr	
18800	18805	18810
Gly Gly Gly Ala Ala Ala	Ala Ala Gly Ala Thr Gly Ala Ala Ala	
18815	18820	18825
Cys Thr Gly Thr Thr Thr	Ala Thr Gly Ala Gly Thr Thr Thr Ala	
18830	18835	18840
Ala Thr Cys Ala Ala Ala	Thr Thr Gly Gly Cys Ala Ala Gly Gly	
18845	18850	18855
Gly Gly Gly Ala Thr Ala	Thr Cys Thr Ala Thr Gly Cys Cys Ala	
18860	18865	18870
Thr Gly Gly Ala Gly Ala	Thr Cys Ala Ala Cys Cys Thr Gly Cys	
18875	18880	18885
Ala Gly Gly Cys Cys Ala	Ala Cys Cys Thr Gly Thr Gly Gly Ala	
18890	18895	18900
Ala Gly Ala Gly Thr Thr	Thr Thr Cys Thr Gly Thr Ala Cys Thr	
18905	18910	18915
Cys Gly Ala Ala Cys Gly	Thr Gly Gly Cys Cys Cys Thr Gly Thr	
18920	18925	18930
Ala Cys Cys Thr Gly Cys	Cys Cys Gly Ala Cys Thr Cys Cys Thr	
18935	18940	18945
Ala Cys Ala Ala Gly Thr	Ala Cys Ala Cys Gly Cys Cys Gly Gly	
18950	18955	18960
Cys Cys Ala Ala Cys Gly	Thr Cys Ala Ala Gly Cys Thr Gly Cys	
18965	18970	18975
Cys Cys Gly Cys Cys Ala	Ala Cys Ala Cys Cys Ala Ala Cys Ala	
18980	18985	18990
Cys Cys Thr Ala Cys Gly	Ala Gly Thr Ala Cys Ala Thr Gly Ala	
18995	19000	19005
Ala Cys Gly Gly Cys Cys	Gly Cys Gly Thr Gly Gly Thr Ala Gly	
19010	19015	19020
Cys Cys Cys Cys Cys Thr	Cys Gly Cys Thr Gly Gly Thr Gly Gly	
19025	19030	19035
Ala Cys Gly Cys Cys Thr	Ala Cys Ala Thr Cys Ala Ala Cys Ala	
19040	19045	19050

Thr Cys Gly Gly Cys Gly Cys Cys Cys Gly Cys Thr Gly Gly Thr 19055	19060	19065
Cys Gly Thr Thr Gly Gly Ala Thr Cys Cys Cys Ala Thr Gly Gly 19070	19075	19080
Ala Cys Ala Ala Cys Gly Thr Cys Ala Ala Cys Cys Cys Cys Thr 19085	19090	19095
Thr Cys Ala Ala Cys Cys Ala Cys Cys Ala Cys Cys Gly Cys Ala 19100	19105	19110
Ala Thr Gly Cys Gly Gly Gly Cys Cys Thr Gly Cys Gly Cys Thr 19115	19120	19125
Ala Cys Cys Gly Cys Thr Cys Cys Ala Thr Gly Cys Thr Gly Cys 19130	19135	19140
Thr Gly Gly Gly Cys Ala Ala Cys Gly Gly Cys Cys Gly Cys Thr 19145	19150	19155
Ala Cys Gly Thr Gly Cys Cys Cys Thr Thr Cys Cys Ala Cys Ala 19160	19165	19170
Thr Cys Cys Ala Ala Gly Thr Gly Cys Cys Cys Cys Ala Ala Ala 19175	19180	19185
Ala Gly Thr Thr Cys Thr Thr Thr Gly Cys Cys Ala Thr Cys Ala 19190	19195	19200
Ala Gly Ala Ala Cys Cys Thr Gly Cys Thr Cys Cys Thr Gly Cys 19205	19210	19215
Thr Cys Cys Cys Gly Gly Gly Cys Thr Cys Cys Thr Ala Cys Ala 19220	19225	19230
Cys Cys Thr Ala Cys Gly Ala Gly Thr Gly Gly Ala Ala Cys Thr 19235	19240	19245
Thr Cys Cys Gly Cys Ala Ala Gly Gly Ala Cys Gly Thr Cys Ala 19250	19255	19260
Ala Cys Ala Thr Gly Ala Thr Cys Cys Thr Gly Cys Ala Gly Ala 19265	19270	19275
Gly Thr Thr Cys Cys Cys Thr Cys Gly Gly Cys Ala Ala Cys Gly 19280	19285	19290
Ala Cys Cys Thr Gly Cys Gly Cys Gly Thr Cys Gly Ala Cys Gly 19295	19300	19305
Gly Cys Gly Cys Cys Thr Cys Cys Gly Thr Cys Cys Gly Cys Thr 19310	19315	19320
Thr Cys Gly Ala Cys Ala Gly Cys Gly Thr Cys Ala Ala Cys Cys 19325	19330	19335
Thr Ala Thr Ala Cys Gly Cys Cys Ala Cys Thr Thr Thr Cys Thr		

19340	19345	19350
Thr Cys Cys Cys Cys Ala	Thr Gly Gly Cys Gly	Cys Ala Cys Ala
19355	19360	19365
Ala Cys Ala Cys Cys Gly	Cys Thr Thr Cys Ala	Ala Cys Cys Thr
19370	19375	19380
Thr Gly Gly Ala Ala Gly	Cys Cys Ala Thr Gly	Cys Thr Gly Cys
19385	19390	19395
Gly Cys Ala Ala Cys Gly	Ala Cys Ala Cys Cys	Ala Ala Cys Gly
19400	19405	19410
Ala Cys Cys Ala Gly Thr	Cys Cys Thr Thr Cys	Ala Ala Cys Gly
19415	19420	19425
Ala Cys Thr Ala Cys Cys	Thr Cys Thr Cys Gly	Gly Cys Cys Gly
19430	19435	19440
Cys Cys Ala Ala Cys Ala	Thr Gly Cys Thr Cys	Thr Ala Cys Cys
19445	19450	19455
Cys Cys Ala Thr Cys Cys	Cys Gly Gly Cys Cys	Ala Ala Gly Gly
19460	19465	19470
Cys Cys Ala Cys Cys Ala	Ala Cys Gly Thr Gly	Cys Cys Cys Ala
19475	19480	19485
Thr Cys Thr Cys Cys Ala	Thr Cys Cys Cys Ala	Thr Cys Gly Cys
19490	19495	19500
Gly Cys Ala Ala Cys Thr	Gly Gly Gly Cys Cys	Gly Cys Cys Thr
19505	19510	19515
Thr Cys Cys Gly Cys Gly	Gly Cys Thr Gly Gly	Ala Gly Thr Thr
19520	19525	19530
Thr Cys Ala Cys Cys Cys	Gly Gly Cys Thr Cys	Ala Ala Gly Ala
19535	19540	19545
Cys Cys Ala Ala Gly Gly	Ala Ala Ala Cys Thr	Cys Cys Thr Thr
19550	19555	19560
Cys Cys Cys Thr Cys Gly	Gly Cys Thr Cys Gly	Gly Gly Thr Thr
19565	19570	19575
Thr Cys Gly Ala Cys Cys	Cys Cys Thr Ala Cys	Thr Thr Thr Gly
19580	19585	19590
Thr Cys Thr Ala Cys Thr	Cys Gly Gly Gly Cys	Thr Cys Cys Ala
19595	19600	19605
Thr Cys Cys Cys Cys Thr	Ala Cys Cys Thr Cys	Gly Ala Cys Gly
19610	19615	19620
Gly Gly Ala Cys Cys Thr	Thr Cys Thr Ala Cys	Cys Thr Cys Ala
19625	19630	19635

Ala Cys Cys Ala Cys Ala Cys Cys Thr Thr Cys Ala Ala Gly Ala 19640	19645	19650
Ala Gly Gly Thr Cys Thr Cys Cys Ala Thr Cys Ala Thr Gly Thr 19655	19660	19665
Thr Cys Gly Ala Cys Thr Cys Cys Thr Cys Gly Gly Thr Cys Ala 19670	19675	19680
Gly Cys Thr Gly Gly Cys Cys Cys Gly Gly Cys Ala Ala Cys Gly 19685	19690	19695
Ala Cys Cys Gly Gly Cys Thr Gly Cys Thr Cys Ala Cys Gly Cys 19700	19705	19710
Cys Gly Ala Ala Cys Gly Ala Gly Thr Thr Cys Gly Ala Gly Ala 19715	19720	19725
Thr Cys Ala Ala Gly Cys Gly Cys Ala Gly Cys Gly Thr Cys Gly 19730	19735	19740
Ala Cys Gly Gly Gly Gly Ala Gly Gly Gly Cys Thr Ala Cys Ala 19745	19750	19755
Ala Cys Gly Thr Gly Gly Cys Cys Cys Ala Ala Thr Gly Cys Ala 19760	19765	19770
Ala Cys Ala Thr Gly Ala Cys Cys Ala Ala Gly Gly Ala Cys Thr 19775	19780	19785
Gly Gly Thr Thr Cys Cys Thr Cys Gly Thr Cys Cys Ala Gly Ala 19790	19795	19800
Thr Gly Cys Thr Cys Thr Cys Cys Cys Ala Cys Thr Ala Cys Ala 19805	19810	19815
Ala Cys Ala Thr Cys Gly Gly Cys Thr Ala Cys Cys Ala Gly Gly 19820	19825	19830
Gly Cys Thr Thr Cys Cys Ala Cys Gly Thr Gly Cys Cys Cys Gly 19835	19840	19845
Ala Gly Gly Gly Cys Thr Ala Cys Ala Ala Gly Gly Ala Cys Cys 19850	19855	19860
Gly Cys Ala Thr Gly Thr Ala Cys Thr Cys Cys Thr Thr Cys Thr 19865	19870	19875
Thr Cys Cys Gly Cys Ala Ala Cys Thr Thr Cys Cys Ala Gly Cys 19880	19885	19890
Cys Cys Ala Thr Gly Ala Gly Cys Ala Gly Gly Cys Ala Gly Gly 19895	19900	19905
Thr Gly Gly Thr Cys Gly Ala Thr Gly Ala Gly Ala Thr Cys Ala 19910	19915	19920
Ala Cys Thr Ala Cys Ala Ala Gly Gly Ala Cys Thr Ala Cys Ala		

19925	19930	19935
Ala Gly Gly Cys Cys Gly	Thr Cys Ala Cys Cys	Cys Thr Gly Cys
19940	19945	19950
Cys Cys Thr Thr Cys Cys	Ala Gly Cys Ala Cys	Ala Ala Thr Ala
19955	19960	19965
Ala Cys Thr Cys Gly Gly	Gly Cys Thr Thr Cys	Ala Cys Cys Gly
19970	19975	19980
Gly Cys Thr Ala Cys Cys	Thr Cys Gly Cys Ala	Cys Cys Cys Ala
19985	19990	19995
Cys Cys Ala Thr Gly Cys	Gly Cys Cys Ala Gly	Gly Gly Gly Cys
20000	20005	20010
Ala Gly Cys Cys Cys Thr	Ala Cys Cys Cys Cys	Gly Cys Cys Ala
20015	20020	20025
Ala Cys Thr Thr Cys Cys	Cys Cys Thr Ala Cys	Cys Cys Gly Cys
20030	20035	20040
Thr Cys Ala Thr Cys Gly	Gly Thr Cys Ala Gly	Ala Cys Ala Gly
20045	20050	20055
Cys Cys Gly Thr Gly Cys	Cys Cys Thr Cys Cys	Gly Thr Cys Ala
20060	20065	20070
Cys Cys Cys Ala Gly Ala	Ala Ala Ala Ala Gly	Thr Thr Cys Cys
20075	20080	20085
Thr Cys Thr Gly Cys Gly	Ala Cys Ala Gly Gly	Gly Thr Cys Ala
20090	20095	20100
Thr Gly Thr Gly Gly Cys	Gly Cys Ala Thr Cys	Cys Cys Cys Thr
20105	20110	20115
Thr Cys Thr Cys Cys Ala	Gly Cys Ala Ala Cys	Thr Thr Cys Ala
20120	20125	20130
Thr Gly Thr Cys Cys Ala	Thr Gly Gly Gly Cys	Gly Cys Cys Cys
20135	20140	20145
Thr Cys Ala Cys Cys Gly	Ala Cys Cys Thr Gly	Gly Gly Thr Cys
20150	20155	20160
Ala Gly Ala Ala Cys Ala	Thr Gly Cys Thr Cys	Thr Ala Cys Gly
20165	20170	20175
Cys Cys Ala Ala Cys Thr	Cys Gly Gly Cys Cys	Cys Ala Cys Gly
20180	20185	20190
Cys Gly Cys Thr Cys Gly	Ala Cys Ala Thr Gly	Ala Cys Cys Thr
20195	20200	20205
Thr Cys Gly Ala Gly Gly	Thr Gly Gly Ala Cys	Cys Cys Cys Ala
20210	20215	20220

Thr Gly Gly Ala Thr Gly Ala Gly Cys Cys Cys Ala Cys Cys Cys	20225	20230	20235
Thr Cys Cys Thr Cys Thr Ala Thr Cys Thr Thr Cys Thr Cys Thr	20240	20245	20250
Thr Cys Gly Ala Ala Gly Thr Thr Thr Thr Cys Gly Ala Cys Gly	20255	20260	20265
Thr Gly Gly Thr Cys Ala Gly Ala Gly Thr Ala Cys Ala Cys Cys	20270	20275	20280
Ala Gly Cys Cys Gly Cys Ala Cys Cys Gly Cys Gly Gly Cys Gly	20285	20290	20295
Thr Cys Ala Thr Cys Gly Ala Gly Gly Cys Cys Gly Thr Cys Thr	20300	20305	20310
Ala Cys Cys Thr Gly Cys Gly Cys Ala Cys Gly Cys Cys Cys Thr	20315	20320	20325
Thr Cys Thr Cys Cys Gly Cys Cys Gly Gly Cys Ala Ala Cys Gly	20330	20335	20340
Cys Cys Ala Cys Cys Ala Cys Cys Thr Ala Ala Gly Cys Ala Thr	20345	20350	20355
Gly Ala Gly Cys Gly Gly Cys Thr Cys Cys Ala Gly Cys Gly Ala	20360	20365	20370
Ala Cys Gly Ala Gly Ala Gly Cys Thr Cys Gly Cys Gly Gly Cys	20375	20380	20385
Cys Ala Thr Cys Gly Thr Gly Cys Gly Cys Gly Ala Cys Cys Thr	20390	20395	20400
Gly Gly Gly Cys Thr Gly Cys Gly Gly Gly Cys Cys Cys Thr Ala	20405	20410	20415
Cys Thr Thr Thr Thr Thr Gly Gly Gly Cys Ala Cys Cys Cys Ala	20420	20425	20430
Cys Gly Ala Cys Ala Ala Gly Cys Gly Cys Thr Thr Cys Cys Cys	20435	20440	20445
Gly Gly Gly Cys Thr Thr Thr Cys Thr Cys Gly Cys Cys Gly Gly	20450	20455	20460
Cys Gly Ala Cys Ala Ala Gly Cys Thr Gly Gly Cys Cys Thr Gly	20465	20470	20475
Cys Gly Cys Cys Ala Thr Cys Gly Thr Cys Ala Ala Cys Ala Cys	20480	20485	20490
Gly Gly Cys Cys Gly Gly Cys Cys Gly Cys Gly Ala Gly Ala Cys	20495	20500	20505
Cys Gly Gly Ala Gly Gly Cys Gly Thr Gly Cys Ala Cys Thr Gly			

