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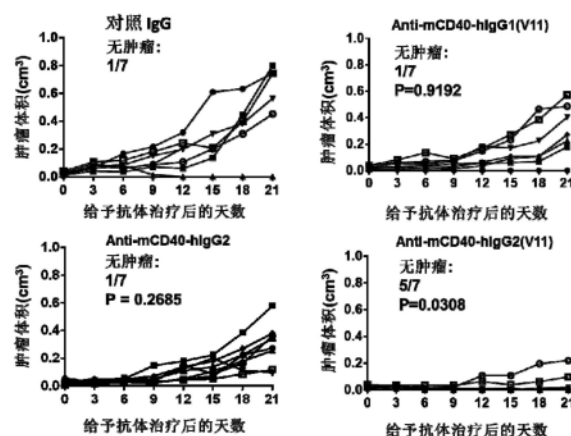
(54) 发明名称

增强激动型抗体活性的抗体重链恒定区序列

(57) 摘要

本发明提供了一种重链恒定区,包含CH1结构域、铰链区、CH2结构域和CH3结构域,所述CH1结构域和铰链区的序列是来源于人IgG2的CH1结构域和铰链区的序列,所述CH2结构域和CH3结构域的序列为来源于人IgG的CH2结构域和CH3结构域序列,并且所述抗体重链恒定区与人Fc γ IIB的亲合力等于或高于人IgG1与人Fc γ IIB的亲合力,所述抗体重链恒定区的I/A比值等于或高于人IgG1的I/A比值。并且提供基于上述重链恒定区的抗体或融合蛋白,该抗体重链恒定区可显著增强所述抗体或融合蛋白的激动活性,提高抗体

或融合蛋白在肿瘤和自身免疫等其它疾病中的治疗效果。



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1. 一种抗体重链恒定区, 包含从N端到C端顺序连接的CH1结构域、绞链区、CH2结构域和CH3结构域, 其特征在于, 所述CH1结构域和绞链区的序列是人IgG2的CH1结构域和绞链区的序列, 所述CH2结构域和CH3结构域的序列是:

人IgG1的CH2结构域和CH3结构域的序列, 并且所述CH2结构域和CH3结构域内包含G237D、P238D、P271G和A330R突变; 或者是

人IgG1的CH2结构域和CH3结构域的序列, 并且所述CH2结构域和CH3结构域内包含G237D、P238D、H268D、P271G和A330R突变; 或者是

人IgG2的CH2结构域和CH3结构域的序列, 并且所述CH2结构域和CH3结构域内包含S267E和L328F突变; 或者是

人IgG2的CH2结构域和CH3结构域的序列, 并且所述CH2结构域和CH3结构域内包含H268D和P271G突变;

并且所述CH2结构域和CH3结构域的序列使得抗体重链恒定区与人Fc γ RIIB的亲合力等于或高于人IgG1与人Fc γ RIIB的亲合力, 所述抗体重链恒定区的I/A比值等于或高于人IgG1的I/A比值。

2. 根据权利要求1所述的抗体重链恒定区, 其特征在于: 所述抗体重链恒定区具有如SEQ ID NO:11或者SEQ ID NO:12或者SEQ ID NO:13或者SEQ ID NO:14所示的序列。

3. 一种融合蛋白, 其特征在于, 包含权利要求1-2任一所述的抗体重链恒定区以及位于所述抗体重链恒定区N端和/或C端的抗原结合模块。

4. 如权利要求3所述的融合蛋白, 其特征在于, 所述抗原结合模块选自于抗体的抗原结合片段、adnectin、纳米抗体、微型抗体、亲和体、affilin、受体的靶结合区、细胞粘附分子、配体、酶、细胞因子或趋化因子中的任意一种。

5. 如权利要求3所述的融合蛋白, 其特征在于, 所述抗原结合模块为纳米抗体。

6. 如权利要求3所述的融合蛋白, 其特征在于, 所述抗原结合模块为配体, 所述配体为免疫共刺激分子, 所述免疫共刺激分子选自于CD80、CD86、ICOSL、OX40L、CD137L、CD40L、CD30L、CD27L、CD244、CD150、CD48、CD84、CD319、Ly118、CD229或SLAMF8中的任意一种。

7. 如权利要求3所述的融合蛋白, 其特征在于, 所述抗原结合模块所靶向的抗原选自于CD40、DR5、OX40、CD137、CD27、CD30、GITR、HVEM、TACI、DR4或FAS中的任意一种。

8. 如权利要求3所述的融合蛋白, 其特征在于, 所述抗原结合模块所靶向的抗原为CD40。

9. 如权利要求3所述的融合蛋白, 其特征在于, 所述抗原结合模块所靶向的抗原选自于PD-1、CTLA-4、VISTA、TIM-3、BTLA或LAG-3中的任意一种。

10. 如权利要求3所述的融合蛋白, 其特征在于, 所述抗原结合模块为配体, 所述配体为免疫抑制性配体分子, 所述免疫抑制性配体分子选自于PD-L1, PD-L2, B7-H3, B7-H4, CD47, VISTA, HVEM或GAL9中的任意一种。

11. 一种抗体, 包括权利要求1-2任一所述的抗体重链恒定区。

12. 如权利要求11所述的抗体, 其特征在于, 所述抗体为激动型抗体。

13. 如权利要求11所述的抗体, 其特征在于, 所述抗体为IgG。

14. 如权利要求11所述的抗体, 其特征在于, 所述抗体为人抗体或者是人源化抗体或者是嵌合抗体。

15. 如权利要求11所述的抗体,其特征在于,所述抗体所靶向的抗原选自于CD40、DR5、OX40、CD137、CD27、CD30、GITR、HVEM、TACI、DR4或FAS中的任意一种。

16. 如权利要求11所述的抗体,其特征在于,所述抗体所靶向的抗原为CD40。

17. 如权利要求16所述的抗体,其特征在于,所述抗体的轻链具有SEQ ID NO:47所示的序列,所述抗体的重链具有SEQ ID NO:27或者SEQ ID NO:43所示的序列。

18. 如权利要求11所述的抗体,其特征在于,所述抗体所靶向的抗原为DR5。

19. 如权利要求11所述的抗体,其特征在于,所述抗体所靶向的抗原为免疫抑制性受体分子,并且所述免疫抑制性受体分子选自于PD-1、CTLA-4、VISTA、TIM-3、BTLA或LAG-3中的任意一种。

20. 如权利要求3-8任一所述的融合蛋白或者权利要求11-18任一所述的抗体在制备抗癌药物中的应用。

21. 一种用于治疗增殖性疾病的药物组合物,包含:

a) 治疗有效剂量的权利要求3-8任一所述的融合蛋白或者权利要求11-18任一所述的抗体,以及

b) 药学上可接受的药物载体。

22. 如权利要求8所述的融合蛋白或者权利要求16-17任一所述的抗体用作疫苗佐剂的用途。

23. 一种疫苗组合物,包含:

a) 治疗有效剂量的权利要求8所述的融合蛋白或者权利要求16-17任一所述的抗体,以及

b) 疫苗。

24. 如权利要求23所述的疫苗组合物在制备用于预防和/或治疗肿瘤的药物中的用途。

25. 如权利要求9-10任一所述融合蛋白或权利要求19所述的抗体在制备减轻炎症和/或减轻自身免疫症状的药物中的应用。

增强激动型抗体活性的抗体重链恒定区序列

技术领域

[0001] 本发明涉及生物制药领域,特别是涉及一种可增强激动型抗体或激动型分子(包含重链恒定区序列的融合蛋白)活性的重链恒定区序列和分子,以及基于该重链恒定区而构建的抗体或融合蛋白。

背景技术

[0002] 基于抗体和重链恒定区(包含Fc片段)的分子靶向治疗,包括抗体和重链恒定区融合蛋白,近三十年来在生物制药领域已经取得了巨大成功并持续成为该领域的重点,为多种疾病的治疗提供了新的方法和可能。已经被批准基于重链恒定区的生物治疗手段(包括重链恒定区融合蛋白的分子)约30个,而在临床试验阶段的超过300个,这些生物治疗基于作用方式主要可以分为三类:清除靶标(分子和细胞)的效应分子、阻断靶标参与的信号通路的阻断型分子、和激活靶标下游信号通路的激动型分子。

[0003] 肿瘤免疫治疗近年取得了重要突破。这得益于通过阻断免疫抑制节点,提高免疫细胞活性杀灭肿瘤的抗体的使用。但是目前仍有大量癌症患者对已有治疗手段没有应答。因此,一方面需要对目前已有的肿瘤免疫治疗手段进行优化;另一方面亟需研发新的肿瘤免疫治疗药物。需要特别指出的是有一类被称为“激动型抗体”的肿瘤免疫治疗手段,能够通过结合免疫细胞表面传递免疫激活信号的靶标分子并激活其控制的重要免疫激活信号通路,进而增强抗肿瘤免疫应答间接杀死肿瘤细胞。然而,虽然激动型肿瘤免疫治疗抗体已经在动物模型中证明了其巨大潜力,并且已经成为一个被广泛接受并看好的肿瘤免疫治疗理念,但是这类抗体的研发至今尚未成功,是肿瘤免疫治疗领域当前的一个主要挑战。此外,激动型抗体激活也是干预和调控其它生物学过程的关键信号通路的有利手段,在疾病防控和治疗领域有着广泛的应用前景。例如激活免疫抑制信号通路,可能有利于减轻炎症和自身免疫症状。

发明内容

[0004] 本发明主要解决的技术问题是提供可增强激动型抗体或激动型分子(包含重链恒定区序列的融合蛋白)活性的重链恒定区序列和分子,以及基于该重链恒定区而构建的抗体或融合蛋白。

[0005] 为解决上述技术问题,本发明采用的一个技术方案是:

[0006] 提供一种重链恒定区,包含CH1结构域、绞链区、CH2结构域和CH3结构域,并且所述CH1结构域和绞链区的序列是来源于人IgG2的CH1结构域和绞链区的序列,所述CH2结构域和CH3结构域的序列选自于:

[0007] a) 来源于人IgG1的CH2结构域和CH3结构域的序列,并且所述CH2结构域和CH3结构域内包含G237D、P238D、P271G和A330R突变;或者

[0008] b) 来源于人IgG1的CH2结构域和CH3结构域的序列,并且所述CH2结构域和CH3结构域内包含G237D、P238D、H268D、P271G和A330R突变;或者

[0009] c) 来源于人IgG2的CH2结构域和CH3结构域的序列,并且所述CH2结构域和CH3 结构域内包含S267E和L328F突变;或者

[0010] d) 来源于人IgG2的CH2结构域和CH3结构域的序列,并且所述CH2结构域和CH3 结构域内包含H268D和P271G突变。

[0011] 较佳地,所述重链恒定区具有如SEQ ID NO:11所示的序列,或者所述重链恒定区具有如SEQ ID NO:12所示的序列,或者所述重链恒定区具有如SEQ ID NO:13所示的序列,或者所述重链恒定区具有如SEQ ID NO:14所示的序列。

[0012] 另外还提供一种重链恒定区,包含CH1结构域、铰链区、CH2结构域和CH3结构域,所述CH1结构域和铰链区的序列是来源于人IgG2的CH1结构域和铰链区的序列,所述 CH2结构域和CH3结构域的序列为来源于人IgG的CH2结构域和CH3结构域序列,并且所述抗体重链恒定区与人Fc γ IIB的亲合力等于或高于人IgG1与人Fc γ IIB的亲合力,所述抗体重链恒定区的I/A比值等于或高于人IgG1的I/A比值。

[0013] 优选地,所述抗体重链恒定区与人Fc γ IIB的亲合力和人IgG1与人Fc γ IIB的亲合力相比提高3.2倍或以上,所述抗体重链恒定区的I/A比值等于或高于0.32;同样优选地,所述抗体重链恒定区与人Fc γ IIB的亲合力等于或高于人IgG1与人Fc γ IIB的亲合力,所述抗体重链恒定区的I/A比值等于或高于1;更优选地,所述抗体重链恒定区与人Fc γ IIB 的亲合力和人IgG1与人Fc γ IIB的亲合力相比提高30倍或以上,所述抗体重链恒定区的 I/A比值等于或高于1;更优选地,所述抗体重链恒定区与人Fc γ IIB的亲合力和人IgG1 与人Fc γ IIB的亲合力相比提高60倍或以上,所述抗体重链恒定区的I/A比值等于或高于 40;特别优选地,所述抗体重链恒定区与人Fc γ IIB的亲合力和人IgG1与人Fc γ IIB的亲合力相比提高90倍或以上,所述抗体重链恒定区的I/A比值等于或高于100。

[0014] 根据本发明实施例的重链恒定区具有较高的抑制型Fc受体的亲合力,可以显著增强激动型抗体或者激动型分子(例如激动型融合蛋白)与抑制性Fc受体的交联,从而提高所述激动型抗体或者激动型分子的激动活性;同时还具有较低激活型Fc受体的亲合力,可以降低通过激活型受体结合而介导的ADCC等细胞毒性。基于本发明实施例的重链恒定区可以开发具有更优活性的激动型抗体或者激动型分子。

[0015] 本发明另一方面提供一种融合蛋白,包含上述的重链恒定区以及位于所述重链恒定区 N端或C端的抗原结合模块。

[0016] 较佳地,所述抗原结合模块选自于抗体的抗原结合片段、adnectin、纳米抗体(nanobody)、微型抗体、亲和体(affibodies)、affilin、受体的靶结合区、细胞粘附分子、配体、酶、细胞因子或趋化因子中的任意一种;更优选地,所述抗原结合模块为纳米抗体。

[0017] 纳米抗体为来源于羊驼的抗体的重链可变区,该可变区与本发明重链恒定区融合,可以构建具有完整骆驼抗体结构(由两条重链构成)的嵌合抗体分子,这种嵌合抗体分子可以同时具有纳米抗体高亲合力、高特异性以及本发明重链可变区增强激动活性的特点,具有非常好的开发前景。

[0018] 在另一个优选的本发明抗体的实施例中,所述抗原结合模块为配体,所述配体为免疫共刺激分子,所述免疫共刺激分子选自于CD80、CD86、ICOSL、OX40L、CD137L、CD40L、CD30L、CD27L、CD244、CD150、CD48、CD84、CD319、Ly118或者CD229中的任意一种。这些融合蛋白可以用作抗癌药物。

[0019] 在又一个优选的本发明融合蛋白的实施例中,所述抗原结合模块所靶向的抗原选自于CD40、DR5、OX40、CD137、CD27、CD30、GITR、HVEM、TACI、DR4或FAS中的任意一种。

[0020] 根据本发明的靶向CD40的激动型分子(融合蛋白)可用于做疫苗佐剂。该疫苗佐剂可以和疫苗(例如OVA)联用,形成疫苗组合物,可用于预防和/或治疗肿瘤;也可用于预防和/或治疗感染。

[0021] 在又一个优选的本发明融合蛋白的实施例中,所述抗原结合模块所靶向的抗原选自于PD-1、CTLA-4、VISTA、TIM-3、BTLA或LAG-3中的任意一种。当用于这些靶点时,所述融合蛋白可用于制备减轻炎症和/或减轻自身免疫症状的药物,例如可用于制备治疗哮喘的药物。

[0022] 在又一个优选的本发明融合蛋白的实施例中,所述抗原结合模块为配体,所述配体为免疫抑制性配体,所述免疫抑制性配体选自于PD-L1,PD-L2,B7-H3,B7-H4,CD47,VISTA,HVEM或GAL9中的任意一种。当用于这些靶点时,所述抗体可用于制备减轻炎症和/或减轻自身免疫症状的药物,例如可用于制备治疗哮喘的药物。

[0023] 本发明另一方面还提供一种抗体,包括本发明上述的重链恒定区。

[0024] 优选地,所述抗体为激动型抗体。

[0025] 优选地,所述抗体为IgG。

[0026] 优选地,所述抗体为人抗体或者是人源化抗体或者是嵌合抗体。

[0027] 在另一个优选的本发明抗体的实施例中,所述抗体所靶向的抗原选自于CD40、DR5、OX40、CD137、CD27、CD30、GITR、HVEM、TACI、DR4、FAS中的任意一种。

[0028] 更进一步地,所述抗体所靶向的抗原为CD40。

[0029] 更优选地,所述抗体的重链具有SEQ ID NO:27所示的序列,所述抗体的轻链具有SEQ ID NO:47所示的序列;或者所述抗体的重链具有SEQ ID NO:43所示的序列,所述抗体的轻链具有SEQ ID NO:47所示的序列。

[0030] 根据本发明的靶向CD40的激动型抗体可用作疫苗佐剂。该疫苗佐剂可以和疫苗(例如OVA)联用,形成疫苗组合物,可用于预防和/或治疗肿瘤,也可用于预防和/或治疗感染。

[0031] 在又一个优选的本发明抗体的实施例中,所述抗体所靶向的抗原为免疫抑制性受体分子,并且所述免疫抑制性受体分子选自于PD-1、CTLA-4、VISTA、TIM-3、BTLA、LAG-3中的任意一种。当用于这些靶点时,所述抗体可用于制备减轻炎症和/或减轻自身免疫症状的药物,例如可用于制备治疗哮喘的药物。

[0032] 本发明还提供本发明融合蛋白或者抗体在制备抗癌药物中的应用。

[0033] 优选地,是用于制备抗结肠癌药物或者抗纤维肉瘤药物。

[0034] 本发明还提供一种药物组合物,包含本发明融合蛋白或者抗体以及药学上可接受的药物载体。该药物组合物可用于制备治疗癌症的药物。优选地,是用于制备抗结肠癌药物或者抗纤维肉瘤药物。

[0035] 本发明还提供一种增强人体内源性免疫应答的方法,包括向人体施用治疗有效剂量的本发明融合蛋白或者抗体。

[0036] 本发明还提供一种免疫治疗方法,包括向人体施用治疗有效剂量的本发明融合蛋白或者抗体。

[0037] 本发明的有益效果是：本发明提供的重链恒定区序列能够显著增强激动型抗体或分子（包含重链恒定区序列的融合蛋白）的活性，与已经报道的同类分子相比具有更好的增强活性的效果；并且具有本发明重链恒定区序列的激动型抗体或融合蛋白具有更优的活性的同时还具有更宽的有效剂量范围，以及更好的安全性，具有显著的市场价值。

附图说明

[0038] 图1是抗体的基本结构示意图。

[0039] 图2是重链恒定区的序列比对图，显示不同人IgG亚型（IgG1、IgG2、IgG3和IgG4）的重链恒定区的结构。

[0040] 图3是抗原结合活性测试，显示根据本发明激动型抗鼠CD40和抗人CD40抗体的实施例能够分别特异结合小鼠和人类CD40抗原。抗CD40抗体与CD40抗原的结合由ELISA 分析，显示的是梯度稀释的各种抗体结合包被的小鼠CD40 (A) 或人类CD40 (B) 之后被抗人IgG检测到的ELISA信号 (A650)。

[0041] 图4是各IgG亚型在OVA特异CD8阳性T细胞扩增模型上的活性测试，显示激动型抗鼠CD40抗体的体内活性特异依赖于抑制型Fc γ 受体Fc γ RIIB。图示小鼠首先接受OVA特异CD8阳性T细胞（OT-I T细胞）过继输送，1天后用模式抗原OVA（以DEC-OVA的形式，OVA和抗DEC205抗体的融合蛋白，是一种有效输送OVA抗原的手段）和对照（Ct1 IgG）或者具有图示抗体恒定区的抗CD40抗体免疫小鼠，6天后通过流式技术分析脾脏中OT-I T细胞的扩增情况。OT-I T细胞的扩增程度反映激动型抗鼠CD40抗体促进 OVA模式抗原特异CD8阳性T细胞在OVA免疫的小鼠中的活化与扩增的活性。实验所用抗鼠CD40抗体剂量为30 μ g/小鼠。(A) 激动型抗CD40抗体的活性需要Fc γ 受体的参与和相互作用；(B) 与Fc γ 受体没有结合能力的人类IgG2 (G2-NA) 抗体没有免疫激活活性；(C) 激动型抗CD40抗体在不表达抑制型Fc γ 受体的小鼠 (R2-/-) 中完全没有活性，而在人源化抑制型Fc γ 受体的小鼠 (R2-/-hR2BTg) 中抑制型Fc γ 受体能单独驱动免疫激活活性。

[0042] 图5是小鼠脾细胞体外刺激实验，显示人类激动型抗CD40抗体的体外活性依赖于抑制型 Fc γ 受体。B细胞激活活性分析显示激动型抗人CD40抗体的体内活性依赖于人抑制型Fc γ 受体体内活性的驱动。从具有图示基因型的小鼠 (hCD40^{Tg}/hFCGR^{Tg}；同时表达人CD40和Fc γ Rs；hCD40^{Tg}/hR2B-/-；表达人CD40和人除Fc γ RIIB之外的Fc γ 受体) 分离脾脏细胞，在含有图示对照或抗人CD40抗体的培养基中培养48小时，然后通过流式技术分析 B细胞活化标识分子CD80、CD86的表达水平，CD80和CD86表达水平的上升程度反映抗CD40抗体的活性。2B6是人抑制性Fc γ 受体Fc γ RIIB特异的阻断抗体。

[0043] 图6。是根据本发明实施例的重链恒定区实施例的ELISA分析试验，显示不同重链恒定区（包括JAC3和JAC4）与人Fc γ 受体（Fc γ RI、Fc γ RIIA-R131以及Fc γ RIIB）的结合特点不同。测试方法为ELISA，用图示的重组抗人CD40抗体包被，检测生物素标记的如图所示人Fc γ 受体分子与包被的抗体的结合。

[0044] 图7是OVA特异CD8阳性T细胞扩增模型上的活性测试，显示含有JAC1序列的抗CD40抗体优于人IgG2抗CD40抗体的活性。分析方法同图4，但是使用的小鼠分别为hFCGR^{Tg}小鼠 (A) 和hCD40^{Tg}/hFCGR^{Tg}小鼠 (B)，抗CD40抗体剂量为10 μ g/小鼠。显示的是 OT-I T细胞的数量，反映抗CD40抗体诱导OT-I T细胞活化与扩增的活性。

[0045] 图8显示包含JAC3 (anti-hCD40-hIgG2-SELF) 和JAC4 (anti-hCD40-hIgG2-HDPG) 的抗人CD40抗体较hIgG2有更强的激动活性。图示的抗人CD40抗体激活B细胞的活性分别在hCD40^{Tg}hFCGR^{Tg}脾脏细胞 (A) 和PMBC细胞 (B) 中进行了检测。B细胞激活活性分析显示anti-hCD40-hIgG2-SELF、anti-hCD40-hIgG2-HDPG较人hIgG2更能支持激动型抗CD40抗体活性。图示的抗人CD40抗体激活B细胞的活性分别在hCD40^{Tg}hFCGR^{Tg}脾脏细胞 (A) 和PMBC细胞 (B) 中进行了检测。用含有图示梯度稀释浓度的对照或者激动型抗人CD40抗体的培养液培养细胞48小时,然后用流式技术分析小鼠B细胞活化标识分子CD86表达水平 (A) 或者人B细胞活化标识分子CD54的表达水平。这些分子表达水平的上升程度反映抗CD40抗体的活性。

[0046] 图9显示与hIgG3相比,hIgG2的CH1-绞链区区域能给予激动型抗CD40抗体更强的体内免疫激活活性。方法如图4和图7,在hFCGR^{Tg}小鼠中用OVA疫苗模型分别分析了图示不同抗鼠CD40抗体的活性,OT-I T细胞的扩增程度反映抗CD40抗体的活性。抗体剂量为10μg/小鼠。(A) 4种hIgG亚型中,hIgG2亚型表出很强的免疫激活活性,而其余 hIgG亚型,即hIgG1,hIgG3和hIgG4基本没有活性。(B) 与对照组相比,hIgG2具有明显的活性,而用hIgG3的CH1-绞链区替换hIgG2的CH1-绞链区后,变异体hIgG2 (H3) 就基本没有活性。

[0047] 图10显示人IgG2的CH1-绞链区较IgG1和IgG3的CH1-绞链区更能支持抗CD40抗体在OVA疫苗模型中的免疫激动活性。方法如图4和图7,在hFCGR^{Tg}小鼠中用OVA疫苗模型分别分析了图示不同抗鼠CD40抗体的活性,OT-I T细胞的扩增程度 (A) 和 CD8:CD4比例 (B) 反映抗CD40抗体的活性。抗体剂量为10μg/小鼠。

[0048] 图11显示包含JAC1的抗鼠CD40抗体 (Anti-mCD40-hIgG2 (V11)) 在OVA疫苗模型中具有优于人IgG2 (Anti-mCD40-hIgG2) 和包含V11 (H1) 的抗鼠CD40抗体 (Anti-mCD40-hIgG1 (V11)) 的活性。方法如图4和图7,在hFCGR^{Tg}小鼠中用OVA疫苗模型分别分析了图示不同抗鼠CD40抗体的活性,OT-I T细胞的扩增程度 (A) 和 CD8:CD4比例 (B) 反映抗CD40抗体的活性。抗体剂量为10μg/小鼠。

[0049] 图12显示在PBMC体外刺激实验中包含JAC1的抗人CD40抗体 (Anti-hCD40-hIgG2 (V11)) 具有优于人IgG2 (Anti-hCD40-hIgG2) 和包含V11 (H1) 的抗人CD40抗体 (Anti-hCD40-hIgG1 (V11)) 的活性。

[0050] 图13MC38肿瘤生长曲线,显示包含JAC1的抗鼠CD40抗体 (Anti-mCD40-hIgG2 (V11)) 在MC38肿瘤模型中具有优于人IgG2 (Anti-mCD40-hIgG2) 和包含V11 (H1) 的抗鼠CD40抗体 (Anti-mCD40-hIgG1 (V11)) 的活性。hFCGR^{Tg}小鼠在第0天皮下种植MC38肿瘤细胞,成瘤后于第7和10天两次经腹腔注射给予图示抗体进行治疗,剂量为每只小鼠每次31.6μg,然后测量肿瘤的体积 (Tumor Volume) 的变化 (每组7只小鼠)。

[0051] 图14为图13所示试验结果的另外一种表达形式。

[0052] 图15M04肿瘤生长曲线,显示包含JAC1的抗鼠CD40抗体 (Anti-mCD40-hIgG2 (V11)) 在M04小鼠纤维肉瘤模型具有优于人IgG2 (Anti-mCD40-hIgG2) 和包含V11 (H1) 的抗鼠CD40抗体 (Anti-mCD40-hIgG1 (V11)) 的活性。hFCGR^{Tg}小鼠在第0天皮下种植M04 肿瘤细胞,成瘤后于第7经腹腔注射给予图示抗体和模式抗原OVA (以OVA和抗DEC205 抗体的融合蛋白的形式) 进行治疗,剂量为每只小鼠31.6μg抗体和2μg OVA模式抗原,然后测量肿瘤的体积。

[0053] 图16MC38肿瘤生长曲线,显示激动型抗鼠CD40抗体在IgG Fc受体敲除小鼠 (FcγR^{-/-}) 中没有抗肿瘤活性。

[0054] 图17显示低剂量包含JAC1的抗鼠CD40抗体(Anti-mCD40-hIgG2(V11))在OVA疫苗模型中具有活性。方法如图4和图7,在hFCGR^{Tg}小鼠中用OVA疫苗模型分别分析了图示不同剂量对照和JAC1抗鼠CD40抗体的活性,OT-I T细胞的扩增程度反映抗CD40 抗体的活性。

[0055] 图18显示包含JAC4的抗鼠CD40抗体在OVA疫苗模型中具有强的激动活性。方法如图 4和图7,在hFCGR^{Tg}小鼠中用OVA疫苗模型分别分析了图示不同抗鼠CD40抗体的活性,OT-I T细胞的扩增程度反映抗CD40抗体的活性。

[0056] 图19显示包含JAC1的抗DR5抗体具有更强促凋亡能力。支持抗DR5抗体活性的能力优于人IgG2,并依赖于人抑制性Fc γ 受体。对照和不同抗鼠DR5抗体分别在不存在和存在图示基因型小鼠脾脏细胞(Fc γ R^{-/-}或hFCGR^{Tg})、以及存在或不存在人抑制性Fc γ 受体特异阻断抗体2B6的情况下处理MC38细胞,然后分析MC38细胞中Caspase-3的活化情况(Active caspase-3(%)),反映抗DR5抗体激活DR5下游细胞凋亡信号的活性)。

[0057] 图20显示提高抗体恒定区与激活型Fc γ 受体的结合能力(降低I/A比值)减弱激动型抗 CD40的活性。图中,变体anti-mCD40-hIgG1-SDIE和变体anti-mCD40-hIgG1-GASDALIE与激活型Fc γ 受体的结合能力更强,有更低的I/A比值,其体内免疫激活活性要小于拥有更高I/A比值的抗体anti-mCD40-G1(H2),表现为OT1细胞的比例和OT1细胞的绝对数,以及CD8⁺T细胞比例均显著下调,显示与激活型Fc γ 受体的结合能力对抗的体活性具有重要影响。

具体实施方式

[0058] 除非另有说明,否则本文中所使用的科学与技术术语应具有那些本领域普通技术人员通常理解的含义。此外,除非本文中另有要求,否则单数术语应包括复数,且复数术语应包括单数。通常,本文中所描述的细胞及组织培养、分子生物学、免疫学及蛋白质与核酸化学所涉及的命名法与其技术均是本领域已知且常用的。

[0059] 本发明的方法与技术通常依据本领域已知的传统方法进行,且说明于本说明书所摘录和讨论的多种一般性及较专业性参考书中,除非另有说明。参见例如:Sambrook等人的Molecular Cloning:A Laboratory Manual,第2版(Cold Spring Harbor Laboratory Press, Cold Spring Harbor,N.Y. (1989))及Ausubel等人的Current Protocols in Molecular Biology(Greene Publishing Associates(1992)),及Harlow与Lane的Antibodies:A Laboratory Manual(Cold Spring Harbor Laboratory Press,Cold Spring Harbor,N.Y. (1990)),其内容已以引用的方式并入本文中。酶反应与纯化技术是根据制造商的说明书进行,通常可依本领域已知的方法或依本文说明的方法进行。与本文中描述的生物学、药理学、及医学与医药化学相关的命名法,及实验方法与技术是本领域已知且常用的。化学合成法、化学分析法、医药制法、调配法与传送法,及患者的治疗法均采用标准技术。

[0060] 除非另有说明,否则下列术语具有如下定义:

[0061] 术语“抗体”(“mAb”)或“单抗”,是指具有单一分子组成的抗体分子(即一级序列基本上相同、并且对特定表位显示单一的结合特异性和亲和性的抗体分子)的制备物。抗体可以通过杂交瘤、重组、转基因或本领域技术人员已知的其它技术制造。

[0062] “抗体”包括但不限于免疫球蛋白(Ig)。按理化性质和生物学功能,抗体可将其分为 IgM、IgG、IgA、IgE、IgD五类。人类IgG包含IgG1,IgG2,IgG3和IgG4四个亚类(Vidarsson

G, Dekkers G and Rispen T (2014) IgG subclasses and allotypes: from structure to effector functions. *Front. Immunol.* 5:520。本发明中hIgG1、hIgG2、hIgG3和hIgG4分别表示人的IgG1、IgG2、IgG3和IgG4。

[0063] “抗体”特异性结合抗原,并且至少包括通过二硫键相互连接的两个重链(H)和两个轻链(L)。每个重链包含重链可变区(本文缩写为VH)和重链恒定区(本文缩写为CH);每个轻链包含轻链可变区(VL)和轻链恒定区(CL)。抗体“重链恒定区”包含CH1、CH2和CH3三个结构域以及位于CH1结构域与CH2结构域之间的绞链区(Hinge)。附图1显示了IgG抗体的基本结构的示意图。

[0064] Kabat等收集了重链和轻链可变区的许多一级序列。他们基于序列保守程度,将各个一级序列分为CDR和框架,并制作了他们的列表(参见SEQUENCES OF IMMUNOLOGICAL INTEREST, 5th Edition, NIH publication, No. 91-3242, E.A. Kabat Et Al., 全部引入作为参考)。IMGT数据库整理了人IgG各结构域的EU指数 (http://www.imgt.org/IMGTScientificChart/Numbering/Hu_IGHGnber.html)。在IgG抗体背景中,重链恒定区的CH1结构域指依照Kabat的EU指数进行编号的位点118-215;重链恒定区的CH2结构域指依照Kabat的EU指数进行编号的位点231-340;重链恒定区的CH3结构域指依照Kabat的EU指数进行编号的位点341-447;重链恒定区的绞链区(Hinge)包含位点216(IgG1中的E216)-230(IgG1中的P230),其中依照Kabat等的EU指数进行编号。附图2显示了人的IgG1、IgG2、IgG3和IgG4的重链可变区的序列比对图。

[0065] 每条轻链包含“轻链可变区”(本文缩写为VL)和“轻链恒定区”。轻链恒定区由一个结构域CL组成。VH和VL区可以进一步细分为高变性的区域,称为互补决定区(CDR),它们之间散在着较为保守的称作框架区(FR)的区域。每个VH和VL由三个CDR和四个FR组成,从氨基端向羧基端按以下顺序排列:FR1、CDR1、FR2、CDR2、FR3、CDR3、FR4。重链和轻链的可变区包含与抗原相互作用的结合结构域。

[0066] “Fc区”(可结晶片段区域)或“Fc结构域”或“Fc”是指抗体重链的C-末端区域,其介导免疫球蛋白与宿主组织或因子的结合,包括与位于免疫系统的各种细胞(例如,效应细胞)上的Fc受体的结合,或者与经典补系统的第一组分(C1q)的结合。在IgG、IgA和IgD抗体同种型中,Fc区由来自抗体两条重链的CH2结构域和CH3结构域的两个相同的蛋白片段构成;IgM和IgE的Fc区在每个多肽链中包含三个重链恒定结构域(CH结构域2-4)。虽然免疫球蛋白重链的Fc区的边界可以变化,但是人IgG重链Fc区通常定义为从重链位置C226或P230的氨基酸残基到羧基端的序列段,其中该编号是根据EU索引,如在Kabat中一样。如本文所使用的,Fc区可以是天然序列Fc或变体Fc。

[0067] “Fc受体”或“FcR”是结合免疫球蛋白Fc区的受体。结合IgG抗体的FcR包括Fc γ R家族的受体,包括这些受体的等位基因变体和可变剪接形式。人Fc γ 受体家族包括几个成员:Fc γ RI(CD64)、Fc γ RIIA(CD32a)、Fc γ RIIB(CD32b)、Fc γ RIIIA(CD16a)、Fc γ RIIIB(CD16b)。其中,Fc γ RIIB是唯一的抑制性Fc γ 受体,其它均为活化型Fc γ 受体。大多数天然效应器细胞类型共表达一种或多种激活性Fc γ R和抑制性Fc γ RIIB,而自然杀伤(NK)细胞选择性地表达一种激活性Fc γ 受体(在小鼠中是Fc γ RIII,在人中是Fc γ RIIIA),但在小鼠和人类中不表达抑制性Fc γ RIIB。这些Fc γ 受体的分子结构不同,也因此对各IgG抗体亚类具有不同的亲和力。在这些Fc γ 受体中Fc γ RI是高亲和力受体,而Fc γ RIIA、Fc γ RIIB

和Fc γ RIIIA是低亲和力受体。基因多态性也存在于这些不同的Fc γ 受体中并影响它们的结合亲和力。最常见的基因多态性是Fc γ RIIA的R131/H131和Fc γ RIIIA 的V158/F158等多态形式。这些多态形式中有的被发现与多种疾病有相关性,一些特定治疗抗体的效果也依赖于病人是否带有特定的Fc γ 受体基因多态形式。

[0068] 本发明所述“序列”应当理解为包括与本发明序列实质相同的序列,所述“实质相同的序列”一词指当经过最适比对后,如:采用GAP或BESTFIT程序,使用默认缺口值测定两种肽序列之间具有至少70、75或80%序列同一性,优选为至少90或95%序列同一性,更优选为至少97、98或99%序列同一性。优选的,不相同的残基位置的差异最好为保守性氨基酸取代。“保守性氨基酸取代”指其中氨基酸残基被另一种具有化学性质(例如:电荷或亲水性)类似的侧链R基的氨基酸残基取代。通常,保守性氨基酸取代实质上不会改变蛋白质的功能性质。若其中两种或多种氨基酸序列的差异在于保守性取代时,可使序列同一性百分比或相似度上调,以校正取代作用的保守性质。参见例如:Pearson, Methods Mol.Biol.243:307-31 (1994)。具有相似化学性质的侧链的氨基酸基团实例包括:1) 脂肪族侧链:甘氨酸、丙氨酸、缬氨酸、亮氨酸、与异亮氨酸;2) 脂肪族-羟基侧链:丝氨酸与苏氨酸;3) 含酰胺侧链:天冬酰胺与谷氨酰胺;4) 芳香族侧链:苯丙氨酸、酪氨酸、与色氨酸;5) 碱性侧链:赖氨酸、精氨酸、与组氨酸;6) 酸性侧链:天冬氨酸与谷氨酸;及7) 含硫侧链:半胱氨酸与甲硫氨酸。优选保守性氨基酸取基组为:缬氨酸-亮氨酸-异亮氨酸、苯丙氨酸-酪氨酸、赖氨酸-精氨酸、丙氨酸-缬氨酸、谷氨酸-天冬氨酸、及天冬酰胺-谷氨酰胺。

[0069] 本发明抗体及其片段或者结构域的氨基酸的序号是以IgG EU编号 (http://www.imgt.org/IMGTScientificChart/Numbering/Hu_IGHGnber.html) 为依据的。

[0070] 抗体通常以高亲和力特异性结合其关联抗原,这表现为 10^{-5} - 10^{-11} M或更小的解离常数(KD)。任何大于大约 10^{-4} M⁻¹的KD通常被认为指示非特异性结合。如本文所使用的,与抗原“特异性结合”的抗体是指以高亲和力与抗原和基本上相同的抗原结合的抗体,这意味着KD为 10^{-7} M或更小,优选地 10^{-8} M或更小,甚至更优选地 5×10^{-9} M或更小,最优选地 10^{-8} - 10^{-10} M或更小,但是不会以高亲和力与无关抗原结合。如果抗原与给定抗原显示高度的序列同一性,例如,如果它与给定抗原的序列显示至少80%,至少90%,优选至少95%,更优选至少97%,或甚至更优选至少99%的序列同一性,则该抗原与给定抗原是“基本上相同的”。