20510	20515	20520
Gly Cys Thr Cys Gly Cys Cys Thr Thr Cys Gly Gly Cys Thr Gly		
20525	20530	20535
Gly Ala Ala Cys Cys Cys Gly Cys Gly Cys Thr Cys Gly Cys Gly		
20540	20545	20550
Cys Ala Cys Cys Thr Gly Cys Thr Ala Cys Ala Thr Gly Thr Thr		
20555	20560	20565
Cys Gly Ala Cys Cys Cys Cys Thr Thr Thr Gly Gly Gly Thr Thr		
20570	20575	20580
Cys Thr Cys Gly Gly Ala Cys Cys Gly Cys Cys Gly Gly Cys Thr		
20585	20590	20595
Cys Ala Ala Gly Cys Ala Gly Ala Thr Thr Thr Ala Cys Ala Gly		
20600	20605	20610
Cys Thr Thr Cys Gly Ala Gly Thr Ala Cys Gly Ala Gly Gly Cys		
20615	20620	20625
Cys Ala Thr Gly Cys Thr Gly Cys Gly Cys Cys Gly Cys Ala Gly		
20630	20635	20640
Cys Gly Cys Cys Cys Thr Gly Gly Cys Cys Thr Cys Cys Thr Cys		
20645	20650	20655
Gly Cys Cys Cys Gly Ala Cys Cys Gly Cys Thr Gly Thr Cys Thr		
20660	20665	20670
Cys Ala Gly Cys Cys Thr Cys Gly Ala Gly Cys Ala Gly Thr Cys		
20675	20680	20685
Cys Ala Cys Thr Cys Ala Gly Ala Cys Cys Gly Thr Gly Cys Ala		
20690	20695	20700
Gly Gly Gly Gly Cys Cys Cys Gly Ala Cys Thr Cys Cys Gly Cys		
20705	20710	20715
Cys Gly Cys Cys Thr Gly Cys Gly Gly Ala Cys Thr Cys Thr Thr		
20720	20725	20730
Cys Thr Gly Thr Thr Gly Cys Ala Thr Gly Thr Thr Cys Thr Thr		
20735	20740	20745
Gly Cys Ala Thr Gly Cys Cys Thr Thr Cys Gly Thr Gly Cys Ala		
20750	20755	20760
Cys Thr Gly Gly Cys Cys Cys Gly Ala Cys Cys Gly Ala Cys Cys		
20765	20770	20775
Cys Ala Thr Gly Gly Ala Cys Gly Gly Ala Ala Ala Cys Cys Cys		
20780	20785	20790
Cys Ala Cys Cys Ala Thr Gly Ala Ala Cys Thr Thr Gly Cys Thr		
20795	20800	20805

Gly Ala Cys Gly Gly Gly Gly Gly Thr Gly Cys Cys Cys Ala Ala	20810	20815	20820
Cys Gly Gly Cys Ala Thr Gly Cys Thr Ala Cys Ala Ala Thr Cys	20825	20830	20835
Gly Cys Cys Ala Cys Ala Gly Gly Thr Gly Cys Thr Gly Cys Cys	20840	20845	20850
Cys Ala Cys Cys Cys Thr Cys Ala Gly Gly Cys Gly Cys Ala Ala	20855	20860	20865
Cys Cys Ala Gly Gly Ala Gly Gly Ala Ala Cys Thr Cys Thr Ala	20870	20875	20880
Cys Cys Gly Cys Thr Thr Cys Cys Thr Cys Gly Cys Gly Cys Gly	20885	20890	20895
Cys Cys Ala Cys Thr Cys Cys Cys Cys Thr Thr Ala Cys Thr Thr	20900	20905	20910
Thr Cys Gly Cys Thr Cys Cys Cys Ala Cys Cys Gly Cys Gly Cys	20915	20920	20925
Cys Gly Cys Cys Ala Thr Cys Gly Ala Ala Cys Ala Cys Gly Cys	20930	20935	20940
Cys Ala Cys Cys Gly Cys Thr Thr Thr Thr Gly Ala Cys Ala Ala	20945	20950	20955
Ala Ala Thr Gly Ala Ala Ala Cys Ala Ala Cys Thr Gly Cys Gly	20960	20965	20970
Thr Gly Thr Ala Thr Cys Thr Cys Ala Ala Thr Ala Ala Ala Cys	20975	20980	20985
Ala Gly Cys Ala Cys Thr Thr Thr Thr Ala Thr Thr Thr Thr Ala	20990	20995	21000
Cys Ala Thr Gly Cys Ala Cys Thr Gly Gly Ala Gly Thr Ala Thr	21005	21010	21015
Ala Thr Gly Cys Ala Ala Gly Thr Thr Ala Thr Thr Thr Ala Ala	21020	21025	21030
Ala Ala Gly Thr Cys Gly Ala Ala Gly Gly Gly Gly Thr Thr Cys	21035	21040	21045
Thr Cys Gly Cys Gly Cys Thr Cys Gly Thr Cys Gly Thr Thr Gly	21050	21055	21060
Thr Gly Cys Gly Cys Cys Gly Cys Gly Cys Thr Gly Gly Gly Gly	21065	21070	21075
Ala Gly Gly Gly Cys Cys Ala Cys Gly Thr Thr Gly Cys Gly Gly	21080	21085	21090
Thr Ala Cys Thr Gly Gly Thr Ala Cys Thr Thr Gly Gly Gly Cys			

21095	21100	21105
Thr Gly Cys Cys Ala Cys	Thr Thr Gly Ala Ala	Cys Thr Cys Gly
21110	21115	21120
Gly Gly Gly Ala Thr Cys	Ala Cys Cys Ala Gly	Thr Thr Thr Gly
21125	21130	21135
Gly Gly Cys Ala Cys Thr	Gly Gly Gly Gly Thr	Cys Thr Cys Gly
21140	21145	21150
Gly Gly Gly Ala Ala Gly	Gly Thr Cys Thr Cys	Gly Cys Thr Cys
21155	21160	21165
Cys Ala Cys Ala Thr Gly	Cys Gly Cys Cys Gly	Gly Cys Thr Cys
21170	21175	21180
Ala Thr Cys Thr Gly Cys	Ala Gly Gly Gly Cys	Gly Cys Cys Cys
21185	21190	21195
Ala Gly Cys Ala Thr Gly	Thr Cys Cys Gly Gly	Gly Gly Cys Gly
21200	21205	21210
Gly Ala Gly Ala Thr Cys	Thr Thr Gly Ala Ala	Ala Thr Cys Gly
21215	21220	21225
Cys Ala Gly Thr Thr Gly	Gly Gly Gly Cys Cys	Gly Gly Thr Gly
21230	21235	21240
Cys Thr Cys Thr Gly Cys	Gly Cys Gly Cys Gly	Cys Gly Ala Gly
21245	21250	21255
Thr Thr Gly Cys Gly Gly	Thr Ala Cys Ala Cys	Gly Gly Gly Gly
21260	21265	21270
Thr Thr Gly Cys Ala Gly	Cys Ala Cys Thr Gly	Gly Ala Ala Cys
21275	21280	21285
Ala Cys Cys Ala Thr Cys	Ala Gly Ala Cys Thr	Gly Gly Gly Gly
21290	21295	21300
Thr Ala Cys Thr Thr Cys	Ala Cys Ala Cys Thr	Ala Gly Cys Cys
21305	21310	21315
Ala Gly Cys Ala Cys Gly	Cys Thr Cys Thr Thr	Gly Thr Cys Gly
21320	21325	21330
Cys Thr Gly Ala Thr Cys	Thr Gly Ala Thr Cys	Cys Thr Thr Gly
21335	21340	21345
Thr Cys Cys Ala Gly Ala	Thr Cys Cys Thr Cys	Gly Gly Cys Gly
21350	21355	21360
Thr Thr Gly Cys Thr Cys	Ala Gly Gly Cys Cys	Gly Ala Ala Cys
21365	21370	21375
Gly Gly Gly Gly Thr Cys	Ala Thr Cys Thr Thr	Gly Cys Ala Cys
21380	21385	21390

Ala Gly Cys Thr Gly Gly Cys Gly Thr Cys Cys Cys Ala Gly Gly	21395	21400	21405
Ala Ala Gly Gly Gly Cys Ala Cys Gly Cys Thr Cys Thr Gly Ala	21410	21415	21420
Gly Gly Cys Thr Thr Gly Thr Gly Gly Thr Thr Ala Cys Ala Cys	21425	21430	21435
Thr Cys Gly Cys Ala Gly Thr Gly Cys Ala Cys Gly Gly Gly Cys	21440	21445	21450
Ala Thr Cys Ala Gly Cys Ala Thr Cys Ala Thr Cys Cys Cys Cys	21455	21460	21465
Gly Cys Gly Cys Cys Gly Cys Gly Cys Thr Gly Cys Ala Thr Ala	21470	21475	21480
Thr Thr Cys Gly Gly Gly Thr Ala Gly Ala Gly Gly Gly Cys Cys	21485	21490	21495
Thr Thr Gly Ala Cys Ala Ala Ala Gly Gly Cys Cys Gly Cys Gly	21500	21505	21510
Ala Thr Cys Thr Gly Cys Thr Thr Gly Ala Ala Ala Gly Cys Thr	21515	21520	21525
Thr Gly Cys Thr Gly Gly Gly Cys Cys Thr Thr Gly Gly Cys Cys	21530	21535	21540
Cys Cys Cys Thr Cys Gly Cys Thr Gly Ala Ala Ala Ala Ala Cys	21545	21550	21555
Ala Gly Gly Cys Cys Gly Cys Ala Gly Cys Thr Cys Thr Thr Cys	21560	21565	21570
Cys Cys Gly Cys Thr Gly Ala Ala Cys Thr Gly Gly Thr Thr Ala	21575	21580	21585
Thr Thr Cys Cys Cys Ala Cys Ala Cys Cys Cys Gly Gly Cys Ala	21590	21595	21600
Thr Cys Cys Thr Gly Cys Ala Cys Gly Cys Ala Gly Cys Ala Gly	21605	21610	21615
Cys Gly Cys Gly Cys Gly Thr Cys Ala Thr Gly Gly Cys Thr Gly	21620	21625	21630
Gly Thr Cys Ala Gly Thr Thr Gly Cys Ala Cys Cys Ala Cys Gly	21635	21640	21645
Cys Thr Cys Cys Gly Thr Cys Cys Cys Cys Ala Gly Cys Gly Gly	21650	21655	21660
Thr Thr Cys Thr Gly Gly Gly Thr Cys Ala Cys Cys Thr Thr Ala	21665	21670	21675
Gly Cys Cys Thr Thr Gly Cys Thr Gly Gly Gly Cys Thr Gly Cys			

21680	21685	21690
Thr Cys Cys Thr Thr Cys	Ala Ala Cys Gly Cys	Gly Cys Gly Cys
21695	21700	21705
Thr Gly Cys Cys Cys Gly	Thr Thr Cys Thr Cys	Gly Cys Thr Gly
21710	21715	21720
Gly Thr Cys Ala Cys Ala	Thr Cys Cys Ala Thr	Cys Thr Cys Cys
21725	21730	21735
Ala Cys Cys Ala Cys Gly	Thr Gly Gly Thr Cys	Cys Thr Thr Gly
21740	21745	21750
Thr Gly Gly Ala Thr Cys	Ala Thr Cys Ala Thr	Cys Gly Thr Cys
21755	21760	21765
Cys Cys Gly Thr Gly Cys	Ala Gly Ala Cys Ala	Cys Thr Thr Gly
21770	21775	21780
Ala Gly Cys Thr Gly Gly	Cys Cys Thr Thr Cys	Cys Ala Cys Cys
21785	21790	21795
Thr Cys Gly Gly Thr Gly	Cys Ala Gly Cys Cys	Gly Thr Gly Ala
21800	21805	21810
Thr Cys Cys Cys Ala Cys	Ala Gly Gly Gly Cys	Gly Cys Ala Ala
21815	21820	21825
Cys Cys Gly Gly Thr Gly	Cys Ala Cys Thr Cys	Cys Cys Ala Gly
21830	21835	21840
Thr Thr Cys Thr Thr Gly	Thr Gly Cys Gly Cys	Ala Ala Thr Cys
21845	21850	21855
Cys Cys Gly Cys Thr Gly	Thr Gly Gly Cys Thr	Gly Ala Ala Gly
21860	21865	21870
Ala Thr Gly Thr Ala Ala	Cys Cys Thr Thr Gly	Cys Ala Ala Cys
21875	21880	21885
Ala Thr Gly Cys Gly Gly	Cys Cys Cys Ala Thr	Gly Ala Thr Gly
21890	21895	21900
Gly Thr Gly Cys Thr Ala	Ala Ala Thr Gly Cys	Thr Thr Thr Cys
21905	21910	21915
Thr Gly Gly Gly Thr Gly	Gly Thr Gly Ala Ala	Gly Gly Thr Cys
21920	21925	21930
Ala Gly Thr Thr Gly Cys	Ala Thr Cys Cys Cys	Gly Cys Gly Gly
21935	21940	21945
Gly Cys Cys Thr Cys Cys	Thr Cys Gly Thr Thr	Cys Ala Thr Cys
21950	21955	21960
Cys Ala Gly Gly Thr Cys	Thr Gly Gly Cys Ala	Cys Ala Thr Cys
21965	21970	21975