[0071] 本发明所述的“对抑制性Fc γ 受体以及活化性Fc γ 受体的亲和力比值”或者“I/A比值”指蛋白分子对抑制性Fc受体的亲和力和对激活性Fc受体的亲和力的比值,在本发明中 I/A比值采用如下方式计算:I/A比值=[KD(hFc γ RIIA)或者KD(hFc γ RIIIA)中的较低的KD值]/KD(hFc γ RIIB);其中KD(hFc γ RIIA)为该分子对hFc γ RIIA受体(以变体hFc γ RIIA-R131为代表)的平衡解离常数,KD(hFc γ RIIIA)为该分子对hFc γ RIIIA 受体(以变体hFc γ RIIIA-F158为代表)的平衡解离常数,KD(hFc γ RIIB)为该分子对hFc γ RIIB受体的平衡解离常数;hFc γ RIIA是指人的Fc γ RIIA受体,hFc γ RIIIA是指人的Fc γ RIIIA受体,hFc γ RIIB是指人的Fc γ RIIB受体。所述的“亲和力”是指两个分子之间的结合能力的大小,通常地可以用KD来衡量。

[0072] “KD”指两个分子(例如:特定抗体和抗原或者配体和受体)相互作用的平衡解离常数。“抗原结合模块”是指以高亲和力特异性结合抗原的蛋白质,包括,但不仅限于,抗体的抗原结合片段、adnectin、纳米抗体(nanobody)、微型抗体、亲和体(affibodies)、affilin、

受体的靶结合区、细胞粘附分子、配体、酶、细胞因子、和趋化因子等。抗原结合模块所靶向的抗原包括,但不限于,TNF受体超家族成员、免疫抑制性受体分子等。

[0073] 术语“抗体的抗原结合部分”指负责抗原结合的抗体的氨基酸残基。抗体的抗原结合部分包含来自“互补决定区”或“CDR”的氨基酸残基。“构架”或“FR”区是非如本文中定义的高变区残基的这些可变区区域。因此,抗体的轻链和重链可变结构域从N末端到C末端包含区域FR1、CDR1、FR2、CDR2、FR3、CDR3和FR4。特别地,重链的CDR3是最有助于抗原结合的和定义抗体性能的区域。CDR和FR根据Kabat等,SEQ ID NO:uences of Proteins of Immunological Interest,第5版,Public HealthService,National Institutes of Health,Bethesda,MD(1991)的标准定义和/或来自“高变环”的残基确定。

[0074] 本发明“抗体”包括例如天然存在的和非天然存在的抗体;单克隆和多克隆抗体;嵌合和人源化抗体;人或非人抗体;全合成抗体。

[0075] “人”抗体是指这样的抗体,其可变区具有来自人种系免疫球蛋白序列的框架区和CDR区。而且,如果抗体含有恒定区,则恒定区也来自人种系免疫球蛋白序列。本发明的人抗体可以包括不是由人种系免疫球蛋白序列编码的氨基酸残基(例如,通过体外随机或定点突变或者通过体内体细胞突变引入的突变)。然而,如本文所使用的,术语“人抗体”,不意图包括来自其它哺乳动物物种(如小鼠)的种系的CDR序列被嫁接到人框架序列上的抗体。术语“人”抗体和“完全人”抗体被同义使用。

[0076] “人源化”抗体是指其中非人抗体CDR结构域以外的一些、大部分或全部的氨基酸被来自人免疫球蛋白的相应氨基酸所替换的抗体。在人源化形式抗体的一个实施方案中,CDR结构域以外的一些、大部分或全部氨基酸被来自人免疫球蛋白的氨基酸代替,而一个或多个CDR区域内的一些、大部分或全部氨基酸都不变。允许对氨基酸进行小的添加、删除、插入、取代或修饰,只要它们不会消除抗体结合特定抗原的能力即可。“人源化”抗体保留与原始抗体相似的抗原特异性。

[0077] “嵌合抗体”是指可变区来自一个物种而恒定区来自另一个物种的抗体,例如可变区来自小鼠抗体而恒定区来自人抗体的抗体。

[0078] “激动型抗体”是与受体结合并激活受体的抗体。激动型抗体的功能实例包括,但不限于:1)抗DR5的激动型抗体与DR5结合并诱导表达DR5受体的细胞凋亡;2)抗CD40 的激动型抗体能够通过结合免疫细胞表面传递免疫激活信号的靶标分子并激活其控制的重要免疫激活信号通路,进而增强抗肿瘤免疫应答间接杀死肿瘤细胞。

[0079] 一些已经进入临床研究阶段的激动型抗体的实例如下表1。

[0080] 表1:已经进入临床研究阶段的激动型抗体。

[0081]	TNF 受体 家族	产品(开发单位)	抗体类型	适应症
	OX40	MEDI6469(Providence Health &	鼠源抗体	癌症 (实体瘤, 前列腺癌)

[0082]

	Services)		
CD27	CDX-1127(Celldex Therapeutics)	人抗体	多种癌症
CD40	Dacetuzumab/SGN-40(Genentech)	人源化抗体	癌症 (CLL, non-Hodgkin's 淋巴瘤, 多发性骨髓瘤)
	HCD122(Novartis)		多发性骨髓瘤
	ASKP1240(Astellas Pharma/Kyowa Hakko Kirin Company)		
	Chi Lob 7/4(Cancer Research UK)	嵌合抗体	癌症 (non-Hodgkin's 淋巴瘤)
	CP-870893(Pfizer)	人抗体	癌症(黑色素瘤, 胰腺癌)
	ADC-1013(Alligator Bioscience)	全人抗体	瘤;实体瘤
	RO7009789(Roche)		晚期/转移性实体瘤
	SEA-CD40(Seattle Genetics)		癌症
	APX005M(Apexigen)		癌症
CD30	SGN-30(Seattle Genetics)	嵌合抗体	癌症 (non-Hodgkin's 淋巴瘤)
	XmAb2513(Xencor)	人源化抗体	癌症 (non-Hodgkin's 淋巴瘤)
	MDX-1401(Bristol-Myers Squibb)	人抗体	癌症 (non-Hodgkin's 淋巴瘤)
4-1BB	BMS-663513(Bristol-Myers Squibb)	人抗体	Cancer (melanoma, solid tumour)
	PF-05082566(Pfizer/Kyowa Hakko Kirin Company)	人抗体	癌症 (non-Hodgkin's 淋巴瘤)
DR4	Mapatumumab/HGS-ETR1(Human Genome Sciences Inc/GSK)	人抗体	多种癌症
DR5	Conatumumab/AMG 655(Amgen)	人抗体	多种癌症
	Drozitumab/Apomab/PRO95780(Genentech)	人抗体	多种癌症
	Lexatumumab/HGS-ETR2(National Cancer Institute)	人抗体	癌症
OPG	Tigatuzumab/CS-1008/TRA-8(Ludwig Institute for Cancer Research/ Daiichi Sankyo Inc)	人源化抗体	多种癌症
Fn14	Enavatuzumab/PDL192(Abbott)	人源化抗体	癌症(实体瘤)
GITR	TRX518(GITR)	人源化抗体	癌症(黑色素瘤, 胰腺癌)
	MEDI1873(MedImmune)		晚期实体瘤

[0083] 上表所列的激动型抗体可以通过将重链恒定区替换为本发明的重链恒定区而获得更高的激动活性。或者本发明的激动型抗体可以采用上表所列的激动型抗体的抗原结合片段,以构成针对特定TNF受体超家族成员的活性增强的激动型抗体。

[0084] “免疫共刺激因子”是为免疫细胞活化提供第二活化信号的配体分子。T细胞除了MHC/抗原肽-T细胞受体(TCR)提供第一信号之外,活化还需要包括B7/CD28、ICOSL/ICOS、OX40L/OX40、4-1BBL/4-1BB等提供共刺激信号。B细胞活化也需要抗原/B细胞受体(BCR)之外由CD40L/CD40等提供的共刺激信号。这类信号通路中的配体分子就是免疫共刺激因子。

本发明优选的免疫共刺激因子的实例包括,但不限于,B7 (CD80、CD86)、ICOSL、OX40L/CD134、4-1BBL/CD137L、CD40L/CD154、CD30L/CD153、CD27L/CD70或者SLAM家族分子(CD244、CD150、CD48、CD84、CD319、Ly108、CD229、SLAMF8)等。

[0085] 本文的“肿瘤坏死因子受体超家族”或“TNF受体超家族”,是指可与TNF家族的细胞因子结合的受体多肽。一般而言,这些受体是在其胞外区具有一个或多个半胱氨酸丰富的重复序列的I型跨膜受体。TNF基因家族中细胞因子的实例包括:肿瘤坏死因子- α (TNF- α)、肿瘤坏死因子- β (TNF- β 或淋巴毒素)、CD30配体、CD27配体、CD40配体、OX-40配体、4-1BB配体、Apo-1配体(也称作Fas配体或CD95配体)、Apo-2配体(也称作TRAIL)、Apo-3配体(也称作TWEAK)、osteoprotegerin (OPG), APRIL、RANK配体(也称作 TRANCE),和TALL-1(也称作BlyS、BAFF或THANK)。TNF受体超家族中受体的实例包括:1型肿瘤坏死因子受体(TNFR1)、2型肿瘤坏死因子受体(TNFR2)、p75神经生长因子受体(NGFR)、B细胞表面抗原CD40、T细胞抗原OX-40、Apo-1受体(也称作Fas或 CD95)、Apo-3受体(也称作DR3、sw1-1、TRAMP和LARD)、称作“跨膜激活剂和CAML-相互作用子(interactor)”或“TACI”的受体、BCMA蛋白、DR4、DR5(或者,也称作Apo-2; TRAIL-R2, TR6, Tango-63, hAP08, TRICK2或KILLER)、DR6、DcR1(也称作TRID、LIT或TRAIL-R3)、DcR2(也称作TRAIL-R4或TRUNDD)、OPG、DcR3(也称作TR6或M68)、CAR1、HVEM(也称作ATAR或TR2)、GITR、ZTNFR-5、NTR-1、TNFL1、CD30、淋巴毒素 β 受体(LTBr)、4-1BB受体和TR9 (EP988, 371A1)。本发明优选的TNF受体超家族成员的实例包括,但不限于,CD40、DR5、OX40、CD137、CD27、CD30、GITR、HVEM、TACI、DR4或者FAS等。

[0086] “免疫抑制性受体”是一类跨膜糖蛋白,能够抑制或阻断免疫细胞内活化信号的传递,本发明的实施例中免疫抑制性受体分子包括,但不限于,PD-1、CTLA-4、VISTA、TIM-3、BTLA或者LAG-3等。

[0087] “免疫抑制性配体”免疫抑制性受体的配体,能够结合免疫抑制性受体并激活其下游抑制性信号,本发明的实施例中免疫抑制性配体分子包括,但不限于,PD-L1,PD-L2, B7-H3, B7-H4, VISTA, HVEM或GAL9中的任意一种。

[0088] “免疫应答”是指脊椎动物体内针对外来作用介质的生物学应答,该应答可保护生物体免于被这些作用介质或者由其造成的疾病的伤害。免疫应答是由免疫系统的细胞(例如, T淋巴细胞, B淋巴细胞, 自然杀伤NK)细胞, 巨噬细胞, 嗜酸性粒细胞, 肥大细胞, 树突细胞或嗜中性粒细胞)和由这些细胞的任一种或肝脏产生的可溶性大分子(包括抗体, 细胞因子和补体)的作用介导的,其导致脊椎动物机体入侵病原体、细胞或被病原体感染的组织、癌细胞或其它异常细胞,或者,在自身免疫性或病理性炎症中,针对正常的人细胞或组织的选择性靶向、结合、损害、破坏,和/或消除。

[0089] “免疫疗法”是指用包括诱导、强化、抑制或者修饰免疫应答的方法对患有疾病、具有发生疾病风险、或者疾病复发的受试者进行治疗。

[0090] “增强内源性免疫应答”意思是强化受试者体内现有的免疫应答的有效性或强度。此类效率和潜力的强化可以通过,例如,克服抑制内源性宿主免疫应答的机制,或者通过刺激强化内源性宿主免疫应答的机制来实现。

[0091] 药物或治疗剂(例如本发明融合蛋白或者抗体)的“治疗有效量”或“治疗有效剂量”是药物的任何如下所述的量,当单独使用或与另一种治疗剂组合使用该量的药物时,可促进疾病消退,疾病消退表现为疾病症状的严重度降低、无疾病症状期的频率和持续时间

增加、或者防止由患病导致的障碍或失能。药物的治疗有效量或剂量包括“预防有效量”或“预防有效剂量”，“预防有效量”或“预防有效剂量”是药物的任何如下所述的量，当将该量的药物单独施用或者与另一种治疗剂组合施用于具有发生疾病的风险或者遭受疾病复发的受试者时，可抑制疾病的发生或复发。治疗剂促进疾病消退或抑制疾病发展或复发的能力可以用技术人员已知的各种方法进行评估，例如在人类受试者的临床试验中，在可预测在人类中的效力的动物模型系统中，或者通过在体外测定系统中测定试剂的活性。

[0092] 作为举例，抗癌剂(治疗癌症的药物组合物)促进受试者体内的肿瘤消退。在优选的实施方案中，治疗有效量的药物促进癌细胞消退乃至消除癌症。“促进癌症消退”意思是单独施用或与抗肿瘤剂(anti-neoplastic agent)组合施用治疗有效量的药物导致肿瘤生长减少或大小减小、肿瘤坏死、至少一种疾病症状的严重程度降低，无疾病症状期的频率和持续时间增加，防止由患病导致的障碍或失能，或者以其他方式改善患者的疾病症状。此外，术语关于治疗的“有效”和“有效性”包括药理学有效性和生理学安全性二者。药理学有效性是指药物促进患者癌症消退的能力。生理学安全性是指由于药物施用导致的细胞、器官和/或生物体水平上的毒性或者其它不良生理效果(不良作用)的水平。

[0093] 作为肿瘤治疗的例子，与未经治疗的受试者相比，治疗有效量或剂量的药物优选地可以抑制细胞生长或肿瘤生长达至少大约20%，更优选至少大约40%，甚至更优选至少大约60%，并且还更优选至少大约80%。在最优选的实施方案中，治疗有效量或剂量的药物可完全抑制细胞生长或肿瘤生长，即优选地抑制细胞生长或肿瘤生长达100%。化合物抑制肿瘤生长的能力可以在动物模型系统中进行评价，例如本文描述的MC38结肠腺癌小鼠肿瘤模型，它们能够预测在人肿瘤中的效力。作为替代，组合物的这一性质可以通过检验化合物抑制细胞生长的能力进行评估，这样的抑制可以通过技术人员已知的测定法在体外加以测量。在本发明的其他优选实施方案中，肿瘤消退可以观察到，并持续至少约20天，更优选至少约40天，或甚至更优选至少约60天的时间。

[0094] 对受试者的“治疗”或“疗法”是指以逆转、减轻、改善、抑制、减缓或防止与疾病有关的症状、并发症、病症或生化指标的出现、进展、发展、严重程度或复发为目的对受试者进行任何类型的干预或处理，或者向其施用活性剂。

[0095] 在本发明免疫治疗方法的优选实施方案中，受试者是人。

[0096] “癌症”是指一大类以异常细胞在体内不受控制地生长为特征的各种疾病。不受控制的细胞分裂和生长分裂和生长导致形成恶性肿瘤或细胞，它们侵入邻近组织，还可以通过淋巴系统或血流转移到身体的远端部分。在本发明中“治疗癌症”的另一种等同的描述是“治疗肿瘤”或者“抗癌”或者“抗肿瘤”

[0097] 如所述，本发明包含本发明重链恒定区序列的抗体或融合蛋白在治疗增殖性疾病如癌症中的用途。癌症是不受控制的妨碍身体器官和系统的正常功能的细胞生长的病症。患有癌症的受试者是具有客观可测量的存在于受试者机体内的癌症细胞的受试者。处于发展癌症的危险中的受试者是易于发展癌症(例如基于家族史、遗传倾向)的受试者、接触放射或其他引起癌症的试剂的受试者。从其原先部位迁移并且接种重要器官的癌症可通过受影响器官的功能退化最终导致受试者的死亡。造血性癌症(如白血病)能竞争得过受试者的正常的造血室，因此导致造血衰竭(以贫血症、血小板减少症和中性粒细胞减少症的形式)，最终导致死亡。

[0098] 本发明包含本发明重链恒定区序列的抗体或融合蛋白可用于治疗多种癌症或处于发展癌症的危险中的受试者。这种癌症的例子包括乳腺癌、前列腺癌、肺癌、卵巢癌、宫颈癌、皮肤癌、黑素瘤、结肠癌、胃癌、肝癌、食道癌、肾癌、咽喉癌、甲状腺癌、胰腺癌、睾丸癌、脑癌、骨癌和血癌(如白血病、慢性淋巴细胞性白血病)等。在一个实施例中,本发明的疫苗组合物可用于刺激免疫反应以通过抑制或延缓肿瘤的生长或减少肿瘤的大小来治疗肿瘤。肿瘤相关抗原也可以是主要(但不限于)由肿瘤细胞表达的抗原。

[0099] 其他的癌症包括但不限于基底细胞癌、胆道癌、膀胱癌、骨癌、脑和中枢神经系统(CNS)癌、宫颈癌、绒毛膜癌、结肠直肠癌、结缔组织癌、消化系统癌、子宫内膜癌、食道癌、眼癌、头颈癌、胃癌、上皮内肿瘤、肾癌、喉癌、肝癌、肺癌(小细胞、大细胞)、淋巴瘤(包括霍奇金淋巴瘤和非霍奇金淋巴瘤);黑素瘤;神经母细胞瘤;口腔癌(例如唇、舌头、口和咽);卵巢癌;胰腺癌;视网膜母细胞瘤;横纹肌肉瘤;直肠癌;呼吸系统癌;肉瘤;皮肤癌;胃癌;睾丸癌;甲状腺癌;子宫癌;泌尿系统癌;以及其他癌和肉瘤。

[0100] “疫苗”是指在单独施用或与佐剂的结合施用导致免疫上的抗原特异性效应的组合物。这包括赋予保护的预防性疫苗和治疗性疫苗。

[0101] 可用本发明的疫苗组合物治疗或预防的感染包括细菌、病毒、真菌或寄生虫。其他不常见类型的感染也包括立克次体(rickettsiae)、支原体(mycoplasmas)和病原体(agents)引起的羊瘙痒病(scrapie)、牛海绵样脑病(BSE)以及朊病毒病(例如库鲁病(kuru)和克雅病(Creutzfeldt-Jacobdisease))。感染人的细菌、病毒、真菌或寄生虫的例子是已知的。感染可以是急性的、亚急性的、慢性或潜在的,并且它可以是局部的或全身的。此外,感染可在宿主中感染性生物体的因子的生活周期的至少一个阶段期间主要是细胞内或细胞外的。

[0102] 可使用本发明的疫苗组合物和方法对抗的细菌感染包括革兰氏阴性和革兰氏阳性菌。革兰氏阳性菌的例子包括但不限于巴氏杆菌属(Pasteurella)物种、葡萄球菌属(Staphylococci)物种和链球菌属(Streptococci)物种。革兰氏阴性菌的例子包括但不限于大肠杆菌(Escherichiacoli)、假单胞菌属(Pseudomonas)物种和沙门氏菌属(Salmonella)物种。感染性细菌的特定例子包括但不限于幽门螺杆菌(Heliobacterpyloris)、布氏疏螺旋体(Borrelia burgdorferi)、嗜肺性军团病菌(Legionellapneumophila)、分枝杆菌属(Mycobacteria)物种(例如结核分枝杆菌(M.tuberculosis)、鸟分枝杆菌(M.avium)、胞内分枝杆菌(M.intracellulare)、堪萨斯分枝杆菌(M.kansaii)、戈登分枝杆菌(M.gordoniae))、金黄色葡萄球菌(Staphylococcus aureus)、淋病奈瑟氏球菌(Neisseria gonorrhoeae)、脑膜炎奈瑟氏球菌(Neisseriameningitidis)、单核细胞增生利斯特氏菌(Listeriamonocytogenes)、酿脓链球菌(Streptococcus pyogenes)(A组链球菌属)、无乳链球菌(Streptococcusagalactiae)(B组链球菌属)、链球菌属(草绿色组)、粪链球菌(Streptococcusfaecalis)、牛链球菌(streptococcusbovis)、链球菌属(Streptococcus)(aerobicspp.)、肺炎链球菌(Streptococcus pneumoniae)、病原性弯曲杆菌属(pathogenicCampylobacter)物种、肠球菌属(Enterococcus)物种、流感嗜血杆菌(Haemophilus influenzae)、炭疽芽孢杆菌(Bacillus anthracis)、白喉棒杆菌(Corynebacterium diphtheriae)、棒状杆菌属(Corynebacterium)物种、猪红斑丹毒丝菌(Erysipelothrix rhusiopathiae)、产气荚膜梭

菌 (*Clostridium perfringens*)、破伤风梭菌 (*Clostridium tetani*)、产气肠杆菌 (*Enterobacter aerogenes*)、肺炎克雷伯氏菌 (*Klebsiella pneumoniae*)、多杀巴斯德氏菌 (*Pasteurella multocida*)、类杆菌属 (*Bacteroides*) 物种、具核梭杆菌 (*Fusobacterium nucleatum*)、念珠状链杆菌 (*Streptobacillus moniliformis*)、梅毒密螺旋体 (*Treponema pallidum*)、极细密螺旋体 (*Treponema pertenuis*)、钩端螺旋体属 (*Leptospira*)、立克次氏体属 (*Rickettsia*) 和衣氏放线菌 (*Actinomyces israelii*)。

[0103] 引起人类感染的病毒的例子包括但不限于逆转录病毒科 (*Retroviridae*) (例如人类缺陷性病毒, 如 HIV-1 (也称为 HTLV-III)、HIV-II、LAC 或 IDLV-III/LAV 或 HIV-III 以及其他分离株, 如 HIV-LP)、小 RNA 病毒科 (*Picornaviridae*) (例如脊髓灰质炎病毒 (*poliovirus*)、甲型肝炎、肠道病毒 (*enteroviruses*)、人类柯萨奇病毒 (*human Coxsackieviruses*)、鼻病毒 (*rhinoviruses*)、艾柯病毒 (*echoviruses*))、杯状病毒科 (*Caliciviridae*) (例如导致胃肠炎的菌株)、披膜病毒科 (*Togaviridae*) (例如马脑炎病毒 (*equine encephalitis viruses*)、风疹病毒 (*rubellaviruses*))、黄病毒科 (*Flaviviridae*) (例如登革病毒 (*dengue viruses*)、脑炎病毒 (*encephalitis viruses*)、黄热病毒 (*yellow fever viruses*))、冠状病毒科 (*Coronaviridae*) (例如冠状病毒 (*coronaviruses*))、弹状病毒科 (*Rhabdoviridae*) (例如水泡性孔病毒 (*vesicular stomatitis viruses*)、狂犬病毒 (*rabies viruses*))、纤丝病毒科 (*Filoviridae*) (例如依波拉病毒 (*Ebolaviruses*))、副黏病毒科 (*Paramyxoviridae*) (例如副流感病毒 (*parainfluenza viruses*)、腮腺炎病毒 (*mumps viruses*)、麻疹病毒 (*measles virus*)、呼吸道合胞病毒 (*respiratory syncytial virus*))、正黏病毒科 (*Orthomyxoviridae*) (例如流感病毒 (*influenza viruses*))、布尼亚病毒科 (*Bunyaviridae*) (例如汉坦病毒 (*Hantaan viruses*)、布尼亚病毒 (*bunyaviruses*)、白蛉热病毒 (*phleboviruses*) 和 Nairo 病毒))、沙粒病毒科 (*Arenaviridae*) (出血热病毒 (*hemorrhagic fever viruses*))、呼肠孤病毒科 (*Reoviridae*) (例如呼肠病毒 (*reoviruses*))、环状病毒 (*orbiviruses*)、轮状病毒 (*rotaviruses*))、双 RNA 病毒科 (*Bimaviridae*)、嗜肝 DNA 病毒科 (*Hepadnaviridae*) (乙型肝炎病毒)、细小病毒科 (*Parvoviridae*) (细小病毒 (*parvoviruses*))、乳多空病毒科 (*Papovaviridae*) (乳头瘤病毒 (*papillomaviruses*)、多瘤病毒 (*polyomaviruses*))、腺病毒科 (*Adenoviridae*) (腺病毒 (*adenoviruses*))、疱疹病毒科 (*Herpeviridae*) (例如单纯疱疹病毒 (*herpes simplex virus*) (HSV) I 和 II、水痘带状疱疹病毒 (*varicella zoster virus*)、痘病毒 (*pox viruses*)) 和虹彩病毒科 (*Iridoviridae*) (例如非洲猪瘟病毒 (*African swine fever virus*)) 和未分类病毒 (例如海绵状脑病的致病因子 (*etiologic agents*)、丁型肝炎的因子、非甲型非乙型肝炎的因子 (1 类肠道传播; 2 类胃肠外传播如丙型肝炎); 诺沃克 (Norwalk) 及相关的病毒和星状病毒 (*astroviruses*))。

[0104] 真菌的例子包括曲霉菌属 (*Aspergillus*) 物种、粗球孢子菌 (*Coccidioides immitis*)、新型隐球菌 (*Cryptococcus neoformans*)、白色念珠菌 (*Candida albicans*) 及其他念珠菌属物种、皮炎芽生菌 (*Blastomyces dermatidis*)、荚膜组织胞浆菌 (*Histoplasma capsulatum*)、沙眼衣原体 (*Chlamydia trachomatis*)、诺卡氏菌属 (*Nocardia*) 物种和卡氏肺孢子虫 (*Pneumocystis carinii*)。

[0105] 寄生虫包括但不限于血源性和/或组织寄生虫, 如田鼠巴贝虫 (*Babesia microti*)、

分歧巴贝虫 (*Babesia divergens*)、溶组织内阿米巴 (*Entamoeba histolytica*)、蓝氏贾第虫 (*Giardia lamblia*)、热带利什曼原虫 (*Leishmania tropica*)、利什曼原虫属 (*Leishmania*) 物种、巴西利什曼原虫 (*Leishmania braziliensis*)、杜氏利什曼原虫 (*Leishmania donovani*)、恶性疟原虫 (*Plasmodium falciparum*)、三日疟原虫 (*Plasmodium malariae*)、卵形疟原虫 (*Plasmodium ovale*)、间日疟原虫 (*Plasmodium vivax*)、刚地弓形虫 (*Toxoplasma gondii*)、冈比亚锥虫 (*Trypanosoma gambiense*)、罗德西亚锥虫 (*Trypanosoma rhodesiense*) (非洲睡眠病)、克氏锥虫 (*Trypanosoma cruzi*) (恰加斯病 (*Chagas' disease*)) 和刚地弓形虫 (*Toxoplasma gondii*)、扁虫 (flatworms) 和蛔虫 (roundworms)。

[0106] “药学上可接受的药物载体”包括生理上相容的任何及所有溶剂、分散介质、包衣、抗菌剂和抗真菌剂、等渗剂和吸收延迟剂等等。优选载体适于静脉内、肌肉、皮下、肠胃外、脊髓 (spinal) 或表皮给药 (例如通过注射或输注)。

[0107] 本发明的药物组合物/疫苗组合物可通过本领域公知的多种方法给药。正如技术人员将会理解的那样, 给药路径和/或方式将随期望的结果而变动。为通过某些给药路径给药本发明的化合物, 可能需要用防止化合物失活的材料对其进行包衣, 或化合物与之共给药。例如, 可以向受试者给药处于适宜载体例如脂质体或稀释剂中的化合物。可药用稀释剂包括盐溶液和水性缓冲溶液。

[0108] 可药用载体包括无菌水性溶液或分散液, 以及用于临时制备无菌注射液或分散液的无菌粉剂。此类介质和药剂用于药物活性物质的用途是本领域公知的。

[0109] 下面结合附图对本发明的较佳实施例进行详细阐述, 以使本发明的优点和特征能更易于被本领域技术人员理解, 从而对本发明的保护范围做出更为清楚明确的界定。

[0110] 材料与方法

[0111] 本发明具体的实施例中所采用的部分材料和试验方法列举如下。本文列举的材料和方法中未尽的事项以及本文所涉及的其他材料和方法均属于现有技术中常规的技术手段, 本领域的技术人员可以根据现有技术而获得, 在此不做更多的描述。

[0112] 1、抗体

[0113] 在具体的实施例中, 抗鼠CD40和DR5抗体的重链可变区和轻链序列已经在以前的研究中获得 (Li F, Ravetch JV. 2011. Inhibitory Fcγ receptor engagement drives adjuvant and anti-tumor activities of agonistic CD40 antibodies. *Science* 333: 1030-4; Li F, Ravetch JV. 2012. Apoptotic and antitumor activity of death receptor antibodies require inhibitory Fcγ receptor engagement. *Proc Natl Acad Sci U S A* 109: 10966-71)。抗人CD40抗体重链可变区和轻链序列已经在US7338660中披露。

[0114] 本发明的人IgG的抗体重链恒定区序列 (包括人IgG1、IgG2、IgG3和IgG4的抗体重链恒定区) 已经在以前的研究中获得 (Li F, Ravetch JV. 2011. Inhibitory Fcγ receptor engagement drives adjuvant and anti-tumor activities of agonistic CD40 antibodies. *Science* 333: 1030-4; Li F, Ravetch JV. 2012. Apoptotic and antitumor activity of death receptor antibodies require inhibitory Fcγ receptor engagement. *Proc Natl Acad Sci U S A* 109: 10966-71), 没有的通过基因合成。本发明的抗体重链恒定区的变体是在上述人IgG的抗体重链恒定区序列的基础上通过

点突变等方法构建的。所用抗体均通过瞬时转染HEK 293T细胞表达,并通过protein G Sepharose 4 Fast Flow (GE Healthcare) 纯化上清获得。对照小鼠和人类IgG抗体从 Jackson ImmunoResearch Laboratory 购得。

[0115] 2、小鼠

[0116] Fc γ 受体缺陷鼠即Fc γ 受体 α 链缺陷型鼠 (Fc γ R^{-/-}), 和Fc γ 受体人源化小鼠 (Fc γ R^{-/-}hFCGR^{Tg}, 简称hFCGR^{Tg}) 都已经在文献中描述过 (Smith P, DiLillo DJ, Bournazos S, Li F, Ravetch JV. 2012. Mouse model recapitulating human Fc γ receptor structural and functional diversity. *Proc Natl Acad Sci U S A* 109:6181-6)。Fc γ II受体缺陷鼠R2^{-/-} (Fc γ R2b^{-/-}) 和Fc γ II B受体人源化小鼠R2^{-/-}hR2B^{Tg} (Fc γ R2b^{-/-}hFCGR2B^{Tg}) 已经在文献中描述过 (Li F, Ravetch JV. 2011. Inhibitory Fc γ receptor engagement drives adjuvant and anti-tumor activities of agonistic CD40 antibodies. *Science* 333:1030-4; Li F, Ravetch JV. 2012. Apoptotic and antitumor activity of death receptor antibodies require inhibitory Fc γ receptor engagement. *Proc Natl Acad Sci U S A* 109:10966-71)。表达人类CD40的转基因小鼠为表达人CD40的BAC转基因小鼠 (hCD40^{Tg})。hCD40⁺小鼠和hFCGR^{Tg}小鼠杂交可以获得CD40以及Fc γ 受体均人源化的小鼠 (hCD40^{Tg} hFCGR^{Tg}) , 同时也可以获得表达hCD40⁺小鼠和除了hFCGR2B^{Tg}之外的其它hFCGR^{Tg}的小鼠 (hCD40^{Tg} hR2B^{-/-})。所有实验鼠养殖在上海交通大学医学院动物科学实验中心, 所有实验的开展均符合我国法律和各级规章并获得上海交通大学医学院动物护理和使用委员会的许可。

[0117] 3、酶联免疫吸附实验 (ELISA) 测定抗CD40抗体的CD40结合能力分析

[0118] 分析抗人CD40抗体时, 用重组人CD40蛋白 (近岸蛋白质科技有限公司) 包被酶联板, 常温过夜, 1% BSA室温封闭2h后用PBST (含0.05%吐温20的PBS) 洗三次, 每孔加入100 μ L梯度稀释的人激动型CD40抗体, 室温孵育1h后用PBST洗四次, 加入浓度为100ng/ml生物素标记的抗人Ig κ 轻链的二抗, 室温孵育1h后PBST洗4次, 加入适宜浓度的SAV-HRP, 室温孵育1h后加入显色底物, 5分钟后于650nm处测吸光值。

[0119] 分析抗鼠CD40抗体时, 使用重组鼠CD40蛋白 (近岸蛋白质科技有限公司) 包被, HRP标记的山羊抗人IgG-Fc抗体作为二抗进行检测, 其他实验方法同上。

[0120] 4、OVA特异CD8阳性T细胞扩增模型

[0121] 年龄2-4月的小鼠通过尾静脉注射过继转移 2×10^6 个重悬于200 μ L PBS中的OT-I脾细胞 (CD45.1⁺) , 之后通过腹腔注射进行免疫。对照组注射2 μ g的DEC-OVA蛋白和对照抗体 (Li F, Ravetch JV. 2011. Inhibitory Fc γ receptor engagement drives adjuvant and anti-tumor activities of agonistic CD40 antibodies. *Science* 333:1030-4), 其余组同时注射2 μ g的DEC-OVA蛋白和抗CD40抗体。6天以后, 取小鼠脾脏细胞并用ACK裂解液裂解红细胞后重悬于FACS缓冲液 (PBS加0.5% FBS, 2mM EDTA和0.1% Na₃N) 中制备单个脾细胞悬液; 然后通过流式染色分析OVA特异性CD8⁺T细胞 (OT-1) 的扩增。用到的抗体包括荧光标记的抗小鼠CD45.1, CD4, CD8, 和TCR-V α 2抗体。流式分析用DAPI染色排除死细胞, CD45.1⁺/CD8⁺/TCR-V α 2⁺被鉴定为OT-1/CD8⁺T细胞。

[0122] 5、小鼠脾细胞体外刺激实验

[0123] 取小鼠脾脏细胞并用ACK裂解液裂解红细胞后重悬于脾细胞培养液 (RPMI+10%

FBS+1%P/S双抗)中,每孔 2×10^5 细胞铺板,用梯度稀释的激动型抗CD40抗体进行处理,37℃培养48小时,然后用FACS分析小鼠B细胞表面活化标识分子(CD80、CD86)的表达情况。活化标识分子的表达情况反映为平均荧光强度(MFI),与激动型抗CD40抗体激活B细胞的活性正相关。

[0124] 6、PBMC体外刺激实验

[0125] Ficoll分离获得健康人外周血单个核细胞(PBMC),每孔 2×10^5 细胞铺板,用梯度稀释的激动型抗CD40抗体进行处理,37度培养48小时,然后用FACS分析PBMC中B细胞表面活化标识分子(CD54、CD80、CD86、HLA-DR)的表达情况,活化标识分子的表达情况反映为平均荧光强度(MFI),与激动型抗CD40抗体激活B细胞的活性正相关。

[0126] 7、ELISA分析抗体与FcγR的结合特性

[0127] 取适当浓度的100μL的抗体加入酶联板中包被过夜,弃上清,用含1%BSA的PBS封闭2小时,PBST(含0.05%吐温20的PBS)洗涤,然后加入适当浓度的biotin标签的FcγR胞外结构域蛋白(北京义翘神州生物技术有限公司)室温孵育1小时后弃掉上清,PBST洗涤。加入Streptavidin-HRP(BD Biosciences)室温孵育1小时检测biotin蛋白,去除上清,加入显色液显色20-40分钟后测定650nm的吸光值A650。

[0128] 8、表面等离子共振

[0129] 所有的表面等离子共振(SPR)分析实验所用的缓冲体系为:10mM Hepes(pH 7.4),150mM NaCl,3.4mM EDTA,0.005%表面活性剂P20,实验均在Biacore T100(GE医疗)SPR系统上进行,设定温度为25℃。在pH 4.5的条件下His标签的可溶性鼠FcγR胞外结构域蛋白(北京义翘神州生物技术有限公司)通过胺基偶联固定在CM5芯片,达到约2000的响应单位(response units,RUs)密度。两倍梯度稀释的具有适当浓度范围的抗体样品以30μL/min的速度注入流动相,结合3分钟后解离5分钟。每次分析循环结束后,以一定浓度的NaOH,50μL/min的流速注入传感器表面30秒对其进行再生。在Biacore T100分析软件(版本1.1,GE医疗)中扣除未固定通道的背景结合信号以后,利用1:1的结合动力学模式进行拟和计算出亲和常数KD值。

[0130] 9、MC38肿瘤模型

[0131] MC38是小鼠结肠癌细胞株,2到4个月年龄的hFCGR^{Tg}小鼠通过皮下注射接种 2×10^6 个MC38细胞,每隔3天使用游标卡尺测量肿瘤大小,并使用公式 $(L1^2 \times L2)/2$ 计算肿瘤体积,其中L1是肿瘤组织的最短直径,L2是最长直径。接种肿瘤细胞7天以后,根据肿瘤大小将小鼠进行随机分组(第0天),通过腹腔注射对照组小鼠给予31.6μg同型对照IgG,其余组给予31.6μg相应抗体。第3天时,给予与第0天相同的处理,即对照组小鼠给予同型对照IgG,其余组给予相应抗体。之后,继续测量肿瘤大小,计算肿瘤体积。