Thr Thr Cys Thr Gly Gly Ala Ala Gly Ala Thr Cys Thr Cys Gly 21980	21985	21990
Gly Thr Cys Thr Gly Cys Thr Cys Gly Gly Gly Cys Ala Thr Gly 21995	22000	22005
Ala Gly Cys Thr Thr Gly Thr Ala Ala Gly Cys Ala Thr Cys Gly 22010	22015	22020
Cys Gly Cys Ala Gly Gly Cys Cys Gly Cys Thr Gly Thr Cys Gly 22025	22030	22035
Ala Cys Gly Cys Gly Gly Thr Ala Gly Cys Gly Thr Thr Cys Cys 22040	22045	22050
Ala Thr Cys Ala Gly Cys Ala Cys Gly Thr Thr Cys Ala Thr Gly 22055	22060	22065
Gly Thr Ala Thr Cys Cys Ala Thr Gly Cys Cys Cys Thr Thr Cys 22070	22075	22080
Thr Cys Cys Cys Ala Gly Gly Ala Cys Gly Ala Gly Ala Cys Cys 22085	22090	22095
Ala Gly Ala Gly Gly Cys Ala Gly Ala Cys Thr Cys Ala Gly Ala 22100	22105	22110
Gly Gly Gly Thr Thr Gly Cys Gly Thr Ala Cys Gly Thr Thr Cys 22115	22120	22125
Ala Gly Gly Ala Cys Ala Cys Cys Gly Gly Gly Gly Gly Thr Cys 22130	22135	22140
Gly Cys Gly Gly Gly Cys Thr Cys Gly Ala Cys Gly Ala Thr Gly 22145	22150	22155
Cys Gly Thr Thr Thr Thr Cys Cys Gly Thr Cys Cys Thr Thr Gly 22160	22165	22170
Cys Cys Thr Thr Cys Cys Thr Thr Cys Ala Ala Thr Ala Gly Ala 22175	22180	22185
Ala Cys Cys Gly Gly Cys Gly Gly Cys Thr Gly Gly Cys Thr Gly 22190	22195	22200
Ala Ala Thr Cys Cys Cys Ala Cys Thr Cys Cys Cys Ala Cys Gly 22205	22210	22215
Ala Thr Cys Ala Cys Gly Gly Cys Ala Thr Cys Thr Thr Cys Cys 22220	22225	22230
Thr Gly Gly Gly Gly Cys Ala Thr Cys Thr Cys Thr Thr Cys Gly 22235	22240	22245
Thr Cys Gly Gly Gly Gly Thr Cys Thr Ala Cys Cys Thr Thr Gly 22250	22255	22260
Gly Thr Cys Ala Cys Ala Thr Gly Cys Thr Thr Gly Gly Thr Cys		

22265	22270	22275
Thr Thr Thr Cys Thr Gly	Gly Cys Thr Thr Gly	Cys Thr Thr Cys
22280	22285	22290
Thr Thr Thr Thr Thr Thr	Gly Gly Ala Gly Gly	Gly Cys Thr Gly
22295	22300	22305
Thr Cys Cys Ala Cys Gly	Gly Gly Gly Ala Gly	Cys Ala Cys Gly
22310	22315	22320
Thr Cys Cys Thr Cys Cys	Thr Cys Gly Gly Ala	Ala Gly Ala Cys
22325	22330	22335
Cys Cys Gly Gly Ala Gly	Cys Cys Cys Ala Cys	Cys Cys Gly Cys
22340	22345	22350
Thr Gly Ala Thr Ala Cys	Thr Thr Thr Cys Gly	Gly Cys Gly Cys
22355	22360	22365
Thr Thr Gly Gly Thr Gly	Gly Gly Cys Ala Gly	Ala Gly Gly Ala
22370	22375	22380
Gly Gly Thr Gly Gly Cys	Gly Gly Cys Gly Ala	Gly Gly Gly Gly
22385	22390	22395
Cys Thr Cys Cys Thr Cys	Thr Cys Cys Thr Gly	Cys Thr Cys Cys
22400	22405	22410
Gly Gly Cys Gly Gly Ala	Thr Ala Gly Cys Gly	Cys Gly Cys Cys
22415	22420	22425
Gly Ala Cys Cys Cys Gly	Thr Gly Gly Cys Cys	Cys Cys Gly Gly
22430	22435	22440
Gly Gly Cys Gly Gly Ala	Gly Thr Gly Gly Cys	Cys Thr Cys Thr
22445	22450	22455
Cys Gly Gly Cys Cys Cys	Ala Thr Gly Ala Ala	Cys Cys Gly Gly
22460	22465	22470
Cys Gly Cys Ala Cys Gly	Thr Cys Cys Thr Gly	Ala Cys Thr Gly
22475	22480	22485
Cys Cys Gly Cys Cys Gly	Gly Cys Cys Ala Thr	Thr Gly Thr Thr
22490	22495	22500
Thr Cys Cys Thr Ala Gly	Gly Gly Gly Ala Ala	Gly Ala Thr Gly
22505	22510	22515
Gly Ala Gly Gly Ala Gly	Cys Ala Gly Cys Cys	Gly Cys Gly Thr
22520	22525	22530
Ala Ala Gly Cys Ala Gly	Gly Ala Gly Cys Ala	Gly Gly Ala Gly
22535	22540	22545
Gly Ala Gly Gly Ala Cys	Thr Thr Ala Ala Cys	Cys Ala Cys Cys
22550	22555	22560

Cys Ala Cys Gly Ala Gly Cys Ala Ala Cys Cys Cys Ala Ala Ala	22565	22570	22575
Ala Thr Cys Gly Ala Gly Cys Ala Gly Gly Ala Cys Cys Thr Gly	22580	22585	22590
Gly Gly Cys Thr Thr Cys Gly Ala Ala Gly Ala Gly Cys Cys Gly	22595	22600	22605
Gly Cys Thr Cys Gly Thr Cys Thr Ala Gly Ala Ala Cys Cys Cys	22610	22615	22620
Cys Cys Ala Cys Ala Gly Gly Ala Thr Gly Ala Ala Cys Ala Gly	22625	22630	22635
Gly Ala Gly Cys Ala Cys Gly Ala Gly Cys Ala Ala Gly Ala Cys	22640	22645	22650
Gly Cys Ala Gly Gly Cys Cys Ala Gly Gly Ala Gly Gly Ala Gly	22655	22660	22665
Ala Cys Cys Gly Ala Cys Gly Cys Thr Gly Gly Gly Cys Thr Cys	22670	22675	22680
Gly Ala Gly Cys Ala Thr Gly Gly Cys Thr Ala Cys Cys Thr Gly	22685	22690	22695
Gly Gly Ala Gly Gly Ala Gly Ala Gly Gly Ala Gly Gly Ala Thr	22700	22705	22710
Gly Thr Gly Cys Thr Gly Cys Thr Gly Ala Ala Ala Cys Ala Cys	22715	22720	22725
Cys Thr Gly Cys Ala Gly Cys Gly Cys Cys Ala Gly Thr Cys Cys	22730	22735	22740
Cys Thr Cys Ala Thr Cys Cys Thr Cys Cys Gly Gly Gly Ala Cys	22745	22750	22755
Gly Cys Cys Cys Thr Gly Gly Cys Cys Gly Ala Cys Cys Gly Gly	22760	22765	22770
Ala Gly Cys Gly Ala Ala Ala Cys Cys Cys Cys Cys Cys Thr Cys	22775	22780	22785
Ala Gly Cys Gly Thr Cys Gly Ala Gly Gly Ala Gly Cys Thr Gly	22790	22795	22800
Thr Gly Thr Cys Gly Gly Gly Cys Cys Thr Ala Cys Gly Ala Gly	22805	22810	22815
Cys Thr Cys Ala Ala Cys Cys Thr Cys Thr Thr Cys Thr Cys Gly	22820	22825	22830
Cys Cys Gly Cys Gly Cys Gly Thr Ala Cys Cys Cys Cys Cys Cys	22835	22840	22845
Ala Ala Ala Cys Gly Cys Cys Ala Gly Cys Cys Cys Ala Ala Cys			

22850	22855	22860
Gly Gly Cys Ala Cys Cys Thr Gly Cys Gly Ala Gly Cys Cys Cys		
22865	22870	22875
Ala Ala Cys Cys Cys Gly Cys Gly Thr Cys Thr Cys Ala Ala Cys		
22880	22885	22890
Thr Thr Cys Thr Ala Thr Cys Cys Cys Gly Thr Cys Thr Thr Thr		
22895	22900	22905
Gly Cys Gly Gly Thr Cys Cys Cys Cys Gly Ala Ala Gly Cys Cys		
22910	22915	22920
Cys Thr Cys Gly Cys Cys Ala Cys Cys Thr Ala Thr Cys Ala Cys		
22925	22930	22935
Ala Thr Cys Thr Thr Thr Thr Thr Thr Cys Ala Ala Gly Ala Ala Cys		
22940	22945	22950
Cys Ala Ala Ala Ala Gly Ala Thr Cys Cys Cys Cys Gly Thr Cys		
22955	22960	22965
Thr Cys Cys Thr Gly Cys Cys Gly Cys Gly Cys Cys Ala Ala Cys		
22970	22975	22980
Cys Gly Cys Ala Cys Cys Ala Gly Cys Gly Cys Cys Gly Ala Cys		
22985	22990	22995
Gly Cys Gly Cys Thr Cys Cys Thr Cys Gly Cys Thr Thr Thr Gly		
23000	23005	23010
Gly Gly Gly Cys Cys Cys Gly Gly Cys Gly Cys Gly Cys Gly Cys		
23015	23020	23025
Ala Thr Ala Cys Cys Thr Gly Ala Thr Ala Thr Cys Gly Cys Thr		
23030	23035	23040
Thr Cys Cys Cys Thr Gly Gly Ala Ala Gly Ala Gly Gly Thr Gly		
23045	23050	23055
Cys Cys Cys Ala Ala Gly Ala Thr Cys Thr Thr Cys Gly Ala Ala		
23060	23065	23070
Gly Gly Gly Cys Thr Cys Gly Gly Thr Cys Gly Gly Gly Ala Cys		
23075	23080	23085
Gly Ala Gly Ala Cys Gly Cys Gly Cys Gly Cys Gly Gly Cys Gly		
23090	23095	23100
Ala Ala Cys Gly Cys Thr Cys Thr Gly Ala Ala Ala Gly Ala Ala		
23105	23110	23115
Ala Cys Ala Gly Cys Ala Gly Ala Gly Gly Ala Ala Gly Ala Gly		
23120	23125	23130
Gly Gly Thr Cys Ala Cys Ala Cys Thr Ala Gly Cys Gly Cys Cys		
23135	23140	23145

Cys Thr Gly Gly Thr Ala Gly Ala Gly Thr Thr Gly Gly Ala Ala 23150	23155	23160
Gly Gly Cys Gly Ala Cys Ala Ala Cys Gly Cys Cys Ala Gly Gly 23165	23170	23175
Cys Thr Gly Gly Cys Cys Gly Thr Gly Cys Thr Cys Ala Ala Gly 23180	23185	23190
Cys Gly Cys Ala Gly Cys Gly Thr Cys Gly Ala Gly Cys Thr Thr 23195	23200	23205
Ala Cys Cys Cys Ala Cys Thr Thr Cys Gly Cys Cys Thr Ala Cys 23210	23215	23220
Cys Cys Cys Gly Cys Cys Gly Thr Cys Ala Ala Cys Cys Thr Cys 23225	23230	23235
Cys Cys Gly Cys Cys Cys Ala Ala Gly Gly Thr Cys Ala Thr Gly 23240	23245	23250
Cys Gly Thr Cys Gly Cys Ala Thr Cys Ala Thr Gly Gly Ala Thr 23255	23260	23265
Cys Ala Gly Cys Thr Cys Ala Thr Cys Ala Thr Gly Cys Cys Cys 23270	23275	23280
Cys Ala Cys Ala Thr Cys Gly Ala Gly Gly Cys Cys Cys Thr Cys 23285	23290	23295
Gly Ala Thr Gly Ala Ala Ala Gly Thr Cys Ala Gly Gly Ala Gly 23300	23305	23310
Cys Ala Gly Cys Gly Cys Cys Cys Cys Gly Ala Gly Gly Ala Cys 23315	23320	23325
Gly Cys Cys Cys Gly Gly Cys Cys Cys Gly Thr Gly Gly Thr Cys 23330	23335	23340
Ala Gly Cys Gly Ala Cys Gly Ala Gly Ala Thr Gly Cys Thr Cys 23345	23350	23355
Gly Cys Gly Cys Gly Cys Thr Gly Gly Cys Thr Cys Gly Gly Gly 23360	23365	23370
Ala Cys Cys Cys Gly Cys Gly Ala Cys Cys Cys Cys Cys Ala Gly 23375	23380	23385
Gly Cys Thr Thr Thr Gly Gly Ala Ala Cys Ala Gly Cys Gly Gly 23390	23395	23400
Cys Gly Cys Ala Ala Ala Cys Thr Cys Ala Thr Gly Cys Thr Gly 23405	23410	23415
Gly Cys Cys Gly Thr Gly Gly Thr Cys Cys Thr Gly Gly Thr Cys 23420	23425	23430
Ala Cys Cys Cys Thr Thr Gly Ala Gly Cys Thr Cys Gly Ala Ala		

23435	23440	23445
Thr Gly Cys Ala Thr Gly Cys Gly Cys Cys Gly Cys Thr Thr Thr		
23450	23455	23460
Thr Thr Cys Ala Gly Cys Gly Ala Cys Cys Cys Cys Gly Ala Gly		
23465	23470	23475
Ala Cys Cys Cys Thr Gly Cys Gly Cys Ala Ala Gly Gly Thr Cys		
23480	23485	23490
Gly Ala Gly Gly Ala Gly Ala Cys Cys Cys Thr Gly Cys Ala Cys		
23495	23500	23505
Thr Ala Cys Ala Cys Thr Thr Thr Cys Ala Gly Gly Cys Ala Cys		
23510	23515	23520
Gly Gly Thr Thr Thr Cys Gly Thr Cys Ala Gly Gly Cys Ala Gly		
23525	23530	23535
Gly Cys Cys Thr Gly Cys Ala Ala Gly Ala Thr Cys Thr Cys Cys		
23540	23545	23550
Ala Ala Cys Gly Thr Gly Gly Ala Gly Cys Thr Gly Ala Cys Cys		
23555	23560	23565
Ala Ala Cys Cys Thr Gly Gly Thr Cys Thr Cys Cys Thr Gly Cys		
23570	23575	23580
Cys Thr Gly Gly Gly Gly Ala Thr Cys Cys Thr Gly Cys Ala Cys		
23585	23590	23595
Gly Ala Gly Ala Ala Cys Cys Gly Cys Cys Thr Gly Gly Gly Cys		
23600	23605	23610
Cys Ala Gly Ala Cys Cys Gly Thr Gly Cys Thr Cys Cys Ala Cys		
23615	23620	23625
Thr Cys Thr Ala Cys Cys Cys Thr Gly Ala Ala Gly Gly Gly Cys		
23630	23635	23640
Gly Ala Gly Gly Cys Gly Cys Gly Gly Cys Gly Gly Gly Ala Cys		
23645	23650	23655
Thr Ala Thr Gly Thr Cys Cys Gly Cys Gly Ala Cys Thr Gly Cys		
23660	23665	23670
Gly Thr Cys Thr Thr Thr Cys Thr Cys Thr Thr Thr Cys Thr Cys		
23675	23680	23685
Thr Gly Cys Cys Ala Cys Ala Cys Ala Thr Gly Gly Cys Ala Ala		
23690	23695	23700
Gly Cys Gly Gly Cys Cys Ala Thr Gly Gly Gly Cys Gly Thr Gly		
23705	23710	23715
Thr Gly Gly Cys Ala Gly Cys Ala Gly Thr Gly Thr Cys Thr Cys		
23720	23725	23730