10、M04肿瘤模型

[0132] M04是小鼠纤维肉瘤细胞株,2到4个月年龄的hFCGR^{Tg}小鼠通过皮下注射接种 2×10^6 个M04细胞,每隔3天使用游标卡尺测量肿瘤大小,并使用公式 $(L1^2 \times L2)/2$ 计算肿瘤体积,其中L1是肿瘤组织的最长直径,L2是最短直径。接种肿瘤细胞7天以后,根据肿瘤大小将小鼠进行随机分组(第0天),通过腹腔注射对照组小鼠给予31.6μg同型对照IgG和2μg OVA抗原(以DEC205抗体和OVA融合蛋白的形式),其余组给予31.6μg相应抗体和2μg OVA抗原(以DEC205抗体和OVA融合蛋白的形式)。之后,继续测量肿瘤大小,计算肿瘤体积。

[0133] 11、抗DR5抗体的DR5结合能力分析

[0134] 为了分析不同抗DR5抗体对DR5的结合能力,MC38细胞用冰FACS缓冲液(PBS+0.5%FBS+2mM EDTA+0.1%NaN₃)重悬,加入3.16倍梯度稀释对照和抗DR5抗体,浓度范围2ng-20μg/mL,室温孵育15分钟后用冰FACS缓冲液洗两次;然后再用FITC标记的山羊抗人抗体(VECTOR FI-3080)进行流式染色,冰上避光孵育25分钟,FACS缓冲液洗两次,然后进行流式分析。抗体结合DR5的能力与FITC平均荧光强度(MFI)正相关,结果显示抗DR5抗体的DR5结合能力相当。

[0135] 12、抗DR5抗体促凋亡活性分析

[0136] 为了分析抗DR5抗体的促凋亡活性,将MC38细胞铺在平底96孔板,培养过夜,弃掉培养液,每孔加入100μL新鲜培养液,分别含或不含10⁶个取自FcγR^{-/-}、hFCGR^{Tg}基因型(B6背景)鼠裂红脾细胞,同时每孔另加100μL新鲜培养液,含或不含1μg/mL 2B6 抗体的1μg/mL对照或抗DR5抗体,37℃孵育4小时。取出96孔板置冰上,轻轻吸弃上清,200μL冰PBS洗;100μL胰酶消化3-5分钟,等体积全培养液终止,收取细胞,4℃,400×g离心5分钟收集,然后用CD45抗体(clone:30-F11;Biolegend)进行表面分子流式染色,再进行激活caspase-3胞内染色(抗体clone C92-605;BD Biosciences),进行流式分析。MC38细胞依次用前散射角FSC和侧散射角SSC,以及CD45阴性圈出,分析激活 caspase-3(激活型半胱天冬酶)的表达。促凋亡能力和激活caspase-3染色的平均荧光强度(MFI)正相关。

[0137] 实施例1.本发明重链恒定区以及包含本发明重链恒定区序列的激动型抗体

[0138] 通过上文所提到的基因克隆和表达纯化技术,本发明构建了一系列不同的重链恒定区的具体的实施例,并基于这些重链恒定区构建了抗人CD40或者抗鼠CD40的抗体以及抗鼠DR5的抗体。

[0139] 概括地讲,在本发明具体的实施例中,重链恒定区被分成两部分进行研究优化,包括 CH1-绞链区部分以及CH2-CH3结构域部分。所述CH1-绞链区部分意指由抗体CH1结构域和绞链区构成的区段,CH2-CH3结构域部分意指由抗体CH2结构域和CH3结构域构成的区段。在具体的实施例中,CH1-绞链区采用了未经突变的hIgG1的CH1-绞链区(SEQ ID NO:1),或者hIgG2的CH1-绞链区(SEQ ID NO:2),或者hIgG3的CH1-绞链区(SEQ ID NO:3),或者hIgG4的CH1-绞链区(SEQ ID NO:4);CH2-CH3结构域采用了未经突变的hIgG1的CH2-CH3结构域(SEQ ID NO:5),或者hIgG2的CH2-CH3结构域(SEQ ID NO:6),或者hIgG3的CH2-CH3结构域(SEQ ID NO:7),或者hIgG4的CH2-CH3结构域(SEQ ID NO:8),或者是在hIgG CH2-CH3结构域的基础上进行了氨基酸突变的 CH2-CH3结构域,例如:带V11突变的CH2-CH3结构域(SEQ ID NO:9)是在hIgG1 的CH2-CH3结构域的基础上进行了G237D/P238D/H268D/P271G/A330R五个突变得到的 CH2-CH3结构域;带V9突变的CH2-CH3结构域(SEQ ID NO:10)是在hIgG1的CH2-CH3 结构域的基础上进行了G237D/P238D/P271G/A330R四个突变得到的CH2-CH3结构域。

[0140] 在本发明重链恒定区的实施例中,重链恒定区的序列是由相应的CH1-绞链区序列以及CH2-CH3结构域序列组合得到的。本发明重链恒定区的实施例的具体信息可以参见表2。

[0141] 需要说明的是,表2中所涉及的重链恒定区的实施例均构架于人的IgG上,hIgG1、hIgG2、hIgG3和hIgG4分别表示人的IgG1、IgG2、IgG3和IgG4。表2中部分序列带有突变,具体的突变列在了括号内,且具体突变氨基酸的序号是以IgG EU编号为依据的。

[0142] 下面具体举例说明表2所列的重链恒定区的结构。名称为G1的重链恒定区的CH1-绞链区的来源为hIgG1,CH2-CH3结构域的来源为hIgG1,由此表示G1的序列是由未经突变的hIgG1的CH1-绞链区的序列同未经突变的hIgG1CH2-CH3结构域的序列拼合而成的。名称为V11(H2)的重链恒定区(在本文中又称JAC1)的CH1-绞链区的来源为hIgG2,CH2-CH3结构域的来源为带有G237D/P238D/H268D/P271G/A330R突变的hIgG1,由此表示V11(H2)的序列(SEQ ID NO:11)是由未经突变的hIgG2的CH1-绞链区的序列同带有G237D/P238D/H268D/P271G/A330R突变的hIgG1CH2-CH3结构域的序列拼合而成的。其他的重链恒定区的实施例的序列均可根据表2以及本发明附属的序列表得出。

[0143] 表2:本发明重链恒定区的实施例。

[0144]

重链恒定区名称	CH1-绞链区的来源	CH2-CH3 结构域的来源 (CH2-CH3 结构域所携带的突变)	序列编号
G1	hIgG1	hIgG1	
G2	hIgG2	hIgG2	
G3	hIgG3	hIgG3	
G4	hIgG4	hIgG4	
V11(H1)	hIgG1	hIgG1(G237D/P238D/H268D/P271G/A330R)	
V9(H1)	hIgG1	hIgG1(G237D/P238D/P271G/A330R)	
V11(H2), 又称 JAC1	hIgG2	hIgG1(G237D/P238D/H268D/P271G/A330R)	SEQ ID NO:11
V9(H2), 又称 JAC2	hIgG2	hIgG1(G237D/P238D/P271G/A330R)	SEQ ID NO:12
V11(H3)	hIgG3	hIgG1(G237D/P238D/H268D/P271G/A330R)	
G3(H2)	hIgG2	hIgG3	
G2(H3)	hIgG3	hIgG2	
G1(H2)	hIgG2	hIgG1	
G1-NA	hIgG1	hIgG1(N297A)	
G2-NA	hIgG2	hIgG2(N297A)	
G2-SELF, 又称 JAC3	hIgG2	hIgG2(S267E/L328F)	SEQ ID NO:13
G2-SE	hIgG2	hIgG2(S267E)	
G2-LF	hIgG2	hIgG2(L328F)	
G2-HDPG, 又称 JAC4	hIgG2	hIgG2(H268D/P271G)	SEQ ID NO:14
G2-PG	hIgG2	hIgG2(P271G)	
G2-HD	hIgG2	hIgG2(H268D)	
G2-GDPDHDPG	hIgG2	hIgG2(G237D/P238D/H268D/P271G)	
G1-SELF	hIgG1	hIgG1(S267E/L328F)	

[0145]

G1-SDIE	hIgG1	hIgG1(S239D/I332E)	
G1-SE	hIgG1	hIgG1(S267E)	
G1-SDSE	hIgG1	hIgG1(S239D/S267E)	
G1-S236DSE	hIgG1	hIgG1(S236D/S267E)	
G1-GASDALIE	hIgG1	hIgG1(G236A/S239D/A330L/I332E)	
G2-GASDALIE	hIgG2	hIgG1(G236A/S239D/A330L/I332E)	
G2-SDIE	hIgG2	hIgG1(S239D/I332E)	

[0146] 本发明具体的实施例中所构建抗体均为人抗体或者嵌合抗体(全部抗体恒定区为人源的,抗人CD40抗体的CDR是人源的,抗鼠CD40和抗鼠DR5抗体的CDR是鼠源的),其中人抗人CD40或者人抗鼠CD40的抗体以及人抗鼠DR5的抗体均是基于相应的本发明的重链恒定区的,因而相应的编号主要是通过不同重链恒定区来区分的,本发明实施例中所涉及抗体的具体信息见表3。本发明实施例中对相同抗原的抗体具有相同的轻链序列以及相同的重链可变区序列,但重链恒定区的序列不同。例如:本发明实施例中人抗人 CD40的抗体(Anti-hCD40-hIgG)具有相同的轻链序列(SEQ ID NO:47)以及相同的重链可变区序列;实际上本发明抗人CD40抗体(Anti-hCD40-hIgG)的轻链序列、重链可变区序列与激动型抗体CP-870893的轻链序列、重链可变区序列相同,而CP-870893是最早由Pfizer开发的针对hCD40靶点的全人IgG2激动型抗体,用于实体瘤免疫治疗以及增强疫苗活性。本发明实施例中人抗鼠CD40的抗体(Anti-mCD40-hIgG)具有相同的轻链序列(SEQ ID NO:48)以及相同的重链可变区序列;本发明实施例中人抗鼠DR5的抗体(Anti-mDR5-hIgG)具有相同的轻链序列(SEQ ID NO:49)以及相同的重链可变区序列。

[0147] 需要说明的是本发明部分的抗体实施例实际上可以看作是运用不同抗体区段构建出来的融合蛋白,其在结构形式上保留了抗体的特征,但是具体的各个功能部分可能源自于不同的抗体IgG亚型,部分还带有氨基酸突变。因而可以理解的是,本发明实施例的重链恒定区的序列还可以应用到其他非本发明上述实施例所提供的激动型抗体或融合蛋白中。

[0148] 在一个具体的实施例中,可以将特异性结合抗原的抗体的重链可变区和轻链与本发明提供的重链恒定区融合以获得效果增强的其他抗体,例如:将上文表1中所列的在研的激动型抗体的重链可变区和轻链与本发明提供的JAC1融合可以获得活性增强的针对不同TNFR的抗体。

[0149] 在另一个具体的实施例中,可以将特异性结合抗原的抗原结合模块与本发明提供的重链恒定区融合以获得效果增强的融合蛋白,例如:将特异性结合CD40的纳米抗体(nanobody)与本发明提供的JAC1融合可以获得活性增强的融合蛋白。

[0150] 在另一个实施例中,本发明的抗体不仅可以使人抗体,还可以是嵌合抗体,人源化抗体等。

[0151] 表3:本发明抗体实施例的具体信息。

[0152]

抗体名称	抗原	轻链序列编号	重链序列编号	重链恒定区名称
Anti-mCD40-hIgG1	鼠 CD40	SEQ ID NO:48	SEQ ID NO:15	G1

[0153]

Anti-hCD40-hIgG1	人 CD40	SEQ ID NO:47	SEQ ID NO:16	G1
Anti-mCD40-hIgG2	鼠 CD40	SEQ ID NO:48	SEQ ID NO:17	G2
Anti-hCD40-hIgG2	人 CD40	SEQ ID NO:47	SEQ ID NO:18	G2
Anti-mCD40-hIgG3	鼠 CD40	SEQ ID NO:48	SEQ ID NO:19	G3
Anti-hCD40-hIgG3	人 CD40	SEQ ID NO:47	SEQ ID NO:20	G3
Anti-mCD40-hIgG4	鼠 CD40	SEQ ID NO:48	SEQ ID NO:21	G4
Anti-hCD40-hIgG4	人 CD40	SEQ ID NO:47	SEQ ID NO:22	G4
Anti-hCD40-hIgG1(V9)	人 CD40	SEQ ID NO:47	SEQ ID NO:23	V9(H1)
Anti-mCD40-hIgG1(V11)	鼠 CD40	SEQ ID NO:48	SEQ ID NO:24	V11(H1)
Anti-hCD40-hIgG1(V11)	人 CD40	SEQ ID NO:47	SEQ ID NO:25	V11(H1)
Anti-mCD40-hIgG2(V11)	鼠 CD40	SEQ ID NO:48	SEQ ID NO:26	V11(H2), 又 称 JAC1
Anti-hCD40-hIgG2(V11)	人 CD40	SEQ ID NO:47	SEQ ID NO:27	V11(H2), 又 称 JAC1
Anti-mCD40-hIgG3(V11)	鼠 CD40	SEQ ID NO:48	SEQ ID NO:28	V11(H3)
Anti-hCD40-hIgG3(V11)	人 CD40	SEQ ID NO:47	SEQ ID NO:29	V11(H3)
Anti-mCD40-hIgG2(H3)	鼠 CD40	SEQ ID NO:48	SEQ ID NO:30	G2(H3)
Anti-hCD40-hIgG2(H3)	人 CD40	SEQ ID NO:47	SEQ ID NO:31	G2(H3)
Anti-mCD40-hIgG3(H2)	鼠 CD40	SEQ ID NO:48	SEQ ID NO:32	G3(H2)
Anti-hCD40-hIgG3(H2)	人 CD40	SEQ ID NO:47	SEQ ID NO:33	G3(H2)
Anti-mCD40-hIgG1-NA	鼠 CD40	SEQ ID NO:48	SEQ ID NO:34	G1-NA
Anti-hCD40-hIgG1-NA	人 CD40	SEQ ID NO:47	SEQ ID NO:35	G1-NA
Anti-mCD40-hIgG2-NA	鼠 CD40	SEQ ID NO:48	SEQ ID NO:36	G2-NA
Anti-hCD40-hIgG2-NA	人 CD40	SEQ ID NO:47	SEQ ID NO:37	G2-NA
Anti-hCD40-hIgG2-SE	人 CD40	SEQ ID NO:47	SEQ ID NO:38	G2-SE
Anti-hCD40-hIgG2-LF	人 CD40	SEQ ID NO:47	SEQ ID NO:39	G2-LF
Anti-hCD40-hIgG2-SELF	人 CD40	SEQ ID NO:47	SEQ ID NO:40	G2-SELF, 又 称 JAC3
Anti-hCD40-hIgG2-HD	人 CD40	SEQ ID NO:47	SEQ ID NO:41	G2-HD
Anti-hCD40-hIgG2-PG	人 CD40	SEQ ID NO:47	SEQ ID NO:42	G2-PG
Anti-hCD40-hIgG2-HDPG	人 CD40	SEQ ID NO:47	SEQ ID NO:43	G2-HDPG , 又称 JAC4
Anti-mDR5-hIgG2	鼠 DR5	SEQ ID NO:49	SEQ ID NO:44	G2
Anti-mDR5-hIgG1(V11)	鼠 DR5	SEQ ID NO:49	SEQ ID NO:45	V11(H1)
Anti-mDR5-IgG2(V11)	鼠 DR5	SEQ ID NO:49	SEQ ID NO:46	V11(H2), 又 称 JAC1
Anti-mCD40-hIgG1-SDIE	鼠 CD40	SEQ ID NO:48	SEQ ID NO:50	G1-SDIE
Anti-mCD40-hIgG2-SDIE	鼠 CD40	SEQ ID NO:48	SEQ ID NO:51	G1-SDIE
Anti-mCD40-hIgG2-GASDA	鼠 CD40	SEQ ID NO:48	SEQ ID NO:52	G1-GASDA

[0154]

LIE				LIE
Anti-mCD40-hIgG1 (H2)	鼠 CD40	SEQ ID NO:48	SEQ ID NO:53	G1(H2)
Anti-mDR5-hIgG1-GASDA	鼠 DR5	SEQ ID NO:49	SEQ ID NO:54	G1-GASDA
LIE				LIE

[0155] 运用上文所提到的酶联免疫吸附实验 (ELISA) 方法,测定了本发明抗CD40抗体实施例的CD40结合能力。如图3所示,抗鼠CD40的抗体(图3A)以及抗人CD的抗体(图3B)均进行了CD40结合能力的测试。结果显示,本发明实施例中构建的抗CD40的抗体均保有对CD40的结合能力。值得注意的是,本实验ELISA分析显示Anti-hCD40-hIgG2 和Anti-hCD40-hIgG2 (V11)对hCD40的结合能力相对其他变体较低。而考虑到结合能力偏低的Anti-hCD40-hIgG2 (V11)在体内外的实验中均表现出活性优势,故判定抗人 CD40抗体 (Anti-hCD40-hIgG) 的变体对人CD40的结合能力没有显著的差异。

[0156] 实施例2. 人类IgG激动型抗体的活性依赖于抗体Fc与Fc γ 受体的相互作用

[0157] 为了研究人类IgG激动型抗体的活性是否受到抗体Fc与Fc γ 受体相互作用的调控,四种IgG亚型(hIgG1、hIgG2、hIgG3、hIgG4)的激动型抗鼠CD40抗体 (Anti-mCD40-hIgG1、Anti-mCD40-hIgG2、Anti-mCD40-hIgG3、Anti-mCD40-hIgG4) 作为模式抗体被首先用于研究其免疫激活活性是否受到Fc γ 受体表达的影响。

[0158] 由于激动型CD40具有促进抗原提呈细胞活化并诱导抗原特异性CD8阳性T细胞的活化与扩增的免疫激活活性,激动型人抗鼠CD40抗体 (Anti-mCD40-hIgG) 促进OVA 模式抗原特异CD8阳性T细胞在OVA免疫的小鼠中的活化与扩增的能力被用来评估其免疫激活活性 (Science.2011Aug 19;333 (6045):1030-4)。在这一分析中,小鼠首先接受 OVA特异CD8阳性T细胞 (OT-I T细胞) 过继输送,1天后接受抗原DEC-OVA (OVA 和抗DEC205抗体的融合蛋白,是一种有效输送OVA抗原的手段) 和抗CD40抗体的免疫,然后在小鼠免疫6天后分析OT-I T细胞的扩增。

[0159] 如图4所示,较高剂量 (30 μ g/小鼠) 的Anti-mCD40-hIgG1、Anti-mCD40-hIgG2、Anti-mCD40-hIgG4抗体在Fc γ 受体人源化小鼠中 (hFCGR^{Tg}) 都具有活性,而同样条件下, Anti-mCD40-hIgG1、Anti-mCD40-hIgG2、Anti-mCD40-hIgG4在Fc γ 受体缺陷小鼠 (Fc γ R^{-/-}) 中却看不到明显活性(图3A)。这说明Fc γ 受体的表达对激动型人IgG抗鼠 CD40抗体的活性是必要的。