Gly Ala Gly Gly Ala Cys Gly Ala Gly Ala Ala Cys Cys Thr Ala 23735	23740	23745
Ala Ala Gly Gly Ala Gly Cys Thr Gly Gly Ala Cys Ala Ala Gly 23750	23755	23760
Cys Thr Thr Cys Thr Thr Gly Cys Thr Ala Gly Ala Ala Ala Cys 23765	23770	23775
Cys Thr Thr Ala Ala Ala Ala Ala Gly Cys Thr Gly Thr Gly Gly 23780	23785	23790
Ala Cys Gly Gly Gly Cys Thr Thr Cys Gly Ala Cys Gly Ala Gly 23795	23800	23805
Cys Gly Cys Ala Cys Cys Gly Thr Cys Gly Cys Cys Thr Cys Gly 23810	23815	23820
Gly Ala Cys Cys Thr Gly Gly Cys Cys Gly Ala Gly Ala Thr Cys 23825	23830	23835
Gly Thr Cys Thr Thr Cys Cys Cys Cys Gly Ala Gly Cys Gly Cys 23840	23845	23850
Cys Thr Gly Ala Gly Ala Cys Ala Gly Ala Cys Gly Cys Thr Gly 23855	23860	23865
Ala Ala Ala Gly Gly Cys Gly Gly Gly Cys Thr Gly Cys Cys Cys 23870	23875	23880
Gly Ala Cys Thr Thr Cys Ala Thr Gly Ala Gly Cys Cys Ala Gly 23885	23890	23895
Ala Gly Cys Ala Thr Gly Thr Thr Gly Cys Ala Ala Ala Ala Cys 23900	23905	23910
Thr Ala Cys Cys Gly Cys Ala Cys Thr Thr Thr Cys Ala Thr Thr 23915	23920	23925
Cys Thr Thr Gly Ala Gly Cys Gly Ala Thr Cys Ala Gly Gly Cys 23930	23935	23940
Ala Thr Cys Cys Thr Gly Cys Cys Cys Gly Cys Cys Ala Cys Cys 23945	23950	23955
Thr Gly Cys Ala Ala Cys Gly Cys Cys Thr Thr Cys Cys Cys Cys 23960	23965	23970
Thr Cys Cys Gly Ala Cys Thr Thr Thr Gly Thr Ala Cys Cys Gly 23975	23980	23985
Cys Thr Gly Ala Gly Cys Thr Ala Cys Cys Gly Cys Gly Ala Gly 23990	23995	24000
Thr Gly Thr Cys Cys Cys Cys Cys Gly Cys Cys Gly Cys Thr Gly 24005	24010	24015
Thr Gly Gly Ala Gly Cys Cys Ala Cys Thr Gly Cys Thr Ala Cys		

24020	24025	24030
Cys Thr Cys Thr Thr Gly Cys Ala Gly Cys Thr Gly Gly Cys Cys		
24035	24040	24045
Ala Ala Cys Thr Ala Cys Ala Thr Cys Gly Cys Cys Thr Ala Cys		
24050	24055	24060
Cys Ala Cys Thr Cys Gly Gly Ala Cys Gly Thr Gly Ala Thr Cys		
24065	24070	24075
Gly Ala Gly Gly Ala Cys Gly Thr Gly Ala Gly Cys Gly Gly Cys		
24080	24085	24090
Gly Ala Gly Gly Gly Gly Cys Thr Gly Cys Thr Cys Gly Ala Gly		
24095	24100	24105
Thr Gly Cys Cys Ala Cys Thr Gly Thr Cys Gly Cys Thr Gly Cys		
24110	24115	24120
Ala Ala Cys Cys Thr Gly Thr Gly Cys Thr Cys Cys Cys Cys Gly		
24125	24130	24135
Cys Ala Thr Cys Gly Cys Thr Cys Cys Cys Thr Gly Gly Thr Cys		
24140	24145	24150
Thr Gly Cys Ala Ala Cys Cys Cys Cys Cys Ala Gly Cys Thr Cys		
24155	24160	24165
Cys Thr Gly Ala Gly Cys Gly Ala Gly Ala Cys Cys Cys Ala Gly		
24170	24175	24180
Gly Thr Cys Ala Thr Cys Gly Gly Thr Ala Cys Cys Thr Thr Cys		
24185	24190	24195
Gly Ala Gly Cys Thr Gly Cys Ala Ala Gly Gly Thr Cys Cys Gly		
24200	24205	24210
Cys Ala Gly Gly Ala Gly Thr Cys Cys Ala Cys Cys Gly Cys Thr		
24215	24220	24225
Cys Cys Gly Cys Thr Gly Ala Ala Ala Cys Thr Cys Ala Cys Gly		
24230	24235	24240
Cys Cys Gly Gly Gly Gly Thr Thr Gly Thr Gly Gly Ala Cys Thr		
24245	24250	24255
Thr Cys Cys Gly Cys Gly Thr Ala Cys Cys Thr Gly Cys Gly Cys		
24260	24265	24270
Ala Ala Ala Thr Thr Thr Gly Thr Ala Cys Cys Cys Gly Ala Ala		
24275	24280	24285
Gly Ala Cys Thr Ala Cys Cys Ala Cys Gly Cys Cys Cys Ala Thr		
24290	24295	24300
Gly Ala Gly Ala Thr Ala Ala Ala Gly Thr Thr Cys Thr Thr Thr		
24305	24310	24315

Gly Ala Gly Gly Ala Cys Cys Ala Ala Thr Cys Gly Cys Gly Thr 24320	24325	24330
Cys Cys Gly Cys Ala Gly Cys Ala Cys Gly Cys Gly Gly Ala Thr 24335	24340	24345
Cys Thr Cys Ala Cys Gly Gly Cys Cys Thr Gly Cys Gly Thr Cys 24350	24355	24360
Ala Thr Cys Ala Cys Cys Cys Ala Gly Gly Gly Cys Gly Cys Gly 24365	24370	24375
Ala Thr Cys Cys Thr Cys Gly Cys Cys Cys Ala Ala Thr Thr Gly 24380	24385	24390
Cys Ala Cys Gly Cys Cys Ala Thr Cys Cys Ala Ala Ala Ala Ala 24395	24400	24405
Thr Cys Cys Cys Gly Cys Cys Ala Ala Gly Ala Gly Thr Thr Thr 24410	24415	24420
Cys Thr Thr Cys Thr Gly Ala Ala Ala Ala Ala Gly Gly Gly Thr 24425	24430	24435
Ala Gly Ala Gly Gly Gly Gly Thr Cys Thr Ala Cys Cys Thr Gly 24440	24445	24450
Gly Ala Cys Cys Cys Cys Cys Ala Gly Ala Cys Gly Gly Gly Cys 24455	24460	24465
Gly Ala Gly Gly Thr Gly Cys Thr Cys Ala Ala Cys Cys Cys Gly 24470	24475	24480
Gly Gly Thr Cys Thr Cys Cys Cys Cys Cys Ala Gly Cys Ala Thr 24485	24490	24495
Gly Cys Cys Gly Ala Gly Gly Ala Ala Gly Ala Ala Gly Cys Ala 24500	24505	24510
Gly Gly Ala Gly Cys Cys Gly Cys Thr Ala Gly Thr Gly Gly Ala 24515	24520	24525
Gly Gly Ala Gly Ala Thr Gly Gly Ala Ala Gly Ala Ala Gly Ala 24530	24535	24540
Ala Thr Gly Gly Gly Ala Cys Ala Gly Cys Cys Ala Gly Gly Cys 24545	24550	24555
Ala Gly Ala Gly Gly Ala Gly Gly Ala Cys Gly Ala Ala Thr Gly 24560	24565	24570
Gly Gly Ala Gly Gly Ala Gly Gly Ala Gly Ala Cys Ala Gly Ala 24575	24580	24585
Gly Gly Ala Gly Gly Ala Ala Gly Ala Ala Thr Thr Gly Gly Ala 24590	24595	24600
Ala Gly Ala Gly Gly Thr Gly Gly Ala Ala Gly Ala Gly Gly Ala		

24605	24610	24615
Gly Cys Ala Gly Gly Cys	Ala Ala Cys Ala Gly	Ala Gly Cys Ala
24620	24625	24630
Gly Cys Cys Cys Gly Thr	Cys Gly Cys Cys Gly	Cys Ala Cys Cys
24635	24640	24645
Ala Thr Cys Cys Gly Cys	Gly Cys Cys Gly Gly	Cys Ala Gly Cys
24650	24655	24660
Cys Cys Cys Gly Cys Cys	Gly Gly Thr Cys Ala	Cys Gly Gly Ala
24665	24670	24675
Thr Ala Cys Ala Ala Cys	Cys Thr Cys Cys Gly	Cys Thr Cys Cys
24680	24685	24690
Gly Gly Thr Cys Ala Ala	Gly Cys Cys Thr Cys	Cys Thr Cys Gly
24695	24700	24705
Thr Ala Gly Ala Thr Gly	Gly Gly Ala Thr Cys	Ala Ala Gly Thr
24710	24715	24720
Gly Ala Ala Gly Gly Gly	Thr Gly Ala Cys Gly	Gly Thr Ala Ala
24725	24730	24735
Gly Cys Ala Cys Gly Ala	Gly Cys Gly Gly Cys	Ala Gly Gly Gly
24740	24745	24750
Cys Thr Ala Cys Cys Gly	Ala Thr Cys Ala Thr	Gly Gly Ala Gly
24755	24760	24765
Gly Gly Cys Cys Cys Ala	Cys Ala Ala Ala Gly	Cys Cys Gly Cys
24770	24775	24780
Gly Ala Thr Cys Ala Thr	Cys Gly Cys Cys Thr	Gly Cys Thr Thr
24785	24790	24795
Gly Cys Ala Ala Gly Ala	Cys Thr Gly Cys Gly	Gly Gly Gly Gly
24800	24805	24810
Gly Ala Ala Cys Ala Thr	Cys Gly Cys Thr Thr	Thr Cys Gly Cys
24815	24820	24825
Cys Cys Gly Cys Cys Gly	Cys Thr Ala Cys Cys	Thr Gly Cys Thr
24830	24835	24840
Cys Thr Thr Cys Cys Ala	Cys Cys Gly Cys Gly	Gly Gly Gly Thr
24845	24850	24855
Gly Ala Ala Cys Ala Thr	Cys Cys Cys Cys Cys	Gly Cys Ala Ala
24860	24865	24870
Cys Gly Thr Gly Thr Thr	Gly Cys Ala Thr Thr	Ala Cys Thr Ala
24875	24880	24885
Cys Cys Gly Thr Cys Ala	Cys Cys Thr Thr Cys	Ala Cys Ala Gly
24890	24895	24900

Cys Thr Ala Ala Gly Ala Ala Ala Ala Ala Gly Cys Ala Ala Gly	24905	24910	24915
Thr Cys Ala Ala Ala Gly Gly Ala Gly Thr Cys Gly Cys Cys Gly	24920	24925	24930
Gly Ala Gly Gly Ala Gly Gly Ala Gly Gly Ala Gly Gly Ala Gly	24935	24940	24945
Gly Cys Cys Thr Gly Ala Gly Gly Ala Thr Cys Gly Cys Gly Gly	24950	24955	24960
Cys Gly Ala Ala Cys Gly Ala Gly Cys Cys Cys Thr Thr Gly Ala	24965	24970	24975
Cys Cys Ala Cys Cys Ala Gly Gly Gly Ala Gly Cys Thr Gly Ala	24980	24985	24990
Gly Gly Ala Ala Cys Cys Gly Gly Ala Thr Cys Thr Thr Cys Cys	24995	25000	25005
Cys Cys Ala Cys Thr Cys Thr Thr Thr Ala Thr Gly Cys Cys Ala	25010	25015	25020
Thr Thr Thr Thr Thr Cys Ala Gly Cys Ala Gly Ala Gly Thr Cys	25025	25030	25035
Gly Ala Gly Gly Thr Cys Ala Gly Cys Ala Gly Cys Ala Ala Gly	25040	25045	25050
Ala Gly Cys Thr Cys Ala Ala Ala Gly Thr Ala Ala Ala Ala Ala	25055	25060	25065
Ala Cys Cys Gly Gly Thr Cys Thr Cys Thr Gly Cys Gly Cys Thr	25070	25075	25080
Cys Gly Cys Thr Cys Ala Cys Cys Cys Gly Cys Ala Gly Thr Thr	25085	25090	25095
Gly Cys Thr Thr Gly Thr Ala Cys Cys Ala Cys Ala Ala Ala Ala	25100	25105	25110
Ala Cys Gly Ala Ala Gly Ala Thr Cys Ala Gly Cys Thr Gly Cys	25115	25120	25125
Ala Gly Cys Gly Cys Ala Cys Thr Cys Thr Cys Gly Ala Ala Gly	25130	25135	25140
Ala Cys Gly Cys Cys Gly Ala Gly Gly Cys Thr Cys Thr Gly Thr	25145	25150	25155
Thr Cys Cys Ala Cys Ala Ala Gly Thr Ala Cys Thr Gly Cys Gly	25160	25165	25170
Cys Gly Cys Thr Cys Ala Cys Thr Cys Thr Thr Ala Ala Ala Gly	25175	25180	25185
Ala Cys Thr Ala Ala Gly Gly Cys Gly Cys Gly Cys Cys Cys Ala			

25190	25195	25200
Cys Cys Cys Gly Gly Ala Ala Ala Ala Ala Ala Gly Gly Cys Gly		
25205	25210	25215
Gly Gly Ala Ala Thr Thr Ala Cys Cys Thr Cys Ala Thr Cys Gly		
25220	25225	25230
Cys Cys Ala Cys Cys Ala Thr Gly Ala Gly Cys Ala Ala Gly Gly		
25235	25240	25245
Ala Gly Ala Thr Thr Cys Cys Cys Ala Cys Cys Cys Cys Thr Thr		
25250	25255	25260
Ala Cys Ala Thr Gly Thr Gly Gly Ala Gly Cys Thr Ala Thr Cys		
25265	25270	25275
Ala Gly Cys Cys Cys Cys Ala Ala Ala Thr Gly Gly Gly Cys Cys		
25280	25285	25290
Thr Gly Gly Cys Cys Gly Cys Gly Gly Gly Cys Gly Cys Cys Thr		
25295	25300	25305
Cys Cys Cys Ala Gly Gly Ala Cys Thr Ala Cys Thr Cys Cys Ala		
25310	25315	25320
Cys Cys Cys Gly Cys Ala Thr Gly Ala Ala Cys Thr Gly Gly Cys		
25325	25330	25335
Thr Cys Ala Gly Thr Gly Cys Cys Gly Gly Cys Cys Cys Cys Thr		
25340	25345	25350
Cys Gly Ala Thr Gly Ala Thr Cys Thr Cys Ala Cys Gly Gly Gly		
25355	25360	25365
Thr Cys Ala Ala Cys Gly Gly Gly Gly Thr Cys Cys Gly Cys Ala		
25370	25375	25380
Gly Thr Cys Ala Thr Cys Gly Ala Ala Ala Cys Cys Ala Gly Ala		
25385	25390	25395
Thr Ala Thr Thr Gly Thr Thr Gly Gly Ala Gly Cys Ala Gly Gly		
25400	25405	25410
Cys Gly Gly Cys Gly Gly Thr Cys Ala Cys Cys Thr Cys Cys Ala		
25415	25420	25425
Cys Gly Cys Cys Cys Ala Gly Gly Gly Cys Ala Ala Ala Gly Cys		
25430	25435	25440
Thr Cys Ala Ala Cys Cys Cys Gly Cys Gly Thr Ala Ala Thr Thr		
25445	25450	25455
Gly Gly Cys Cys Cys Thr Cys Cys Ala Cys Cys Cys Thr Gly Gly		
25460	25465	25470
Thr Gly Thr Ala Thr Cys Ala Gly Gly Ala Ala Ala Thr Cys Cys		
25475	25480	25485

Cys Cys Gly Gly Gly Cys Cys Gly Ala Cys Thr Ala Cys Cys Gly	25490	25495	25500
Thr Ala Cys Thr Ala Cys Thr Thr Cys Cys Gly Cys Gly Thr Gly	25505	25510	25515
Ala Cys Gly Cys Ala Cys Thr Gly Gly Cys Cys Gly Ala Ala Gly	25520	25525	25530
Thr Cys Cys Gly Cys Ala Thr Gly Ala Cys Thr Ala Ala Cys Thr	25535	25540	25545
Cys Ala Gly Gly Thr Gly Thr Cys Cys Ala Gly Cys Thr Gly Gly	25550	25555	25560
Cys Cys Gly Gly Cys Gly Gly Cys Gly Cys Thr Thr Cys Cys Cys	25565	25570	25575
Gly Gly Thr Gly Cys Cys Cys Gly Cys Thr Cys Cys Gly Cys Cys	25580	25585	25590
Cys Ala Cys Ala Ala Thr Cys Gly Gly Gly Thr Ala Thr Ala Ala	25595	25600	25605
Ala Ala Ala Cys Cys Cys Thr Gly Gly Thr Gly Ala Thr Cys Cys	25610	25615	25620
Gly Ala Gly Gly Cys Ala Gly Ala Gly Gly Cys Ala Cys Ala Cys	25625	25630	25635
Ala Gly Cys Thr Cys Ala Ala Cys Gly Ala Cys Gly Ala Gly Thr	25640	25645	25650
Thr Gly Gly Thr Gly Ala Gly Cys Thr Cys Thr Thr Cys Gly Ala	25655	25660	25665
Thr Cys Gly Gly Thr Cys Thr Gly Cys Gly Ala Cys Cys Gly Gly	25670	25675	25680
Ala Cys Gly Gly Ala Gly Thr Gly Thr Thr Cys Cys Ala Ala Cys	25685	25690	25695
Thr Ala Gly Cys Cys Gly Gly Ala Gly Cys Cys Gly Gly Gly Ala	25700	25705	25710
Gly Ala Thr Cys Cys Thr Cys Cys Thr Thr Cys Ala Cys Thr Cys	25715	25720	25725
Cys Cys Ala Ala Cys Cys Ala Gly Gly Cys Cys Thr Ala Cys Cys	25730	25735	25740
Thr Gly Ala Cys Cys Thr Thr Gly Cys Ala Gly Ala Gly Cys Ala	25745	25750	25755
Gly Cys Thr Cys Thr Thr Cys Gly Gly Ala Gly Cys Cys Thr Cys	25760	25765	25770
Gly Cys Thr Cys Cys Gly Gly Ala Gly Gly Cys Ala Thr Cys Gly			

25775	25780	25785
Gly Ala Ala Cys Cys Cys Thr Cys Cys Ala Gly Thr Thr Thr Gly		
25790	25795	25800
Thr Gly Gly Ala Gly Gly Ala Gly Thr Thr Thr Gly Thr Gly Cys		
25805	25810	25815
Cys Cys Thr Cys Gly Gly Thr Cys Thr Ala Cys Thr Thr Cys Ala		
25820	25825	25830
Ala Cys Cys Cys Cys Thr Thr Cys Thr Cys Gly Gly Gly Ala Thr		
25835	25840	25845
Cys Gly Cys Cys Ala Gly Gly Cys Cys Thr Cys Thr Ala Cys Cys		
25850	25855	25860
Cys Gly Gly Ala Cys Gly Ala Gly Thr Thr Cys Ala Thr Ala Cys		
25865	25870	25875
Cys Gly Ala Ala Cys Thr Thr Cys Gly Ala Cys Gly Cys Ala Gly		
25880	25885	25890
Thr Gly Ala Gly Ala Gly Ala Ala Gly Cys Gly Gly Thr Gly Gly		
25895	25900	25905
Ala Cys Gly Gly Cys Thr Ala Cys Gly Ala Cys Thr Gly Ala Ala		
25910	25915	25920
Thr Gly Thr Cys Cys Cys Ala Thr Gly Gly Thr Gly Ala Cys Thr		
25925	25930	25935
Cys Gly Gly Cys Thr Gly Ala Gly Cys Thr Cys Gly Cys Thr Cys		
25940	25945	25950
Gly Gly Thr Thr Gly Ala Gly Gly Cys Ala Thr Cys Thr Gly Gly		
25955	25960	25965
Ala Cys Cys Ala Cys Thr Gly Cys Cys Gly Cys Cys Gly Cys Cys		
25970	25975	25980
Thr Gly Cys Gly Cys Thr Gly Cys Thr Thr Cys Gly Cys Cys Cys		
25985	25990	25995
Gly Gly Gly Ala Gly Ala Gly Cys Thr Gly Cys Gly Gly Ala Cys		
26000	26005	26010
Thr Cys Ala Thr Cys Thr Ala Cys Thr Thr Thr Gly Ala Gly Thr		
26015	26020	26025
Thr Thr Cys Cys Cys Gly Ala Gly Gly Ala Gly Cys Ala Cys Cys		
26030	26035	26040
Cys Cys Ala Ala Cys Gly Gly Cys Cys Cys Thr Gly Cys Ala Cys		
26045	26050	26055
Ala Cys Gly Gly Ala Gly Thr Gly Cys Gly Gly Ala Thr Cys Ala		
26060	26065	26070

Cys Cys Gly Thr Ala Gly Ala Gly Gly Gly Cys Ala Cys Cys Ala	26075	26080	26085
Cys Cys Gly Ala Gly Thr Cys Thr Cys Ala Cys Cys Thr Gly Gly	26090	26095	26100
Thr Cys Ala Gly Gly Thr Thr Cys Thr Thr Cys Ala Cys Cys Cys	26105	26110	26115
Ala Gly Cys Ala Ala Cys Cys Cys Thr Thr Cys Cys Thr Gly Gly	26120	26125	26130
Thr Cys Gly Ala Gly Cys Gly Gly Gly Ala Cys Cys Gly Gly Gly	26135	26140	26145
Gly Cys Gly Cys Cys Ala Cys Cys Ala Cys Cys Thr Ala Cys Ala	26150	26155	26160
Cys Cys Gly Thr Cys Thr Ala Cys Thr Gly Cys Ala Thr Cys Thr	26165	26170	26175
Gly Thr Cys Cys Ala Ala Cys Cys Cys Cys Gly Ala Ala Gly Thr	26180	26185	26190
Thr Gly Cys Ala Thr Gly Ala Gly Ala Ala Thr Thr Thr Thr Thr	26195	26200	26205
Gly Thr Thr Gly Thr Ala Cys Thr Cys Thr Thr Thr Gly Thr Gly	26210	26215	26220
Gly Thr Gly Ala Gly Thr Thr Thr Ala Ala Thr Ala Ala Ala Ala	26225	26230	26235
Gly Cys Thr Ala Ala Ala Cys Thr Cys Thr Thr Gly Cys Ala Ala	26240	26245	26250
Thr Ala Cys Thr Cys Thr Gly Gly Ala Cys Cys Thr Thr Gly Thr	26255	26260	26265
Cys Gly Thr Cys Gly Thr Cys Ala Ala Cys Thr Cys Ala Ala Cys	26270	26275	26280
Gly Ala Gly Ala Cys Cys Gly Thr Cys Thr Ala Cys Cys Thr Cys	26285	26290	26295
Ala Cys Cys Ala Ala Cys Cys Ala Gly Ala Cys Thr Gly Ala Gly	26300	26305	26310
Gly Thr Ala Ala Ala Ala Cys Thr Cys Ala Cys Cys Thr Gly Cys	26315	26320	26325
Ala Gly Ala Cys Cys Ala Cys Ala Cys Ala Ala Gly Ala Cys Cys	26330	26335	26340
Thr Ala Thr Ala Thr Cys Ala Thr Cys Thr Gly Gly Thr Thr Cys	26345	26350	26355
Thr Thr Cys Gly Ala Gly Ala Ala Cys Ala Cys Cys Thr Cys Ala			

26360	26365	26370
Thr Thr Thr Gly Cys Ala Gly Thr Cys Thr Cys Cys Ala Ala Cys		
26375	26380	26385
Ala Cys Thr Cys Ala Cys Thr Gly Cys Ala Cys Thr Ala Gly Thr		
26390	26395	26400
Cys Cys Ala Thr Gly Ala Ala Cys Thr Gly Ala Thr Gly Thr Thr		
26405	26410	26415
Gly Ala Thr Thr Ala Ala Ala Ala Gly Cys Cys Cys Ala Ala Ala		
26420	26425	26430
Ala Ala Cys Cys Ala Ala Thr Cys Ala Gly Cys Cys Cys Cys Thr		
26435	26440	26445
Thr Cys Cys Cys Cys Cys Ala Thr Thr Thr Cys Cys Cys Cys Ala		
26450	26455	26460
Thr Cys Cys Cys Cys Cys Ala Ala Thr Thr Ala Cys Thr Cys Ala		
26465	26470	26475
Thr Ala Ala Ala Ala Ala Ala Thr Ala Ala Ala Thr Cys Ala Thr		
26480	26485	26490
Thr Gly Gly Ala Ala Thr Thr Ala Ala Thr Cys Ala Thr Thr Cys		
26495	26500	26505
Ala Ala Thr Ala Ala Ala Gly Ala Thr Cys Ala Cys Thr Thr Ala		
26510	26515	26520
Cys Thr Thr Gly Ala Ala Ala Thr Cys Thr Gly Ala Ala Ala Gly		
26525	26530	26535
Thr Ala Thr Gly Thr Cys Thr Cys Thr Gly Gly Thr Gly Thr Ala		
26540	26545	26550
Gly Thr Thr Gly Thr Thr Cys Ala Gly Cys Ala Gly Cys Ala Cys		
26555	26560	26565
Cys Thr Cys Gly Gly Thr Ala Cys Cys Cys Thr Cys Cys Thr Cys		
26570	26575	26580
Cys Cys Ala Gly Cys Thr Cys Thr Gly Gly Thr Ala Cys Thr Cys		
26585	26590	26595
Cys Ala Gly Thr Cys Cys Cys Cys Gly Gly Cys Gly Gly Gly Cys		
26600	26605	26610
Gly Gly Cys Gly Ala Ala Cys Thr Thr Cys Cys Thr Cys Cys Ala		
26615	26620	26625
Cys Ala Cys Cys Thr Thr Gly Ala Ala Ala Gly Gly Gly Ala Thr		
26630	26635	26640
Gly Thr Cys Ala Ala Ala Thr Thr Cys Cys Thr Gly Gly Thr Cys		
26645	26650	26655

Cys Ala Cys Ala Ala Thr Thr Thr Thr Cys Ala Thr Thr Gly Thr 26660	26665	26670
Cys Thr Thr Cys Cys Cys Thr Cys Thr Cys Ala Gly Ala Thr Gly 26675	26680	26685
Gly Cys Ala Ala Ala Gly Ala Gly Gly Cys Thr Cys Cys Gly Gly 26690	26695	26700
Gly Thr Gly Gly Ala Ala Gly Ala Thr Gly Ala Cys Thr Thr Cys 26705	26710	26715
Ala Ala Cys Cys Cys Cys Gly Thr Cys Thr Ala Cys Cys Cys Cys 26720	26725	26730
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Phe Lys Pro Tyr Ser Gly Thr Ala Tyr Asn Ser Leu Ala Pro Lys Gly			
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Lys Pro Ile Tyr Ala Asp Lys Thr Phe Gln Pro Glu Pro Gln Ile Gly			
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Arg	Ala	Thr	Asp	Thr	Tyr	Phe	Ser	Leu	Gly	Asn	Lys	Phe	Arg	Asn	Pro
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Thr	Val	Ala	Pro	Thr	His	Asp	Val	Thr	Thr	Asp	Arg	Ser	Gln	Arg	Leu
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Thr	Leu	Arg	Phe	Val	Pro	Val	Asp	Arg	Glu	Asp	Thr	Thr	Tyr	Ser	Tyr
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Lys	Ala	Arg	Phe	Thr	Leu	Ala	Val	Gly	Asp	Asn	Arg	Val	Leu	Asp	Met
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Ala	Ser	Thr	Tyr	Phe	Asp	Ile	Arg	Gly	Val	Leu	Asp	Arg	Gly	Pro	Ser
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Phe	Lys	Pro	Tyr	Ser	Gly	Thr	Ala	Tyr	Asn	Ser	Leu	Ala	Pro	Lys	Gly
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Ala	Pro	Asn	Pro	Cys	Glu	Trp	Asp	Glu	Ala	Ala	Thr	Ala	Leu	Glu	Ile
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 Ile Asn Ile Thr Lys Glu Gly Ile Gln Ile Gly Val Glu Gly Gln Thr
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 Pro Lys Tyr Ala Asp Lys Thr Phe Gln Pro Glu Pro Gln Ile Gly Glu
 195 200 205
 Ser Gln Trp Tyr Glu Thr Glu Ile Asn His Ala Ala Gly Arg Val Leu
 210 215 220
 Lys Lys Asp Thr Lys Met Lys Pro Cys Tyr Gly Ser Phe Ala Arg Pro
 225 230 235 240
 Thr Asn Glu Lys Gly Gly Gln Ala Lys Phe Lys Pro Val Asn Glu Gly
 245 250 255
 Glu Gln Pro Lys Asp Leu Asp Ile Asp Met Gln Phe Phe Ser Thr Thr
 260 265 270
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 Lys Pro Thr Ile Lys Glu Gly Asn Ser Arg Glu Leu Met Gly Gln Gln
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 Gly Leu Met Tyr Tyr Asn Ser Thr Gly Asn Met Gly Val Leu Ala Gly
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 Glu Leu Ser Tyr Gln Leu Leu Leu Asp Ser Leu Gly Asp Arg Thr Arg
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 Phe Pro Leu Gly Gly Val Ile Asn Thr Glu Thr Leu Thr Lys Val Lys
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 Pro Lys Thr Gly Gln Glu Asn Gly Trp Glu Lys Asp Ala Thr Glu Phe
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 Ser Asp Lys Asn Glu Ile Arg Val Gly Asn Asn Phe Ala Met Glu Ile