[0160] 为了研究激动型人IgG抗鼠CD40抗体是否需要具备结合Fc γ 受体的能力,N297糖基化位点的点突变 (N297A) 被引入人IgG2抗鼠CD40抗体 (Anti-mCD40-hIgG2),从而得到 Anti-mCD40-hIgG2-NA。Anti-mCD40-hIgG2-NA抗体Fc结合Fc γ 受体的能力丧失 (图6), Anti-mCD40-hIgG2-NA抗体在OVA疫苗模型中诱导OT-I T细胞活化与扩增的活性也完全丧失(图3B),说明人Anti-mCD40-hIgG2抗体的免疫激活能力依赖于抗体Fc 结合Fc γ 受体的能力。

[0161] 实施例3. 人类抑制性Fc γ 受体 (hFc γ RIIB) 与抗体Fc的特异相互作用促进激动型人抗 CD40抗体的活性。

[0162] 为了分析在Fc γ 受体家族中具体提供人类IgG激动型抗体活性依赖的Fc-Fc γ 受体相互作用的特定Fc γ 受体,人类抑制性Fc γ 受体hFc γ RIIB的贡献被进一步分析。在抑制性 Fc γ 受体人源化小鼠 (Fcgr2b^{-/-}hFCGR2B^{Tg}) 和对照小鼠 (Fcgr2b^{-/-}) 中, Anti-mCD40-hIgG2 抗体在Fcgr2b^{-/-}小鼠中没有活性(图4C),而在抑制性Fc γ 受体人源化小鼠 (Fcgr2b^{-/-}hFCGR2B^{Tg}) 中的活性 (大约有近80%OT-I CD8⁺,图4C) 和在表达全部人类 Fc γ 受体的人源化小鼠 (hFCGR^{Tg}) 中活性 (大约有近60-80%OT-I CD8⁺,图4A) 相当,说明人类抑制性Fc γ 受体足以提供支持Anti-mCD40-hIgG2的活性。

[0163] 同时,当Anti-hCD40-hIgG1、Anti-hCD40-hIgG2、Anti-hCD40-hIgG3、Anti-hCD40-hIgG4体外刺激小鼠B细胞促进活化标识分子(CD80、CD86)表达时,不同Fc γ 受体环境(hCD40^{Tg}hFCGR^{Tg}、hCD40^{Tg}hR2B^{-/-})对抗体的活性影响很显著(图5)。人类Anti-hCD40-hIgG1、Anti-hCD40-hIgG2以及Anti-hCD40-hIgG4的活性在hCD40^{Tg}/hFCGR^{Tg}中活性很好,但在hCD40^{Tg}hR2B^{-/-}环境中活性很弱,几乎完全消失;同时人抑制性Fc γ 受体(hFc γ RIIB)的特异抗体2B6也能够显著的抑制Anti-hCD40-hIgG抗体的活性,说明人抑制性Fc γ 受体对人类IgG(hIgG1,hIgG2,hIgG4)的抗人CD40抗体的活性具有关键正向调控作用。这和基于人类IgG(hIgG1,hIgG2,hIgG4)的抗鼠CD40抗体的研究结果一致,进一步说明人抑制性Fc γ 受体与IgG抗体Fc的相互作用对人类IgG(hIgG1,hIgG2,hIgG4)抗CD40抗体活性的正向调控是一个普遍规律。

[0164] 已有其他文献表明激动型抗体的激动活性依赖于其和抑制性Fc γ 受体的结合,而本发明的试验不仅进一步验证了这一规律,并且显示通过移植相同的重链恒定区,可以使得针对不同抗原的激动型抗体趋向于具有基本类似的Fc γ 结合模式以及激动活性。例如:上述实施例中Anti-mCD40-hIgG2和Anti-hCD40-hIgG2具有相同的重链恒定区;但是Anti-mCD40-hIgG2的抗原为mCD40,而Anti-hCD40-hIgG2的抗原为hCD40。ELISA、OVA模型以及PMBC刺激试验显示Anti-mCD40-hIgG2和Anti-hCD40-hIgG2具有基本类似的Fc γ 结合模式以及激动活性。因此重链恒定区是优化激动型抗体激动活性的关键,并且优选的重链恒定区可以被广泛应用于针对不同抗原的激动型抗体,以获得类似的Fc γ 结合模式以及激动活性。因而,本发明对重链恒定区进行了筛选。

[0165] 实施例4. 优选的具有更好人抑制性Fc γ 受体结合能力和倾向性的人类IgG重链恒定区的选择。

[0166] 已有相当的研究表明较佳活性的激动型抗体除了需要具备高的Fc γ RIIB受体亲和力之外,还需要具有高的抑制性Fc受体:激活性Fc受体亲和力比值(I:A比值)。为了分析人抑制性Fc γ 受体与IgG抗体Fc的相互作用对人类IgG(hIgG1,hIgG2,hIgG4)抗CD40抗体活性的正向调控作用能够被利用增强抗体活性,需要优选具有更好人抑制性Fc γ 受体结合能力和倾向性的重链恒定区序列。虽然已经有多个基于人IgG1的重链恒定区序列变体已经被报道都具有更好人抑制性Fc γ 受体结合能力和倾向性,以其它IgG亚型(hIgG2、3、4)重链恒定区序列为基础的具有更好人抑制性Fc γ 受体结合能力和倾向性的恒定区序列则并不清楚。因此,需要进行筛选和分析。人IgG重链恒定区与抑制性Fc γ 受体的结合能力由亲和力衡量,而与抑制性Fc γ 受体的倾向性由I/A比值衡量。为了优选具有更好人抑制性Fc γ 受体结合能力和倾向性的人类IgG(hIgG2,hIgG4)重链恒定区,首先比较候选重链恒定区或者恒定区的Fc部分与人Fc γ 受体(包括抑制性Fc γ 受体(人Fc γ RIIB)和活化性Fc γ 受体(包括人Fc γ RI、Fc γ RIIA、Fc γ RIIIA、Fc γ RIIIB))的结合能力,挑选具有更好人抑制性Fc γ 受体结合能力(结合亲和力和人IgG1相当或更高)和倾向性(I/A比值等于或高于人IgG1)的人类IgG重链恒定区或恒定区的Fc部分。优选地,所述抗体重链恒定区与人Fc γ IIB的亲和力和人IgG1与人Fc γ IIB的亲和力相比提高3.2倍或以上,所述抗体重链恒定区的I/A比值等于或高于0.32;同样优选地,所述抗体重链恒定区与人Fc γ IIB的亲和力等于或高于人IgG1与人Fc γ IIB的亲和力,所述抗体重链恒定区的I/A比值等于或高于1;更优选地,所述抗体重链恒定区与人Fc γ IIB的亲和力和人IgG1与人Fc γ IIB的亲和力相比提高30倍

或以上,所述抗体重链恒定区的I/A比值等于或高于1;更优选地,所述抗体重链恒定区与人Fc γ IIB的亲力和人IgG1与人Fc γ IIB的亲力和相比提高60倍或以上,所述抗体重链恒定区的I/A比值等于或高于40;特别优选地,所述抗体重链恒定区与人Fc γ IIB的亲力和人IgG1与人Fc γ IIB的亲力和相比提高90倍或以上,所述抗体重链恒定区的I/A比值等于或高于100。

[0167] 候选重链恒定区序列包括自然的、带有一个或多个定点突变、或带有一个或多个随机突变的人类IgG重链恒定区序列;候选重链恒定区的Fc部分包括自然的、带有一个或多个定点突变、或带有一个或多个随机突变的各种Fc序列。通过分析候选重链恒定区或者恒定区的Fc部分的Fc γ 受体结合能力,基于人IgG1恒定区的Fc部分的突变体V11、V9 被发现具有更好人抑制性Fc γ 受体结合能力和倾向性(表4),这些重链恒定区的Fc部分可以和人类IgG重链恒定区的其它部分(CH1-绞链区)结合获得候选人类IgG重链恒定区。通过分析候选完整人类IgG重链恒定区序列的Fc γ 受体结合能力,检验这些抗体是否具有更好人抑制性Fc γ 受体结合能力和倾向性,发现具有JAC1(带有V11Fc序列的人IgG2重链恒定区)和JAC2(带有V9Fc序列的人IgG2重链恒定区)的重链恒定区是具有更好人抑制性Fc γ 受体结合能力和倾向性的人类IgG2重链恒定区序列(图6)。同时,在候选人类IgG2重链恒定区序列中,JAC3(带有S267E/L328F点突变的人IgG2重链恒定区序列)和JAC4(带有H268D/P271G点突变的人IgG2重链恒定区序列)重链恒定区序列也被发现具有更好人抑制性Fc γ 受体结合能力和倾向性(图6)。

[0168] 表4: IgG重链恒定区的Fc片段与人Fc γ 受体的亲和力(KD),全部亲和力由解离常数(KD)表示,KD值通过表面等离子共振试验测得。

抗体 Fc 片段	hFcγRI	hFcγRIIA-R 131	hFcγRIIB	hFcγRIIIA-F 158	hFcγRIIB 结合提升 倍率	I/A 比值*
G1	5.2×10^{-9}	1.2×10^{-6}	3.0×10^{-6}	6.7×10^{-6}	1	0.40
G2	不结合	$> 10^{-5}$	$> 10^{-5}$	$> 10^{-5}$	< 0.4	~1
G1-SE	2.6×10^{-9}	9.8×10^{-8}	8.3×10^{-8}	不结合	36	1.18
G1-SDIE	2.0×10^{-11}	1.2×10^{-7}	1.7×10^{-7}	3.0×10^{-8}	14	0.18
G1-SELF	3.7×10^{-9}	1.8×10^{-8}	4.3×10^{-8}	不结合	70	0.42
V9(H1)	5.8×10^{-7}	4.1×10^{-6}	9.4×10^{-8}	不结合	32	43
V11(H1)	2.3×10^{-7}	3.8×10^{-6}	1.4×10^{-8}	不结合	94	271
G1-GAS DALIE	未测定	6.3×10^{-8}	7.4×10^{-7}	1.0×10^{-7}	1	0.09

[0170] *:I/A比值=[KD(hFc γ RIIA-R131)或者KD(hFc γ RIIB-F158)中的最低值]/KD(hFc γ RIIB)。上述表4中的抗体Fc片段的名称是用表2中重链恒定区的名称来相应表示的,相应名称的Fc片段应该理解为表2中相应名称的重链恒定区的Fc片段。

[0171] 用本发明给出的判断方法,可以对更多的CH1-绞链区以及CH2-CH3结构域进行优选,从而得到其它具有更好人抑制性Fc γ 受体结合能力和倾向性的人类IgG(hIgG2、hIgG4)重链恒定区。同时,由于本发明优选的重链恒定区具有高的I/A比值,即有更低的活化型Fc γ 受体的结合力,因而基于本发明优选的重链恒定区构建的激动型抗体可能具有更低的诱导ADCC的活性,可以有更少的非特异性细胞毒性。

[0172] 实施例5.具有更好人抑制性Fc γ 受体(hFc γ RIIB)结合能力和倾向性的人类IgG重链恒定区支持更强的激动型抗CD40抗体活性

[0173] 为了分析具有更好人抑制性Fc γ 受体(hFc γ RIIB)结合能力和倾向性的人类IgG(hIgG2、hIgG4)重链恒定区是否能够支持更强的激动型抗CD40抗体活性,带有JAC1重链恒定区的抗鼠CD40抗体(Anti-mCD40-hIgG2(V11))和抗人CD40抗体(Anti-hCD40-hIgG2(V11))在OVA疫苗模型中诱导OT-I T细胞活化与扩增的活性被分析,分析结果表明Anti-mCD40-hIgG2(V11)显著优于Anti-mCD40-hIgG2的活性(图7A); Anti-hCD40-hIgG2(V11)显著优于Anti-hCD40-hIgG2的活性(图7B),表现为刺激免疫系统能力增强,其中OT1细胞绝对数和CD8+T细胞比例均明显上调。同时,带有JAC3和JAC4的抗人CD40抗体(Anti-hCD40-hIgG2-SELF, Anti-hCD40-hIgG2-HDPG)的B细胞激活活性分析表明, Anti-hCD40-hIgG2-SELF和Anti-hCD40-hIgG2-HDPG的活性也明显优于人IgG2抗体(图8),表现为刺激小鼠B细胞表达更高的表面活化分子CD86,人B细胞表达更高水平的表面激活分子hCD54。这些结果证明具有更好人抑制性Fc γ 受体(hFc γ RIIB)结合能力和倾向性的人类IgG(hIgG2、hIgG4)重链恒定区支持更强的激动型抗CD40抗体活性。

[0174] 实施例6.CH1-绞链区能够调控激动型人IgG抗CD40抗体的活性

[0175] 低剂量激动型人IgG抗CD40抗体(10 μ g/鼠)的活性分析显示在Anti-mCD40-hIgG1、Anti-mCD40-hIgG2、Anti-mCD40-hIgG3和Anti-mCD40-hIgG4中, Anti-mCD40-hIgG2在Fc γ 受体人源化小鼠中(hFCGR^{Tg})活性最高而Anti-mCD40-hIgG3活性最弱(图9A)。为了分析人类IgG抗体CH1-绞链区是否具有调控激动型人IgG抗CD40抗体的活性,人IgG3的CH1-绞链区段部分被用来替换人IgG2抗体的CH1-绞链区,替换之后的激动型人IgG2抗鼠CD40抗体(Anti-mCD40-hIgG2(H3))失去了免疫激活活性(图9B),说明CH1-绞链区能够调控激动型人IgG抗CD40抗体的活性。

[0176] 实施例7.人类IgG2绞链区较于IgG1和IgG3的绞链区能够支持更强的激动型人IgG抗CD40抗体活性

[0177] 为了比较人IgG1、2、3的CH1-绞链区段支持激动型人IgG抗CD40抗体活性的能力,具有相同的Fc,但CH1-绞链区不同的抗CD40抗体被制备。活性分析显示,这些抗体的活性显著不同,其中具有人IgG2的CH1-绞链区的抗体(Anti-mCD40-hIgG2(V11))活性最高,具有人IgG1的CH1-绞链区的抗体活性其次(Anti-mCD40-hIgG1(V11)),而具有人IgG3的CH1-绞链区的抗体(Anti-mCD40-hIgG3(V11))活性最低(图10),说明人类IgG2绞链区较于IgG1和IgG3的绞链区能够支持更强的激动型人IgG抗CD40抗体活性。

[0178] 实施例8.优选的人类IgG2绞链区和具有更好的人抑制性Fc γ 受体结合能力和倾向性的Fc能够协同提供更强的激动型人IgG抗CD40抗体活性

[0179] 由于人类IgG的Fc和CH1-绞链区段都能够影响激动型人IgG抗CD40抗体的活性,有必要研究使用具有更好的人抑制性Fc γ 受体结合能力和倾向性的Fc与更好的CH1-绞链区是否能够进一步提高激动型人IgG抗CD40抗体的活性。比较具有最好的人抑制性Fc γ 受体结合能力和倾向性的人IgG1抗体变异体(Anti-mCD40-hIgG1(V11),即人IgG1的V11变异体)、具有最好的CH1-绞链区的人IgG2抗体(Anti-mCD40-hIgG2),以及结合了V11的Fc γ 受体结合能力和IgG2的CH1-绞链区(JAC1)的抗体(Anti-mCD40-hIgG2(V11))的活性,结果显示结合了Fc优化和CH1-绞链区优选的Anti-mCD40-hIgG2(V11)明显具有更强的活性,表现

为在OVA疫苗模型中,OT-I细胞的绝对数目以及CD8⁺T细胞的比例显著提高(图11)。同时还在PMBC细胞刺激试验中比较了 Anti-hCD40-hIgG1 (V11)、Anti-hCD40-hIgG2以及Anti-hCD40-hIgG2 (V11)的免疫刺激活性(图12),结果同样显示结合了Fc优化和CH1-绞链区优选的Anti-hCD40-hIgG2 (V11) 明显具有更强的活性。

[0180] hIgG2 (V11) 这种更强的活性超过了hIgG1 (V11) 和hIgG2单独活性的简单叠加,说明优选的人类IgG2CH1-绞链区和具有更好的人抑制性Fc γ 受体结合能力和倾向性的Fc 能够协同提供更强的其它激动型人IgG抗体活性。

[0181] 在MC38肿瘤模型中进一步分析了Anti-mCD40-hIgG1 (V11)、Anti-mCD40-hIgG2以及Anti-mCD40-hIgG2 (V11) 这三种抗体的抗肿瘤活性(试验方法同上文材料和方法部分), Anti-mCD40-hIgG2 (V11) 的抗肿瘤活性也显著超过Anti-mCD40-hIgG1 (V11) 和 Anti-mCD40-hIgG2抗体的抗肿瘤活性(图13,14),在Anti-mCD40-hIgG2 (V11) 治疗组中,7只受试小鼠中有5只小鼠体内的肿瘤被完全清除,显示出极佳的肿瘤治疗活性。

[0182] 同样地又在M04肿瘤模型中进一步分析了Anti-mCD40-hIgG1 (V11)、Anti-mCD40-hIgG2以及Anti-mCD40-hIgG2 (V11) 这三种抗体的抗肿瘤活性(试验方法同上文材料和方法部分),Anti-mCD40-hIgG2 (V11) 的抗肿瘤活性在这个模型中也同样显著超过Anti-mCD40-hIgG1 (V11) 和Anti-mCD40-hIgG2抗体的抗肿瘤活性(图15)。

[0183] 上述抗肿瘤活性测试的结果和基于OVA疫苗模型的分析结果(图11) 基本保持一致。并且Anti-mCD40-hIgG1 (V11)、Anti-mCD40-hIgG2以及Anti-mCD40-hIgG2 (V11) 这三种抗体在Fc受体敲除小鼠(Fc γ R^{-/-})的MC38肿瘤模型中没有显示出抗肿瘤活性(图16)。说明Fc γ 受体的结合对于激动型抗体的抗肿瘤活性是必须的,本发明重链恒定区,例如: G2 (V11),又称JAC1,既能提升人类IgG抗体CD40抗体在疫苗中作为佐剂的活性,又能提升抗体的抗肿瘤活性。

[0184] 而且OVA疫苗模型试验显示,Anti-mCD40-hIgG2 (V11) 在3.16 μ g/小鼠以及1 μ g/ 小鼠的剂量下均表现出显著的活性(图17),而Anti-mCD40-IgG1抗体在10 μ g/小鼠剂量下已经不再具有活性(图9A)。

[0185] 运用OVA疫苗模型还比较了包含JAC4序列的抗CD40抗体 (Anti-mCD40-hIgG2-HDPG) 同未经突变的IgG2抗CD40抗体 (Anti-mCD40-hIgG2) 的免疫激动活性,结果显示, Anti-mCD40-hIgG2-HDPG较Anti-mCD40-hIgG2明显具有更强的活性,表现为OT-I细胞在CD8⁺T细胞中的比例以及CD8⁺T细胞的比例显著提高(图 18)。同时, Anti-mCD40-hIgG2-HDPG抗体的活性至少和Anti-mCD40-hIgG1 (V11) 相当,或更高(图18)。