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Pro Ser Leu Val Asp Ala Tyr Ile Asn Ile Gly Ala Arg Trp Ser Leu		
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Asp Pro Met Asp Asn Val Asn Pro Phe Asn His His Arg Asn Ala Gly		
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Leu Arg Tyr Arg Ser Met Leu Leu Gly Asn Gly Arg Tyr Val Pro Phe		
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His Ile Gln Val Pro Gln Lys Phe Phe Ala Ile Lys Asn Leu Leu Leu		
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Leu Pro Gly Ser Tyr Thr Tyr Glu Trp Asn Phe Arg Lys Asp Val Asn		
	580	585
Met Ile Leu Gln Ser Ser Leu Gly Asn Asp Leu Arg Val Asp Gly Ala		
	595	600
Ser Val Arg Phe Asp Ser Val Asn Leu Tyr Ala Thr Phe Phe Pro Met		
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Asn Asp Gln Ser Phe Asn Asp Tyr Leu Ser Ala Ala Asn Met Leu Tyr		
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Pro Ile Pro Ala Lys Ala Thr Asn Val Pro Ile Ser Ile Pro Ser Arg		
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Asn Trp Ala Ala Phe Arg Gly Trp Ser Phe Thr Arg Leu Lys Thr Lys		
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Glu Thr Pro Ser Leu Gly Ser Gly Phe Asp Pro Tyr Phe Val Tyr Ser		
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Gly Ser Ile Pro Tyr Leu Asp Gly Thr Phe Tyr Leu Asn His Thr Phe		
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Lys Lys Val Ser Ile Met Phe Asp Ser Ser Val Ser Trp Pro Gly Asn		
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Asp Arg Leu Leu Thr Pro Asn Glu Phe Glu Ile Lys Arg Ser Val Asp		
	740	745
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 Gln Pro Met Ser Arg Gln Val Val Asp Glu Ile Asn Tyr Lys Asp Tyr
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 Pro Tyr Pro Leu Ile Gly Gln Thr Ala Val Pro Ser Val Thr Gln Lys
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Lys	Ala	Arg	Phe	Thr	Leu	Ala	Val	Gly	Asp	Asn	Arg	Val	Leu	Asp	Met
				85						90					95
Ala	Ser	Thr	Tyr	Phe	Asp	Ile	Arg	Gly	Val	Leu	Asp	Arg	Gly	Pro	Ser
				100						105					110
Phe	Lys	Pro	Tyr	Ser	Gly	Thr	Ala	Tyr	Asn	Ser	Leu	Ala	Pro	Lys	Gly
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Ala	Pro	Asn	Ala	Ser	Gln	Trp	Ile	Ala	Lys	Gly	Val	Pro	Thr	Ala	Ala
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Ala	Ala	Gly	Asn	Gly	Glu	Glu	Glu	His	Glu	Thr	Glu	Glu	Lys	Thr	Ala
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Thr	Tyr	Thr	Phe	Ala	Asn	Ala	Pro	Val	Lys	Ala	Glu	Ala	Gln	Ile	Thr
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Lys	Pro	Ile	Tyr	Ala	Asp	Lys	Thr	Phe	Gln	Pro	Glu	Pro	Gln	Val	Gly
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Arg	Ala	Leu	Lys	Pro	Asp	Thr	Lys	Met	Lys	Pro	Cys	Tyr	Gly	Ser	Phe
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Thr	Glu	Asn	Val	Asn	Leu	Glu	Thr	Pro	Asp	Thr	His	Val	Val	Tyr	Lys
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Ala	Ser	Gln	Leu	Asn	Ala	Val	Val	Asp	Leu	Gln	Asp	Arg	Asn	Thr	Glu
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	405	410
Pro Leu Asp Gly Ile Gly Val Pro Thr Thr Ser Tyr Lys Ser Ile Val		415
	420	425
Pro Asn Gly Glu Asp Asn Asn Asn Trp Lys Glu Pro Glu Val Asn Gly		430
	435	440
Thr Ser Glu Ile Gly Gln Gly Asn Leu Phe Ala Met Glu Ile Asn Leu		445
	450	455
Gln Ala Asn Leu Trp Lys Ser Phe Leu Tyr Ser Asn Val Ala Leu Tyr		460
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Leu Pro Asp Ser Tyr Lys Tyr Thr Pro Ala Asn Val Lys Leu Pro Ala		480
	485	490
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	500	505
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	515	520
Met Asp Asn Val Asn Pro Phe Asn His His Arg Asn Ala Gly Leu Arg		525
	530	535
Tyr Arg Ser Met Leu Leu Gly Asn Gly Arg Tyr Val Pro Phe His Ile		540
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Gln Val Pro Gln Lys Phe Phe Ala Ile Lys Asn Leu Leu Leu Leu Pro		560
	565	570
Gly Ser Tyr Thr Tyr Glu Trp Asn Phe Arg Lys Asp Val Asn Met Ile		575
	580	585
Leu Gln Ser Ser Leu Gly Asn Asp Leu Arg Val Asp Gly Ala Ser Val		590
	595	600
Arg Phe Asp Ser Val Asn Leu Tyr Ala Thr Phe Phe Pro Met Ala His		605
	610	615
Asn Thr Ala Ser Thr Leu Glu Ala Met Leu Arg Asn Asp Thr Asn Asp		620
625	630	635
Gln Ser Phe Asn Asp Tyr Leu Ser Ala Ala Asn Met Leu Tyr Pro Ile		640
	645	650
Pro Ala Lys Ala Thr Asn Val Pro Ile Ser Ile Pro Ser Arg Asn Trp		655
	660	665
Ala Ala Phe Arg Gly Trp Ser Phe Thr Arg Leu Lys Thr Lys Glu Thr		670
	675	680
		685

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 Ile Pro Tyr Leu Asp Gly Thr Phe Tyr Leu Asn His Thr Phe Lys Lys
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 Val Ser Ile Met Phe Asp Ser Ser Val Ser Trp Pro Gly Asn Asp Arg
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 Leu Leu Thr Pro Asn Glu Phe Glu Ile Lys Arg Ser Val Asp Gly Glu
 740 745 750
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 Gln Met Leu Ser His Tyr Asn Ile Gly Tyr Gln Gly Phe His Val Pro
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 Pro Leu Ile Gly Gln Thr Ala Val Pro Ser Val Thr Gln Lys Lys Phe
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 Ser Ala His Ala Leu Asp Met Thr Phe Glu Val Asp Pro Met Asp Glu
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 Pro Thr Leu Leu Tyr Leu Leu Phe Glu Val Phe Asp Val Val Arg Val
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 35 40 45
 Thr Val Ala Pro Thr His Asp Val Thr Thr Asp Arg Ser Gln Arg Leu
 50 55 60
 Thr Leu Arg Phe Val Pro Val Asp Arg Glu Asp Thr Thr Tyr Ser Tyr
 65 70 75 80
 Lys Ala Arg Phe Thr Leu Ala Val Gly Asp Asn Arg Val Leu Asp Met
 85 90 95
 Ala Ser Thr Tyr Phe Asp Ile Arg Gly Val Leu Asp Arg Gly Pro Ser
 100 105 110
 Phe Lys Pro Tyr Ser Gly Thr Ala Tyr Asn Ser Leu Ala Pro Lys Gly
 115 120 125
 Ala Pro Asn Ser Val Glu Trp Pro Asp Asn Thr Lys Thr Lys Val Arg
 130 135 140
 Ala Gln Ala Pro Phe Val Ser Asp Glu Ile Thr Lys Asp Gly Ile Lys
 145 150 155 160
 Val Gly Thr Asp Thr Ala Thr Thr Gln Gln Ser Ile Tyr Ala Asp Lys
 165 170 175
 Thr Phe Gln Pro Glu Pro Gln Val Gly Glu Thr Gln Trp Asn Ser Asp
 180 185 190
 Val Gly Thr Asn Asp Lys Val Ala Gly Arg Val Leu Lys Lys Asp Thr
 195 200 205
 Lys Met Lys Pro Cys Tyr Gly Ser Phe Ala Arg Pro Thr Asn Glu Lys
 210 215 220
 Gly Gly Gln Ala Lys Phe Lys Pro Val Asn Glu Gly Glu Gln Pro Lys
 225 230 235 240
 Asp Leu Asp Ile Asp Met Gln Phe Phe Ala Thr Thr Ala Ala Asn Thr
 245 250 255
 Thr Pro Lys Ala Val Leu Tyr Thr Glu Asn Val Asn Leu Glu Thr Pro
 260 265 270
 Asp Thr His Val Val Tyr Lys Pro Thr Val Thr Glu Gly Thr Thr Ser
 275 280 285
 Ala Glu Ala Leu Leu Ala Gln Gln Ser Met Pro Asn Arg Pro Asn Tyr

290	295	300
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Gly Asn Met Gly Val Leu Ala Gly Gln Ala Ser Gln Leu Asn Ala Val		
	325	330
Val Asp Leu Gln Asp Arg Asn Thr Glu Leu Ser Tyr Gln Leu Leu Leu		
	340	345
Asp Ser Leu Gly Asp Arg Thr Arg Tyr Phe Ser Met Trp Asn Ser Ala		
	355	360
Val Asp Ser Tyr Asp Pro Asp Val Arg Ile Ile Glu Asn His Gly Val		
370	375	380
Glu Asp Glu Leu Pro Asn Tyr Cys Phe Pro Leu Gly Gly Met Ala Val		
385	390	395
Thr Asp Thr Tyr Ser Pro Ile Lys Ser Asn Asn Gly Ser Gly Trp Gln		
	405	410
Val Asp Asn Asp Thr Phe Ala Asp Arg Gly Val Glu Ile Gly Ser Gly		
	420	425
Asn Met Phe Ala Met Glu Ile Asn Leu Gln Ala Asn Leu Trp Lys Ser		
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Phe Leu Tyr Ser Asn Val Ala Leu Tyr Leu Pro Asp Ser Tyr Lys Tyr		
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Thr Pro Ala Asn Val Lys Leu Pro Ala Asn Thr Asn Thr Tyr Glu Tyr		
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	485	490
Ile Gly Ala Arg Trp Ser Leu Asp Pro Met Asp Asn Val Asn Pro Phe		
	500	505
Asn His His Arg Asn Ala Gly Leu Arg Tyr Arg Ser Met Leu Leu Gly		
	515	520
Asn Gly Arg Tyr Val Pro Phe His Ile Gln Val Pro Gln Lys Phe Phe		
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Ala Ile Lys Asn Leu Leu Leu Leu Pro Gly Ser Tyr Thr Tyr Glu Trp		
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Asn Phe Arg Lys Asp Val Asn Met Ile Leu Gln Ser Ser Leu Gly Asn		
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	580	585
Tyr Ala Thr Phe Phe Pro Met Ala His Asn Thr Ala Ser Thr Leu Glu		
595	600	605

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 625 630 635 640
 Pro Ile Ser Ile Pro Ser Arg Asn Trp Ala Ala Phe Arg Gly Trp Ser
 645 650 655
 Phe Thr Arg Leu Lys Thr Lys Glu Thr Pro Ser Leu Gly Ser Gly Phe
 660 665 670
 Asp Pro Tyr Phe Val Tyr Ser Gly Ser Ile Pro Tyr Leu Asp Gly Thr
 675 680 685
 Phe Tyr Leu Asn His Thr Phe Lys Lys Val Ser Ile Met Phe Asp Ser
 690 695 700
 Ser Val Ser Trp Pro Gly Asn Asp Arg Leu Leu Thr Pro Asn Glu Phe
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 Glu Ile Lys Arg Ser Val Asp Gly Glu Gly Tyr Asn Val Ala Gln Cys
 725 730 735
 Asn Met Thr Lys Asp Trp Phe Leu Val Gln Met Leu Ser His Tyr Asn
 740 745 750
 Ile Gly Tyr Gln Gly Phe His Val Pro Glu Gly Tyr Lys Asp Arg Met
 755 760 765
 Tyr Ser Phe Phe Arg Asn Phe Gln Pro Met Ser Arg Gln Val Val Asp
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 Leu Gly Gln Asn Met Leu Tyr Ala Asn Ser Ala His Ala Leu Asp Met
 865 870 875 880
 Thr Phe Glu Val Asp Pro Met Asp Glu Pro Thr Leu Leu Tyr Leu Leu
 885 890 895
 Phe Glu Val Phe Asp Val Val Arg Val His Gln Pro His Arg Gly Val
 900 905 910
 Ile Glu Ala Val Tyr Leu Arg Thr Pro Phe Ser Ala Gly Asn Ala Thr

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图1A

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PtroAdV-1A.....A.....		ETSTDA-----TT.HS.L.MK.D.SD.QI.A.SGEE.P-	LY	90	
PtroAdV-12		--QNEIN---NK---H.M.MK.FA.DKN.QI.A.DQD.P-		87	
PtroAdV-13	S	--QAKPGN.TME---H.Y.PM.E.KD.QI.A.DQN.P-		91	
HAAdV-26	PQVGEENWQENEAF--YGGRALKK	DTKMKPCYGSFARPTNEKGGQAKFKPVNEGEQPKLDID	FAYFDVPGGSPAGGSGEEYKADILLY	TENVNLE	193	
PtroAdV-1	I.S.TDIDGTNEKF.V	SK.N.....Q.A-T.T.TVEY.V	MNF---RDA.AN---FTPEVV	A...D...179	
PtroAdV-12	D.IDKAD---	K.V.....TTRTKAD---TTEP	MNF.PT--TI--N---TP.VV	A...D.Q.170	
PtroAdV-13	T.S---	NY.....L.VGDD.VPT.EF	L.F.T.TV--NGQD	VM...AY...183	
HAAdV-26	TPDTHVVYKPGTSDNSSEINLV	QQSMPNRPNYIGFRDNFVGLMYNSTGNMGVLAGQASQLNAVVDLQDRNTELSYQLLLDSLGRDRTRYFSMWNSAVD			291	
PtroAdV-1	I.....V.HV.G	AIQ	277	
PtroAdV-12	I.....A.D.V.A	AIQ	268	
PtroAdV-13	I.....KE.A	IQ	281	
HAAdV-26	SYDPDVR I IENHGVEDELPNYCFPL	NGTGTNSTYQGVKI--TNGNDGAEFESEWKDDAISRQNTCKGNVY	AMEINLQANLWKSFLYSNVALYLPDSY		387	
PtroAdV-1	I.....I	DAV.ITK	I.TQ--QT---TT	TSV.TA.E.GI.NII.....RN...A.....369	
PtroAdV-12	D.V.TA	VKTT	ETVYEF.G.DII.....RN...A.....361
PtroAdV-13	D.S.AA	VK--E.DL	N.TVAARI.....R.....377	

图1B

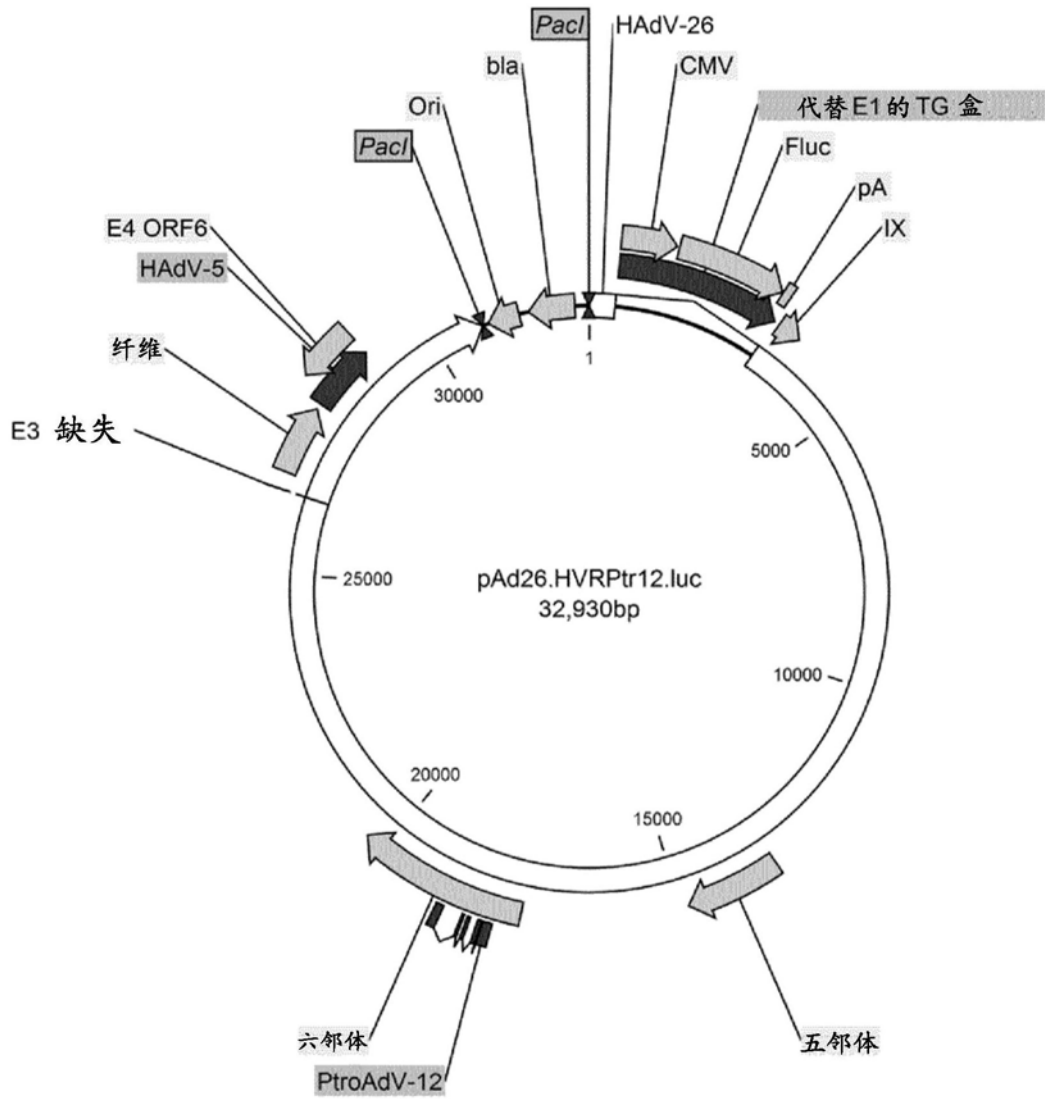


图2A

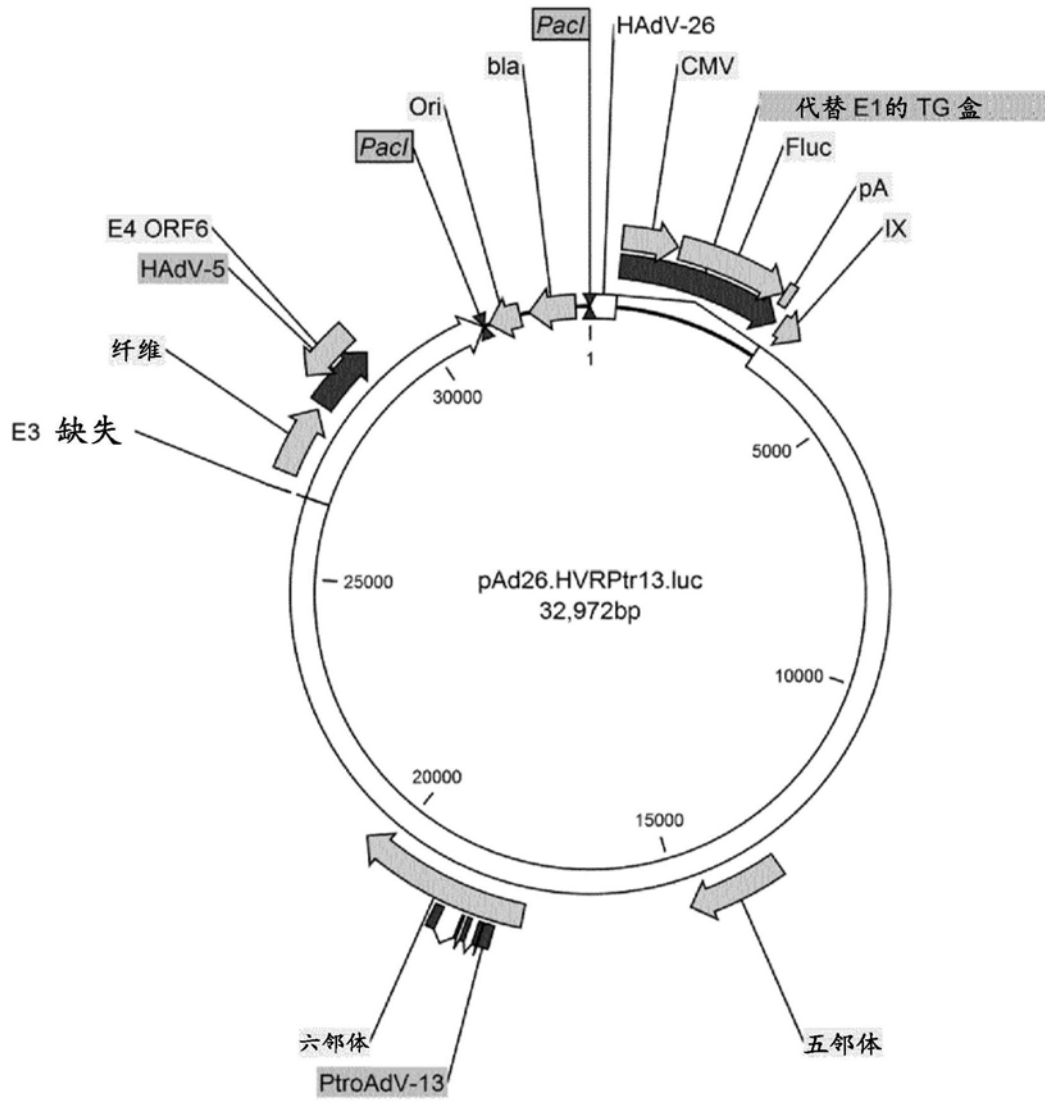


图2B

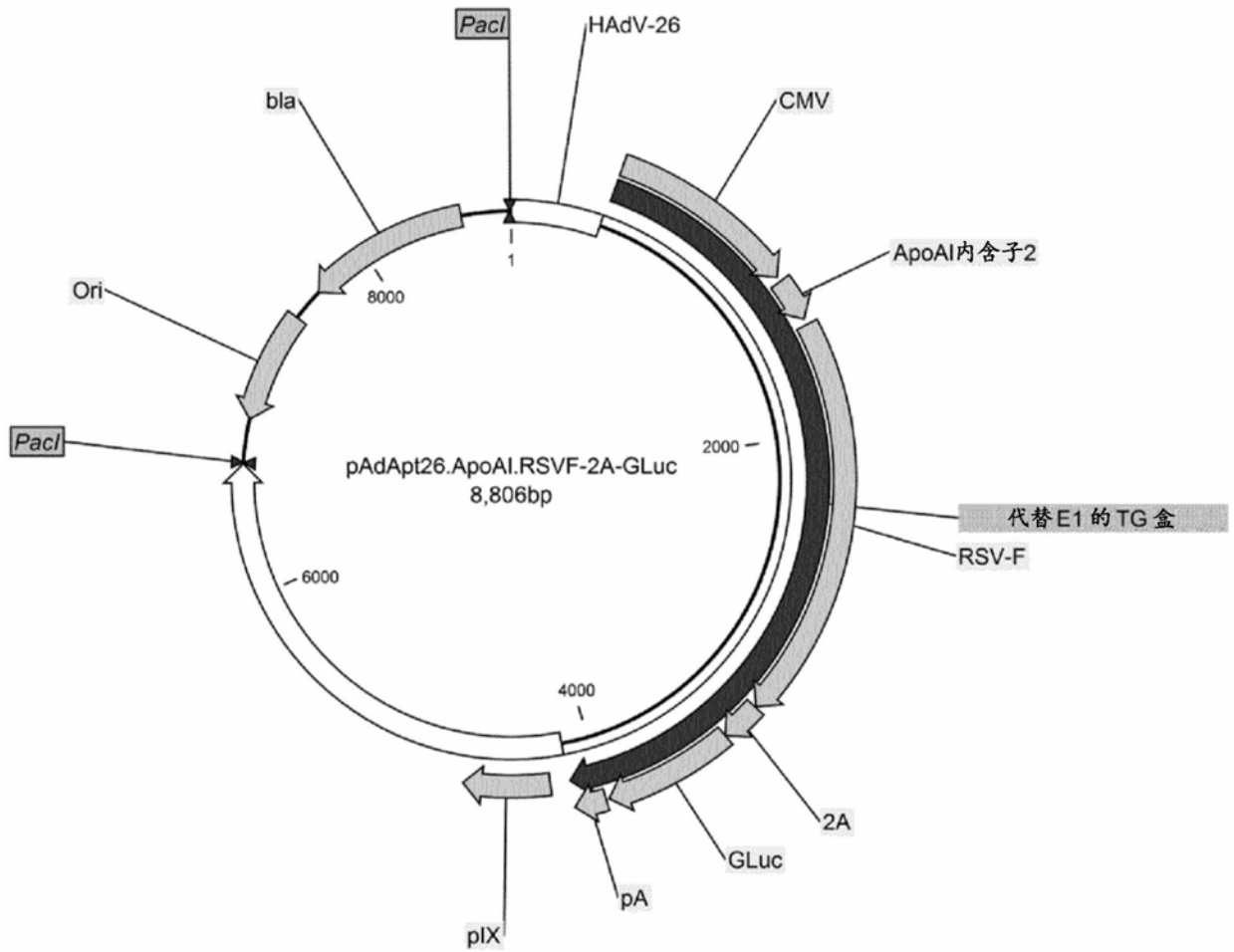


图3

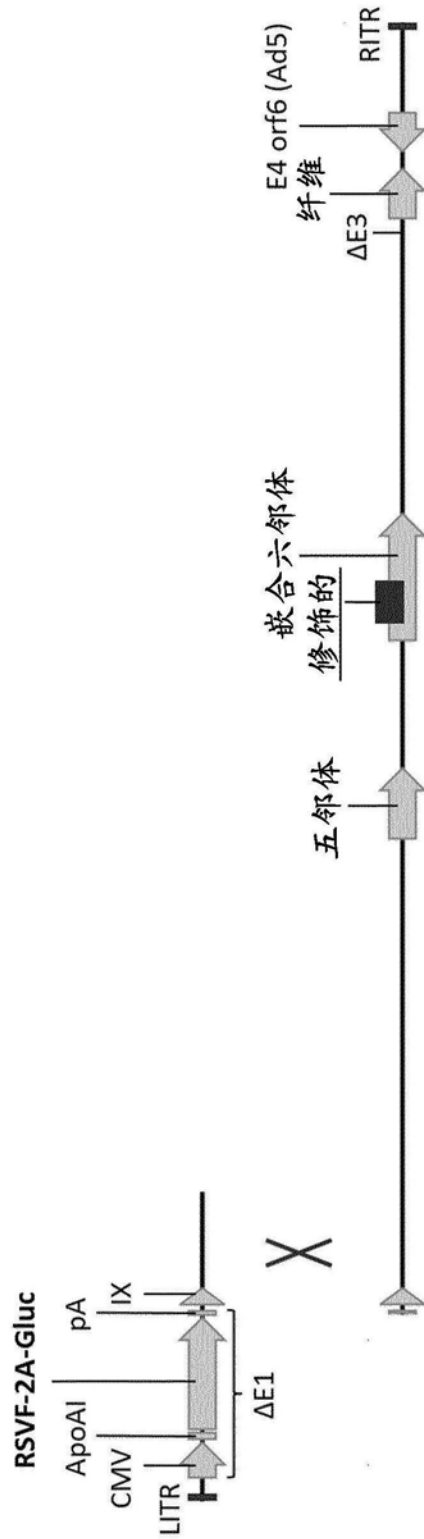


图4

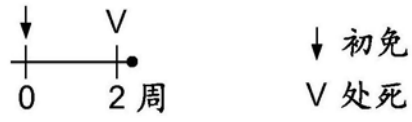


图5A

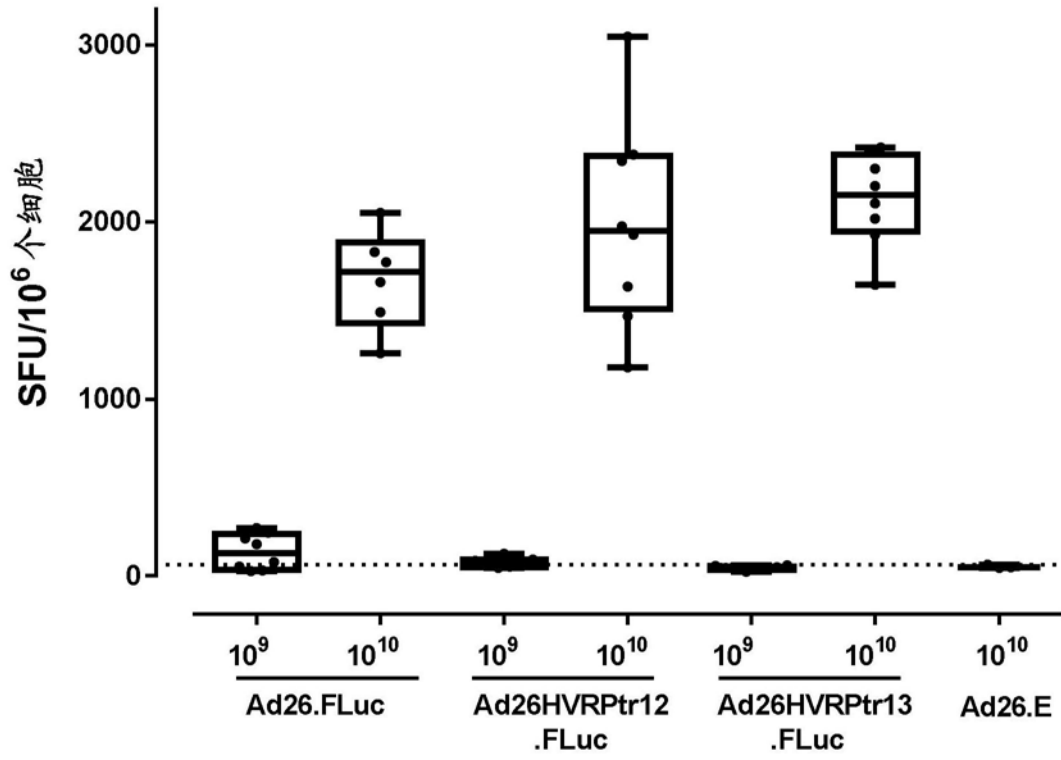


图5B



图6A

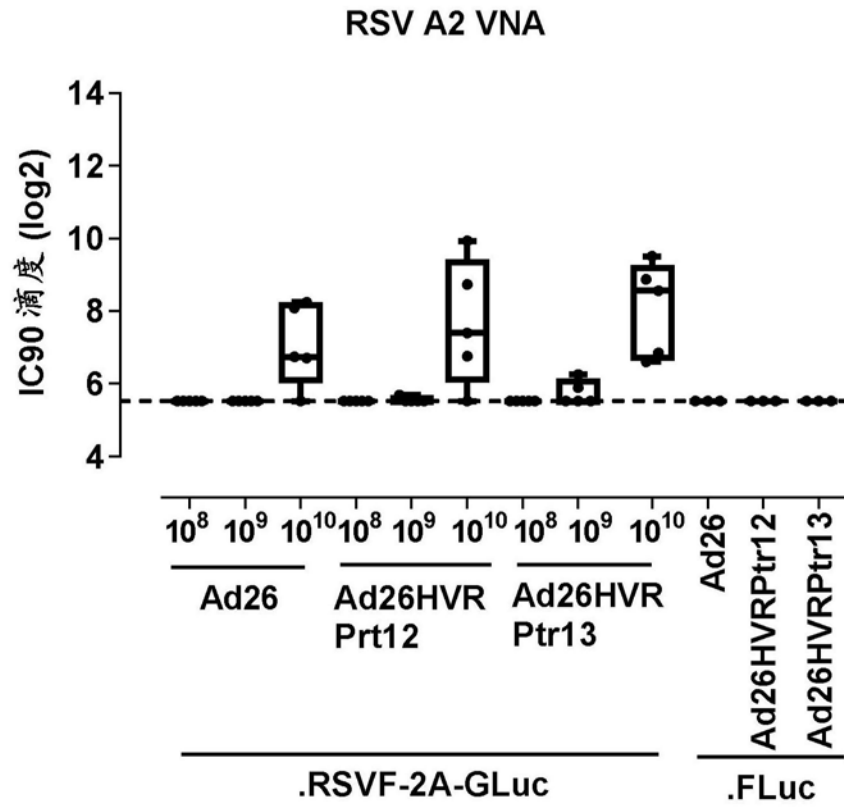


图6B

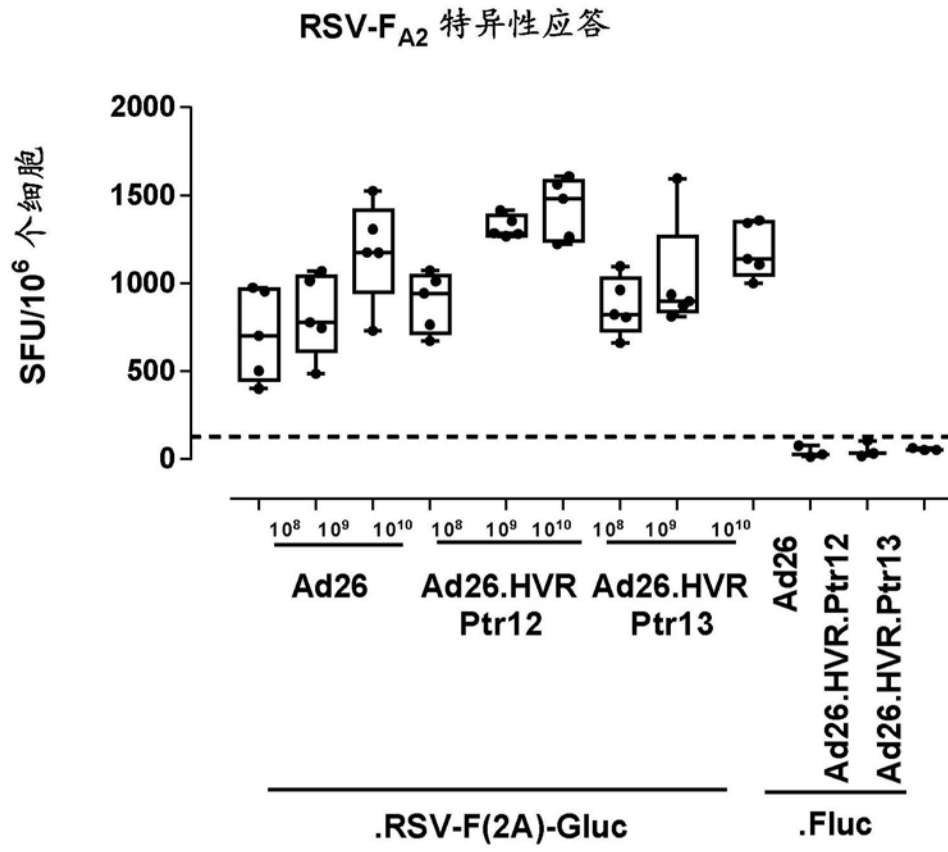


图6C

前 RSV-F 特异性 IgG 抗体滴度

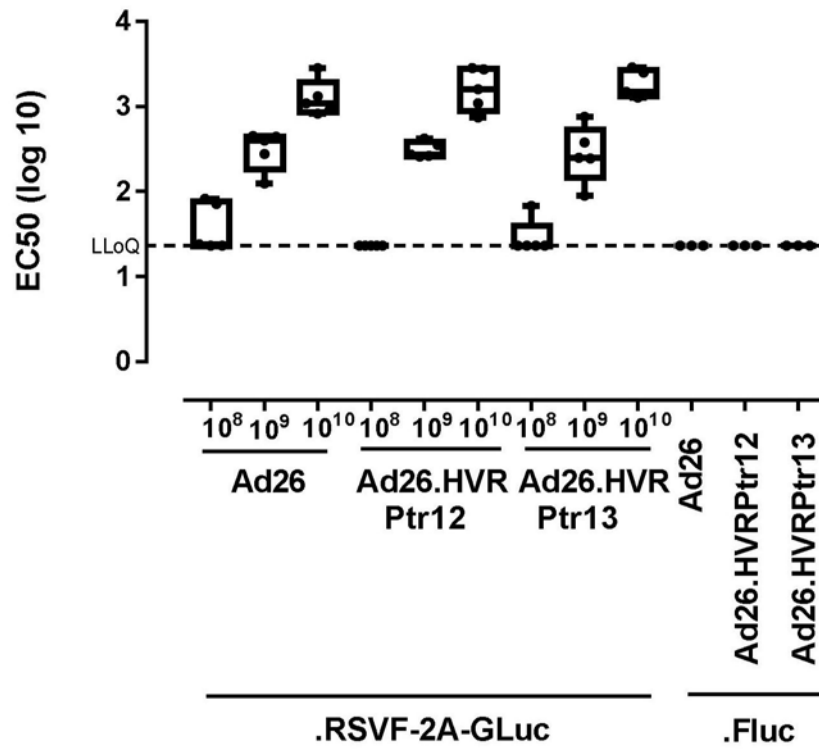


图6D

		腺病毒载体						