[0186] 因而,在本发明重链恒定区(例如:JAC1或者JAC4) 基础上构建的激动型抗CD40 抗体具有更好的免疫刺激活性以及抗肿瘤活性,其最低有效剂量仅为目前在研的基于 IgG1的激动型抗体最低有效剂量的1/10,甚至更低,因而具有更高的活性,更宽的有效剂量范围以及更好的安全性,可以开发作为抗肿瘤药物,也可以用作疫苗佐剂以增强肿瘤疫苗或者针对于感染性疾病的疫苗的免疫效果。

[0187] 实施例9. 优选的人类IgG2CH1-绞链区和具有更好的人抑制性Fc γ 受体结合能力和倾向性的Fc能够协同提供更强的其它激动型人IgG抗体活性。

[0188] 为了进一步研究Fc γ 受体结合能力对其它人激动型抗体活性的影响,以及优选的人类 IgG2CH1-绞链区和具有更好的人抑制性Fc γ 受体结合能力和倾向性的Fc是否能够协

同提供更强的其它激动型人IgG抗体活性,具有不同CH1-绞链区和Fc的激动型抗DR5抗体(Anti-mDR5-IgG)被制备出来,并分析了抗DR5抗体诱导MC38细胞程序性凋亡的活性。结果显示,人IgG2抗DR5抗体(Anti-mDR5-IgG2)没有活性,而带有JAC1序列的抗DR5抗体(Anti-mDR5-IgG2(V11))具有活性,但是必须在表达Fc γ 受体(hFCGR^{Tg})的环境中(图19)。此外,这种活性能够被人抑制性Fc γ 受体特异抗体2B6完全阻断,说明带有JAC1序列抗DR5抗体(Anti-mDR5-IgG2(V11))的活性特异的受到和人抑制性Fc γ 受体相互作用的调控,也进一步说明,激动型抗DR5抗体活性的调控机制和抗CD40抗体的调控机制是一致的。因此,优选的人类IgG2CH1-绞链区和具有更好的人抑制性Fc γ 受体结合能力和倾向性的Fc能够提供更强的激动型人IgG抗DR5抗体活性。

[0189] 实施例10. 优选抗体恒定区仅仅具有优选的人类IgG2CH1-绞链区和具有好的人抑制性Fc γ 受体结合能力的Fc是不够的,Fc还需要好的人抑制性Fc γ 受体结合倾向性,即更高的I/A比值。

[0190] 为了研究人抑制性Fc γ 受体结合倾向性对具有增强的抑制性Fc γ 受体结合能力的抗体重链恒定区激活活性的影响,分别构建了基于重链恒定区G2-SDIE、G2-GASDALIE和G1(H2)的抗鼠CD40抗体Anti-mCD40-hIgG2-SDIE、Anti-mCD40-hIgG2-GASDALIE和Anti-mCD40-hIgG1(H2),并在OVA疫苗模型中比较了具有不同抗体的免疫激活活性。三个抗体都具有优选的人类IgG2的CH1-绞链区;相较于Anti-mCD40-hIgG1(H2),Anti-mCD40-hIgG2-SDIE和Anti-mCD40-hIgG2-GASDALIE都具有更好的人抑制性Fc γ 受体结合能力(表4),但是同时具有更强的结合人活化性Fc γ 受体的能力(表4),因此具有更低的I/A比值(表4)。OVA疫苗模型中的分析结果显示,Anti-mCD40-hIgG2-SDIE和Anti-mCD40-hIgG2-GASDALIE抗体的活性没有比Anti-mCD40-hIgG1(H2)抗体更优,反而更差(图20),说明优选抗体不仅仅需要增强的人抑制性Fc γ 受体结合能力,还需要人抑制性Fc γ 受体结合倾向性。这种倾向性体现为较高的I/A比值,0.32或者更高。

[0191] 本发明所提供的优选的抗体重链恒定区的实施例不仅可用于提高激动型抗CD40和DR5抗体的活性,也可用于针对其它TNF受体超家族成员的激动型抗体,如OX40、CD137、CD27、CD30、GITR、HVEM、TACI、DR4、FAS等,以及针对非TNF受体超家族成员(CD28、SLAM家族分子)的激动型抗体。不仅包括针对调控免疫激活和诱导细胞程序性凋亡的受体分子的激动型抗体,还可用于针对具有其它生物学功能的受体分子的激动型抗体,如针对免疫抑制性受体分子(免疫检查点)(如PD-1、CTLA-4、VISTA、TIM-3、BTLA、LAG-3等)的激动型抗体。不仅包括以人IgG抗体为基础的激动型抗体,还可以用于以含有其它物种序列的嵌合抗体为基础的激动型抗体。不仅包括含有两条重链和两条轻链的典型IgG激动型抗体,还包含只含有重链的IgG激动型抗体,以及其它IgG衍生变体形式的激动型抗体(如具有超过两个抗原结合位点的抗体,抗体重链的C端带有抗原结合位点的双特异或者多特异抗体)。不仅包括以抗体序列为基础的激动型抗体,还包括含有抗体恒定区序列的具有靶点激活功能的融合蛋白,如CD40L-Fc融合蛋白、OX40L-Fc融合蛋白、4-1BBL-Fc融合蛋白、CD27L-Fc融合蛋白、CD30L-Fc融合蛋白、CD95L-Fc融合蛋白、TRAIL-Fc融合蛋白、PD-L1-Fc融合蛋白等;具体的可以是CD40L-JAC1、CD40L-JAC4、OX40L-JAC1、OX40L-JAC4、PD-L1-JAC1、PD-L1-JAC4等。(表5)

[0192] 表5基于本发明重链恒定区的融合蛋白的实例。

[0193]

融合蛋白	抗原结合模块	重链恒定区
CD40L - JAC1	CD40L	JAC1
CD40L - JAC4	CD40L	JAC4
OX40L - JAC1	OX40L	JAC1
OX40L - JAC4	OX40L	JAC4
PD-L1 - JAC1	PDL1	JAC1
PD-L1 - JAC4	PDL1	JAC4
Anti-CD40SCFV - JAC1	Anti-CD40SCFV	JAC1
Anti-CD40nanobody - JAC1	Anti-CD40nanobody	JAC1
Anti-CD40SCFV - JAC4	Anti-CD40SCFV	JAC4
Anti-CD40nanobody - JAC4	Anti-CD40nanobody	JAC4
Anti-OX40SCFV - JAC1	Anti-CD40SCFV	JAC1
Anti-OX40nanobody - JAC1	Anti-CD40nanobody	JAC1
Anti-OX40SCFV - JAC4	Anti-CD40SCFV	JAC4
Anti-OX40nanobody - JAC4	Anti-CD40nanobody	JAC4
Anti-PD1-SCFV - JAC1	Anti-PD1SCFV	JAC1
Anti-PD1nanobody - JAC1	Anti-PD1nanobody	JAC1
Anti-PD1-SCFV - JAC4	Anti-PD1SCFV	JAC4
Anti-PD1nanobody - JAC4	Anti-PD1nanobody	JAC4

[0194] 尽管上文出于举例说明的目的已经描述了本发明的具体实施方案,然而本领域技术人员将领会,可以对细节进行许多改变而不背离如权利要求所描述的本发明。

[0001]	序列表
[0002]	<110> 上海交通大学医学院
[0003]	<120> 增强激动型抗体活性的抗体重链恒定区序列
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[0182]	Asp Ile Ala Val Glu Trp Glu Ser Ser Gly Gln Pro Glu Asn Asn Tyr		
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[0184]	Asn Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr		
[0185]	165	170	175
[0186]	Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Ile Phe		
[0187]	180	185	190
[0188]	Ser Cys Ser Val Met His Glu Ala Leu His Asn Arg Phe Thr Gln Lys		
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[0203]	Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln	
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[0205]	Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln	
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[0207]	Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly	
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[0211]	Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr	
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[0213]	Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser	
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[0215]	Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr	
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[0217]	Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr	
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[0219]	Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe	
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[0234]	Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
[0235]	20 25 30
[0236]	Val Asp Val Ser Asp Glu Asp Gly Glu Val Lys Phe Asn Trp Tyr Val
[0237]	35 40 45
[0238]	Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
[0239]	50 55 60
[0240]	Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
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[0242]	Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
[0243]	85 90 95
[0244]	Leu Pro Arg Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
[0245]	100 105 110
[0246]	Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
[0247]	115 120 125
[0248]	Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
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[0250]	Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
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[0252]	Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
[0253]	165 170 175
[0254]	Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
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[0256]	Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
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[0272]	35 40 45

[0273]	Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
[0274]	50 55 60
[0275]	Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
[0276]	65 70 75 80
[0277]	Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
[0278]	85 90 95
[0279]	Leu Pro Arg Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
[0280]	100 105 110
[0281]	Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr
[0282]	115 120 125
[0283]	Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
[0284]	130 135 140
[0285]	Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
[0286]	145 150 155 160
[0287]	Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
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[0289]	Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
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[0291]	Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
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[0293]	Ser Leu Ser Leu Ser Pro Gly Lys
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[0308]	Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
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[0310]	Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
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[0312]	Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
[0313]	85 90 95
[0314]	Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
[0315]	100 105 110
[0316]	Glu Leu Leu Gly Asp Asp Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
[0317]	115 120 125
[0318]	Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
[0319]	130 135 140
[0320]	Asp Val Ser Asp Glu Asp Gly Glu Val Lys Phe Asn Trp Tyr Val Asp
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[0322]	Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
[0323]	165 170 175
[0324]	Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
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[0326]	Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
[0327]	195 200 205
[0328]	Pro Arg Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
[0329]	210 215 220
[0330]	Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
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[0332]	Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
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[0335]	260 265 270
[0336]	Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
[0337]	275 280 285
[0338]	Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
[0339]	290 295 300
[0340]	Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
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[0353]	Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
[0354]	20 25 30
[0355]	Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
[0356]	35 40 45
[0357]	Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
[0358]	50 55 60
[0359]	Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
[0360]	65 70 75 80
[0361]	Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
[0362]	85 90 95
[0363]	Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
[0364]	100 105 110
[0365]	Glu Leu Leu Gly Asp Asp Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
[0366]	115 120 125
[0367]	Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
[0368]	130 135 140
[0369]	Asp Val Ser His Glu Asp Gly Glu Val Lys Phe Asn Trp Tyr Val Asp
[0370]	145 150 155 160
[0371]	Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
[0372]	165 170 175
[0373]	Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
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[0375]	Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
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[0377]	Pro Arg Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
[0378]	210 215 220
[0379]	Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
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[0381]	Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
[0382]	245 250 255
[0383]	Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
[0384]	260 265 270
[0385]	Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
[0386]	275 280 285
[0387]	Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
[0388]	290 295 300
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[0404]	Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser			
[0405]	35 40 45			
[0406]	Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser			
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[0410]	Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys			
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[0412]	Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro			
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[0414]	Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp			
[0415]	115 120 125			
[0416]	Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp			
[0417]	130 135 140			
[0418]	Val Glu His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly			
[0419]	145 150 155 160			
[0420]	Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn			
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[0422]	Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp			
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[0424]	Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Phe Pro			
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[0426]	Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu			
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[0428]	Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn			

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[0430]	Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile			
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[0432]	Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr			
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[0434]	Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys			
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[0436]	Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys			
[0437]		290	295	300
[0438]	Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu			
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[0453]	Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser			
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[0455]	Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser			
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[0457]	Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr			
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[0461]	Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro			
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[0463]	Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp			
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[0465]	Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp			
[0466]		130	135	140
[0467]	Val Ser Asp Glu Asp Gly Glu Val Gln Phe Asn Trp Tyr Val Asp Gly			

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[0469]	Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn			
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[0471]	Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp			
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[0473]	Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro			
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[0475]	Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu			
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[0477]	Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn			
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[0479]	Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile			
[0480]		245	250	255
[0481]	Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr			
[0482]		260	265	270
[0483]	Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys			
[0484]		275	280	285
[0485]	Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys			
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[0487]	Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu			
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[0489]	Ser Leu Ser Pro Gly Lys			
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[0502]	Pro Gly Arg Ser Leu Lys Leu Pro Cys Ala Ala Ser Gly Phe Thr Phe			
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[0504]	Ser Asp Tyr Tyr Met Ala Trp Val Arg Gln Ala Pro Thr Lys Gly Leu			
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[0506]	Glu Trp Val Ala Ser Ile Ser Tyr Asp Gly Ser Ser Thr Tyr Tyr Arg			

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[0508]	Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser			
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[0510]	Thr Leu Tyr Leu Gln Met Asp Ser Leu Arg Ser Glu Asp Thr Ala Thr			
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[0512]	Tyr Tyr Cys Gly Arg His Ser Ser Tyr Phe Asp Tyr Trp Gly Gln Gly			
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[0514]	Val Met Val Thr Val Ser Ser Ala Thr Thr Lys Gly Pro Ser Val Phe			
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[0516]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu			
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[0518]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp			
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[0520]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu			
[0521]		180	185	190
[0522]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser			
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[0524]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro			
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[0526]	Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys			
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[0528]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro			
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[0530]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser			
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[0532]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp			
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[0534]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn			
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[0536]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val			
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[0538]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu			
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[0540]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys			
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[0544]	Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr			
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[0546]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
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[0548]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
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[0550]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
[0551]	420 425 430
[0552]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
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[0573]	Glu Trp Met Gly Trp Ile Asn Pro Asp Ser Gly Gly Thr Asn Tyr Ala
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[0575]	Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser
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[0581]	Cys Ser Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
[0582]	130 135 140
[0583]	Ser Ala Thr Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
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[0587]	Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
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[0593]	Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
[0594]	225 230 235 240
[0595]	Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
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[0597]	Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
[0598]	260 265 270
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[0604]	305 310 315 320
[0605]	Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
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[0607]	Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
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[0611]	Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
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[0615]	Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
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[0617]	Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
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[0851]	Cys Ser Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser		
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[0853]	Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser		
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[0913]	35 40 45
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[0918]	Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser
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[0926]	Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
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[0936]	Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro		
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[0952]	Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro		
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[0981]	Glu Trp Met Gly Trp Ile Asn Pro Asp Ser Gly Gly Thr Asn Tyr Ala
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[0997]	Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
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[0999]	Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
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[1003]	Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala
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[1082]	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser							
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[1096]	Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
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[1115]	Glu Trp Val Ala Ser Ile Ser Tyr Asp Gly Ser Ser Thr Tyr Tyr Arg
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[1117]	Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser
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[1123]	Val Met Val Thr Val Ser Ser Ala Thr Thr Lys Gly Pro Ser Val Phe
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[1127]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
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[1129]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
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[1131]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
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[1133]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
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[1135]	Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
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[1137]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Asp Asp
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[1143]	Gly Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
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[1145]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
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[1147]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
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[1159]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
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[1196]	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr
[1197]					180					185					190	
[1198]	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr
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[1207]					260					265					270	
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[1212]	Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg		
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[1214]	Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val		
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[1224]	Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu		
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[1226]	Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe		
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[1228]	Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly		
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[1230]	Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr		
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[1245]	Pro Gly Arg Ser Leu Lys Leu Pro Cys Ala Ala Ser Gly Phe Thr Phe		
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[1247]	Ser Asp Tyr Tyr Met Ala Trp Val Arg Gln Ala Pro Thr Lys Gly Leu		

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[1249]	Glu Trp Val Ala Ser Ile Ser Tyr Asp Gly Ser Ser Thr Tyr Tyr Arg		
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[1257]	Val Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe		
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[1259]	Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu		
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[1261]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp		
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[1263]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu		
[1264]	180	185	190
[1265]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser		
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[1267]	Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro		
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[1269]	Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu		
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[1271]	Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Asp Asp Ser Val Phe		
[1272]	245	250	255
[1273]	Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro		
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[1275]	Glu Val Thr Cys Val Val Val Asp Val Ser Asp Glu Asp Gly Glu Val		
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[1279]	Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val		
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[1281]	Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys		
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[1283]	Lys Val Ser Asn Lys Ala Leu Pro Arg Pro Ile Glu Lys Thr Ile Ser		
[1284]	340	345	350
[1285]	Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro		
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[1287]	Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
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[1289]	Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
[1290]	385 390 395 400
[1291]	Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
[1292]	405 410 415
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[1294]	420 425 430
[1295]	Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
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[1297]	Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[1298]	450 455 460
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[1311]	35 40 45
[1312]	Thr Gly Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
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[1314]	Glu Trp Met Gly Trp Ile Asn Pro Asp Ser Gly Gly Thr Asn Tyr Ala
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[1316]	Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser
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[1318]	Thr Ala Tyr Met Glu Leu Asn Arg Leu Arg Ser Asp Asp Thr Ala Val
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[1320]	Tyr Tyr Cys Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val
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[1322]	Cys Ser Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
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[1324]	Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
[1325]	145 150 155 160

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[1634]	Gln	Phe	Asn	Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Val	His
[1635]					370					375					380	
[1636]	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys
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															400	

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[1640]	Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
[1641]	420 425 430
[1642]	Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
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[1644]	Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
[1645]	450 455 460
[1646]	Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
[1647]	465 470 475 480
[1648]	Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
[1649]	485 490 495
[1650]	Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
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[1653]	515 520
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[1666]	35 40 45
[1667]	Ser Asp Tyr Tyr Met Ala Trp Val Arg Gln Ala Pro Thr Lys Gly Leu
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[1669]	Glu Trp Val Ala Ser Ile Ser Tyr Asp Gly Ser Ser Thr Tyr Tyr Arg
[1670]	65 70 75 80
[1671]	Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser
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[1673]	Thr Leu Tyr Leu Gln Met Asp Ser Leu Arg Ser Glu Asp Thr Ala Thr
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[1675]	Tyr Tyr Cys Gly Arg His Ser Ser Tyr Phe Asp Tyr Trp Gly Gln Gly
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[1702]				325						330					335	
[1703]	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser
[1704]			340						345					350		
[1705]	Lys	Thr	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro
[1706]		355						360				365				
[1707]	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val
[1708]		370					375					380				
[1709]	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Ser	Gly
[1710]	385					390					395					400
[1711]	Gln	Pro	Glu	Asn	Asn	Tyr	Asn	Thr	Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp
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[1730]	Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe		
[1731]	35 40 45		
[1732]	Thr Gly Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu		
[1733]	50 55 60		
[1734]	Glu Trp Met Gly Trp Ile Asn Pro Asp Ser Gly Gly Thr Asn Tyr Ala		
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[1736]	Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser		
[1737]	85 90 95		
[1738]	Thr Ala Tyr Met Glu Leu Asn Arg Leu Arg Ser Asp Asp Thr Ala Val		
[1739]	100 105 110		
[1740]	Tyr Tyr Cys Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val		
[1741]	115 120 125		
[1742]	Cys Ser Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser		
[1743]	130 135 140		
[1744]	Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser		
[1745]	145 150 155 160		
[1746]	Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp		
[1747]	165 170 175		
[1748]	Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr		
[1749]	180 185 190		
[1750]	Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr		
[1751]	195 200 205		
[1752]	Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln		
[1753]	210 215 220		
[1754]	Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp		