		Ad35 (B)	Ad26 (D)	Ad5 (C)	Ad4 (E)	Ad26HVR Ptr12 (D)	Ad26HVR Ptr13 (D)	
血清*	Ad35 (B)	13384	<16	<16	<16	<16	<16	
	Ad26 (D)	<16	2786	<16	<16	39.8	31.6	
	Ad5 (C)	<16	<16	6007	<16	<16	<16	
	Ad4 (E)	<16	<16	<16	1914	<16	<16	
	Ad26HVRPtr12 (D)	<16	31.6	<16	<16	501.2	79.4	
	Ad26HVRPtr13 (D)	<16	25.1	<16	<16	50.1	794.3	

*从用指出的血清型进行免疫的小鼠收集的血清

值

<16	无中和
16 - 200	轻微中和
200 - 2000	中和
>2000	强中和

图7

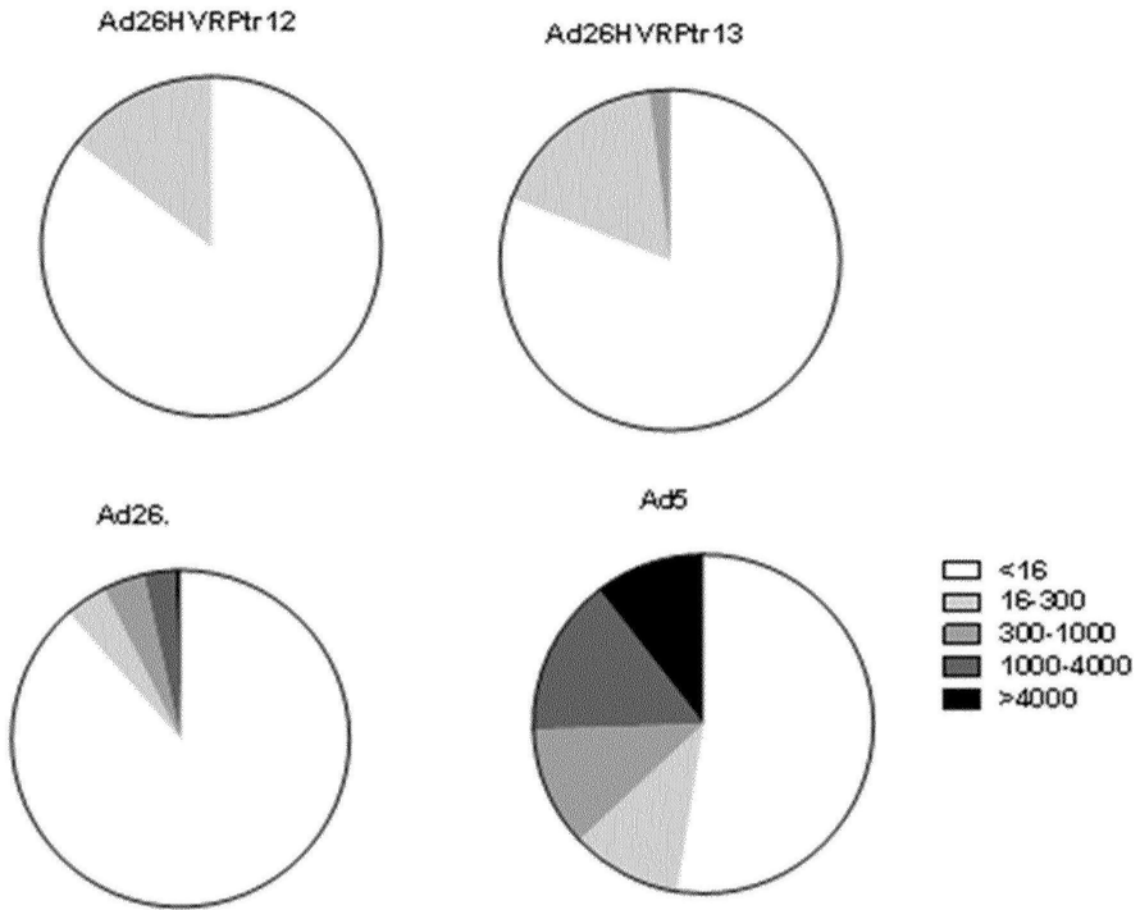


图8

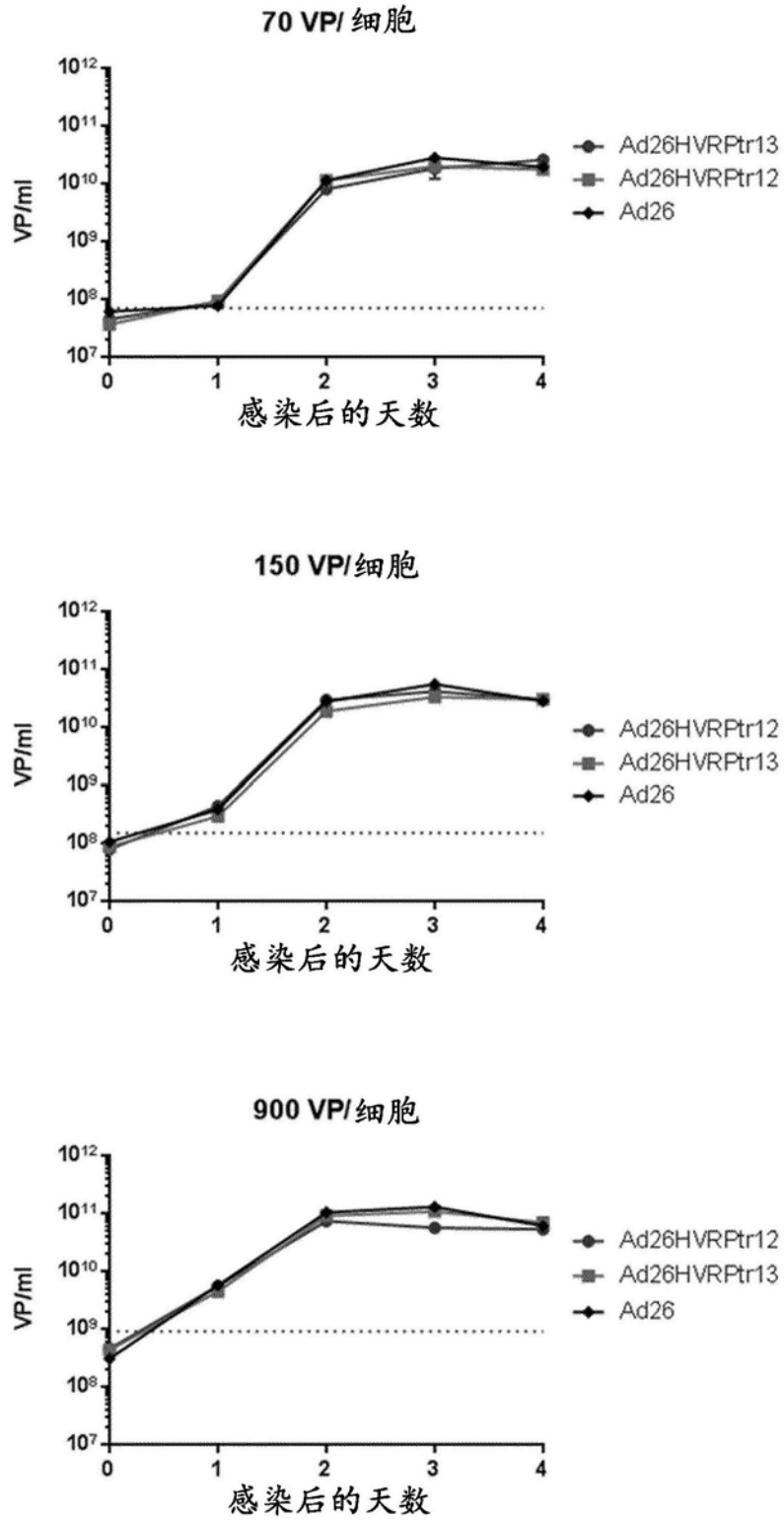


图9