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[1756]	Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala			
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[1758]	Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro			
[1759]		260	265	270
[1760]	Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val			
[1761]		275	280	285
[1762]	Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Lys Trp Tyr Val			
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[1764]	Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln			
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[1766]	Tyr Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Leu His Gln			
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[1768]	Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala			
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[1770]	Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro			
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[1772]	Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr			
[1773]		370	375	380
[1774]	Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser			
[1775]	385	390	395	400
[1776]	Asp Ile Ala Val Glu Trp Glu Ser Ser Gly Gln Pro Glu Asn Asn Tyr			
[1777]		405	410	415
[1778]	Asn Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr			
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[1780]	Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Ile Phe			
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[1782]	Ser Cys Ser Val Met His Glu Ala Leu His Asn Arg Phe Thr Gln Lys			
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[1784]	Ser Leu Ser Leu Ser Pro Gly Lys			
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[1795]	Val Gln Cys Glu Val Gln Leu Val Glu Ser Asp Gly Gly Leu Val Gln			
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[1797]	Pro Gly Arg Ser Leu Lys Leu Pro Cys Ala Ala Ser Gly Phe Thr Phe			
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[1799]	Ser Asp Tyr Tyr Met Ala Trp Val Arg Gln Ala Pro Thr Lys Gly Leu			
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[1801]	Glu Trp Val Ala Ser Ile Ser Tyr Asp Gly Ser Ser Thr Tyr Tyr Arg			
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[1803]	Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser			
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[1805]	Thr Leu Tyr Leu Gln Met Asp Ser Leu Arg Ser Glu Asp Thr Ala Thr			
[1806]	100	105	110	
[1807]	Tyr Tyr Cys Gly Arg His Ser Ser Tyr Phe Asp Tyr Trp Gly Gln Gly			
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[1809]	Val Met Val Thr Val Ser Ser Ala Thr Thr Lys Gly Pro Ser Val Phe			
[1810]	130	135	140	
[1811]	Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu			
[1812]	145	150	155	160
[1813]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp			
[1814]	165	170	175	
[1815]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu			
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[1817]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser			
[1818]	195	200	205	
[1819]	Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro			
[1820]	210	215	220	
[1821]	Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys			
[1822]	225	230	235	240
[1823]	Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro			
[1824]	245	250	255	
[1825]	Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser			
[1826]	260	265	270	
[1827]	Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp			
[1828]	275	280	285	
[1829]	Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn			
[1830]	290	295	300	
[1831]	Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val			
[1832]	305	310	315	320

[1833]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
[1834]	325 330 335
[1835]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
[1836]	340 345 350
[1837]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
[1838]	355 360 365
[1839]	Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
[1840]	370 375 380
[1841]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
[1842]	385 390 395 400
[1843]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
[1844]	405 410 415
[1845]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
[1846]	420 425 430
[1847]	Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
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[1849]	Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
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[1864]	Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
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[1866]	Thr Gly Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
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[1868]	Glu Trp Met Gly Trp Ile Asn Pro Asp Ser Gly Gly Thr Asn Tyr Ala
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[1870]	Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser
[1871]	85 90 95

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[1876]	Cys	Ser	Tyr	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser
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[1878]	Ser	Ala	Thr	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser
[1879]	145					150				155						160
[1880]	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp
[1881]				165						170					175	
[1882]	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr
[1883]			180						185					190		
[1884]	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr
[1885]		195					200						205			
[1886]	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln
[1887]		210					215					220				
[1888]	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp
[1889]	225				230					235						240
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[1895]		275					280					285				
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[1899]	305				310				315							320
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[1905]		355					360					365				
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[1907]		370					375				380					
[1908]	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe
[1909]	385				390				395							400
[1910]	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu

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[1912]	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe		
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[1914]	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly		
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[1916]	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr		
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[1961]	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Gln	
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[1967]	Thr	Val	Val	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	
[1968]		325		330		335											
[1969]	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	
[1970]		340		345		350											
[1971]	Thr	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	
[1972]		355		360		365											
[1973]	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	
[1974]		370		375		380											
[1975]	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	
[1976]	385			390		395											
[1977]	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	
[1978]		405		410		415											
[1979]	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	
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[1982]		435		440		445											
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[1985]	<210>	37															
[1986]	<211>	471															
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[1988]	<213>	人工序列															

[1989]	<220>
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[1995]	20 25 30
[1996]	Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
[1997]	35 40 45
[1998]	Thr Gly Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
[1999]	50 55 60
[2000]	Glu Trp Met Gly Trp Ile Asn Pro Asp Ser Gly Gly Thr Asn Tyr Ala
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[2002]	Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser
[2003]	85 90 95
[2004]	Thr Ala Tyr Met Glu Leu Asn Arg Leu Arg Ser Asp Asp Thr Ala Val
[2005]	100 105 110
[2006]	Tyr Tyr Cys Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val
[2007]	115 120 125
[2008]	Cys Ser Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
[2009]	130 135 140
[2010]	Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
[2011]	145 150 155 160
[2012]	Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
[2013]	165 170 175
[2014]	Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
[2015]	180 185 190
[2016]	Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
[2017]	195 200 205
[2018]	Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln
[2019]	210 215 220
[2020]	Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
[2021]	225 230 235 240
[2022]	Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala
[2023]	245 250 255
[2024]	Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
[2025]	260 265 270
[2026]	Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
[2027]	275 280 285

[2028]	Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
[2029]	290 295 300
[2030]	Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
[2031]	305 310 315 320
[2032]	Ala Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp
[2033]	325 330 335
[2034]	Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
[2035]	340 345 350
[2036]	Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg
[2037]	355 360 365
[2038]	Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
[2039]	370 375 380
[2040]	Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
[2041]	385 390 395 400
[2042]	Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
[2043]	405 410 415
[2044]	Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
[2045]	420 425 430
[2046]	Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
[2047]	435 440 445
[2048]	Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
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[2050]	Leu Ser Leu Ser Pro Gly Lys
[2051]	465 470
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[2060]	1 5 10 15
[2061]	Ala His Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
[2062]	20 25 30
[2063]	Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
[2064]	35 40 45
[2065]	Thr Gly Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
[2066]	50 55 60

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[2073]	Tyr	Tyr	Cys	Ala	Arg	Asp	Gln	Pro	Leu	Gly	Tyr	Cys	Thr	Asn	Gly	Val
[2074]			115					120					125			
[2075]	Cys	Ser	Tyr	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser
[2076]		130					135					140				
[2077]	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser
[2078]	145					150				155						160
[2079]	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp
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[2081]	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr
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[2084]			195					200						205		
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[2086]		210					215					220				
[2087]	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp
[2088]	225					230				235						240
[2089]	Lys	Thr	Val	Glu	Arg	Lys	Cys	Cys	Val	Glu	Cys	Pro	Pro	Cys	Pro	Ala
[2090]				245						250					255	
[2091]	Pro	Pro	Val	Ala	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys
[2092]			260						265					270		
[2093]	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val
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[2095]	Asp	Val	Glu	His	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp
[2096]		290					295					300				
[2097]	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe
[2098]	305					310				315						320
[2099]	Asn	Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Val	His	Gln	Asp
[2100]				325						330					335	
[2101]	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu
[2102]				340					345					350		
[2103]	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Gln	Pro	Arg
[2104]			355					360					365			
[2105]	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys

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[2107]	Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp		
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[2109]	Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys		400
[2110]	405	410	415
[2111]	Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser		
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[2113]	Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser		
[2114]	435	440	445
[2115]	Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser		
[2116]	450	455	460
[2117]	Leu Ser Leu Ser Pro Gly Lys		
[2118]	465	470	
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[2129]	20	25	30
[2130]	Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe		
[2131]	35	40	45
[2132]	Thr Gly Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu		
[2133]	50	55	60
[2134]	Glu Trp Met Gly Trp Ile Asn Pro Asp Ser Gly Gly Thr Asn Tyr Ala		
[2135]	65	70	75
[2136]	Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser		80
[2137]	85	90	95
[2138]	Thr Ala Tyr Met Glu Leu Asn Arg Leu Arg Ser Asp Asp Thr Ala Val		
[2139]	100	105	110
[2140]	Tyr Tyr Cys Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val		
[2141]	115	120	125
[2142]	Cys Ser Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser		
[2143]	130	135	140
[2144]	Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser		

[2145]	145	150	155	160
[2146]	Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp			
[2147]		165	170	175
[2148]	Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr			
[2149]		180	185	190
[2150]	Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr			
[2151]		195	200	205
[2152]	Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln			
[2153]		210	215	220
[2154]	Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp			
[2155]	225	230	235	240
[2156]	Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala			
[2157]		245	250	255
[2158]	Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys			
[2159]		260	265	270
[2160]	Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val			
[2161]		275	280	285
[2162]	Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp			
[2163]		290	295	300
[2164]	Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe			
[2165]	305	310	315	320
[2166]	Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp			
[2167]		325	330	335
[2168]	Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Phe			
[2169]		340	345	350
[2170]	Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg			
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[2172]	Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys			
[2173]		370	375	380
[2174]	Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp			
[2175]	385	390	395	400
[2176]	Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys			
[2177]		405	410	415
[2178]	Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser			
[2179]		420	425	430
[2180]	Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser			
[2181]		435	440	445
[2182]	Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser			
[2183]		450	455	460

[2184]	Leu Ser Leu Ser Pro Gly Lys
[2185]	465 470
[2186]	<210> 40
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[2188]	<212> PRT
[2189]	<213> 人工序列
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[2194]	1 5 10 15
[2195]	Ala His Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
[2196]	20 25 30
[2197]	Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
[2198]	35 40 45
[2199]	Thr Gly Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
[2200]	50 55 60
[2201]	Glu Trp Met Gly Trp Ile Asn Pro Asp Ser Gly Gly Thr Asn Tyr Ala
[2202]	65 70 75 80
[2203]	Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser
[2204]	85 90 95
[2205]	Thr Ala Tyr Met Glu Leu Asn Arg Leu Arg Ser Asp Asp Thr Ala Val
[2206]	100 105 110
[2207]	Tyr Tyr Cys Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val
[2208]	115 120 125
[2209]	Cys Ser Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
[2210]	130 135 140
[2211]	Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
[2212]	145 150 155 160
[2213]	Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
[2214]	165 170 175
[2215]	Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
[2216]	180 185 190
[2217]	Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
[2218]	195 200 205
[2219]	Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln
[2220]	210 215 220
[2221]	Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
[2222]	225 230 235 240

[2223]	Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala		
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[2225]	Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys		
[2226]		260	265 270
[2227]	Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val		
[2228]		275	280 285
[2229]	Asp Val Glu His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp		
[2230]		290	295 300
[2231]	Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe		
[2232]	305	310	315 320
[2233]	Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp		
[2234]		325	330 335
[2235]	Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Phe		
[2236]		340	345 350
[2237]	Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg		
[2238]		355	360 365
[2239]	Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys		
[2240]		370	375 380
[2241]	Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp		
[2242]	385	390	395 400
[2243]	Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys		
[2244]		405	410 415
[2245]	Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser		
[2246]		420	425 430
[2247]	Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser		
[2248]		435	440 445
[2249]	Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser		
[2250]		450	455 460
[2251]	Leu Ser Leu Ser Pro Gly Lys		
[2252]	465	470	
[2253]	<210> 41		
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[2265]			35					40					45			
[2266]	Thr	Gly	Tyr	Tyr	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu
[2267]		50					55					60				
[2268]	Glu	Trp	Met	Gly	Trp	Ile	Asn	Pro	Asp	Ser	Gly	Gly	Thr	Asn	Tyr	Ala
[2269]	65					70					75				80	
[2270]	Gln	Lys	Phe	Gln	Gly	Arg	Val	Thr	Met	Thr	Arg	Asp	Thr	Ser	Ile	Ser
[2271]				85						90					95	
[2272]	Thr	Ala	Tyr	Met	Glu	Leu	Asn	Arg	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val
[2273]				100					105					110		
[2274]	Tyr	Tyr	Cys	Ala	Arg	Asp	Gln	Pro	Leu	Gly	Tyr	Cys	Thr	Asn	Gly	Val
[2275]			115					120					125			
[2276]	Cys	Ser	Tyr	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser
[2277]		130					135					140				
[2278]	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser
[2279]	145					150				155					160	
[2280]	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp
[2281]				165					170					175		
[2282]	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr
[2283]				180					185					190		
[2284]	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr
[2285]			195					200					205			
[2286]	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Asn	Phe	Gly	Thr	Gln
[2287]		210					215					220				
[2288]	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp
[2289]	225					230				235					240	
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[2293]				260					265					270		
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[2295]			275					280					285			
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[2297]		290					295					300				
[2298]	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Phe
[2299]	305					310				315					320	
[2300]	Asn	Ser	Thr	Phe	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Val	His	Gln	Asp

[2301]	325							330							335						
[2302]	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Gly	Leu					
[2303]	340							345							350						
[2304]	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Thr	Lys	Gly	Gln	Pro	Arg					
[2305]	355							360							365						
[2306]	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys					
[2307]	370							375							380						
[2308]	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp					
[2309]	385							390							395					400	
[2310]	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys					
[2311]	405							410							415						
[2312]	Thr	Thr	Pro	Pro	Met	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser					
[2313]	420							425							430						
[2314]	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser					
[2315]	435							440							445						
[2316]	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser					
[2317]	450							455							460						
[2318]	Leu	Ser	Leu	Ser	Pro	Gly	Lys														
[2319]	465							470													
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[2326]	<400> 42																				
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[2328]	1																				

[2340]	100							105							110						
[2341]	Tyr	Tyr	Cys	Ala	Arg	Asp	Gln	Pro	Leu	Gly	Tyr	Cys	Thr	Asn	Gly	Val					
[2342]	115							120							125						
[2343]	Cys	Ser	Tyr	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser					
[2344]	130							135							140						
[2345]	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Cys	Ser					
[2346]	145							150							155						
[2347]	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp					
[2348]	165							170							175						
[2349]	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr					
[2350]	180							185							190						
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[2356]	225							230							235						
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[2381]	Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
[2382]	435 440 445
[2383]	Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
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[2400]	Thr Gly Tyr Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
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[2402]	Glu Trp Met Gly Trp Ile Asn Pro Asp Ser Gly Gly Thr Asn Tyr Ala
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[2404]	Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser
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[2406]	Thr Ala Tyr Met Glu Leu Asn Arg Leu Arg Ser Asp Asp Thr Ala Val
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[2408]	Tyr Tyr Cys Ala Arg Asp Gln Pro Leu Gly Tyr Cys Thr Asn Gly Val
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[2410]	Cys Ser Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
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[2412]	Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
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[2414]	Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
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[2416]	Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
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[2418]	Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr		
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[2420]	Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln		
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[2422]	Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp		
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[2424]	Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala		
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[2426]	Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys		
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[2430]	Asp Val Ser Asp Glu Asp Gly Glu Val Gln Phe Asn Trp Tyr Val Asp		
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[2440]	Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys		
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[2442]	Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp		
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[2444]	Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys		
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[2446]	Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser		
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[2448]	Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser		
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[2450]	Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser		
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[2452]	Leu Ser Leu Ser Pro Gly Lys		
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[2465]	Ala	Gln	Ser	Leu	Ser	Leu	Thr	Cys	Ser	Ile	Thr	Gly	Phe	Pro	Ile	Thr
[2466]					35					40					45	
[2467]	Ala	Gly	Gly	Tyr	Trp	Trp	Thr	Trp	Ile	Arg	Gln	Phe	Pro	Gly	Gln	Lys
[2468]					50					55					60	
[2469]	Leu	Glu	Trp	Met	Gly	Tyr	Ile	Tyr	Ser	Ser	Gly	Ser	Thr	Asn	Tyr	Asn
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[2471]	Pro	Ser	Ile	Lys	Ser	Arg	Ile	Ser	Ile	Thr	Arg	Asp	Thr	Ala	Lys	Asn
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[2473]	Gln	Phe	Phe	Leu	Gln	Leu	Asn	Ser	Val	Thr	Thr	Glu	Glu	Asp	Thr	Ala
[2474]						100					105				110	
[2475]	Ile	Tyr	Tyr	Cys	Ala	Arg	Ala	Gly	Thr	Ser	Tyr	Ser	Gly	Phe	Phe	Asp
[2476]						115					120				125	
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[2478]						130									140	
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[2481]	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro
[2482]						165					170					175
[2483]	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr
[2484]						180					185					190
[2485]	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val
[2486]						195					200				205	
[2487]	Val	Thr	Val	Pro	Ser	Ser	Asn	Phe	Gly	Thr	Gln	Thr	Tyr	Thr	Cys	Asn
[2488]						210					215				220	
[2489]	Val	Asp	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Thr	Val	Glu	Arg
[2490]	225						230					235				240
[2491]	Lys	Cys	Cys	Val	Glu	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Pro	Val	Ala	Gly
[2492]						245					250					255
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[2494]						260					265					270
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[2497]	Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His		
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[2499]	Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg		
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[2501]	Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys		
[2502]	325	330	335
[2503]	Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu		
[2504]	340	345	350
[2505]	Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr		
[2506]	355	360	365
[2507]	Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu		
[2508]	370	375	380
[2509]	Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp		
[2510]	385	390	395
[2511]	Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met		
[2512]	405	410	415
[2513]	Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp		
[2514]	420	425	430
[2515]	Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His		
[2516]	435	440	445
[2517]	Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro		
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[2519]	Gly Lys		
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[2532]	Ala Gln Ser Leu Ser Leu Thr Cys Ser Ile Thr Gly Phe Pro Ile Thr		
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[2534]	Ala Gly Gly Tyr Trp Trp Thr Trp Ile Arg Gln Phe Pro Gly Gln Lys		

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[2536]	Leu Glu Trp Met Gly Tyr Ile Tyr Ser Ser Gly Ser Thr Asn Tyr Asn		
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[2538]	Pro Ser Ile Lys Ser Arg Ile Ser Ile Thr Arg Asp Thr Ala Lys Asn		
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[2540]	Gln Phe Phe Leu Gln Leu Asn Ser Val Thr Thr Glu Glu Asp Thr Ala		
[2541]	100	105	110
[2542]	Ile Tyr Tyr Cys Ala Arg Ala Gly Thr Ser Tyr Ser Gly Phe Phe Asp		
[2543]	115	120	125
[2544]	Ser Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Thr Thr Lys		
[2545]	130	135	140
[2546]	Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly		
[2547]	145	150	155
[2548]	Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro		
[2549]	165	170	175
[2550]	Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr		
[2551]	180	185	190
[2552]	Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val		
[2553]	195	200	205
[2554]	Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn		
[2555]	210	215	220
[2556]	Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro		
[2557]	225	230	235
[2558]	Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu		
[2559]	245	250	255
[2560]	Leu Leu Gly Asp Asp Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp		
[2561]	260	265	270
[2562]	Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp		
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[2564]	Val Ser Asp Glu Asp Gly Glu Val Lys Phe Asn Trp Tyr Val Asp Gly		
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[2566]	Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn		
[2567]	305	310	315
[2568]	Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp		
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[2570]	Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro		
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[2572]	Arg Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu		
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[2576]	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile
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[2578]	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr
[2579]					405					410					415	
[2580]	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys
[2581]				420					425					430		
[2582]	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys
[2583]			435					440					445			
[2584]	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu
[2585]	450						455					460				
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[2607]	Gln	Phe	Phe	Leu	Gln	Leu	Asn	Ser	Val	Thr	Thr	Glu	Glu	Asp	Thr	Ala
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[2609]	Ile	Tyr	Tyr	Cys	Ala	Arg	Ala	Gly	Thr	Ser	Tyr	Ser	Gly	Phe	Phe	Asp
[2610]		115					120					125				
[2611]	Ser	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys
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[2615]	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro
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[2617]	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr
[2618]				180					185					190		
[2619]	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val
[2620]			195					200					205			
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[2668]	Ile Tyr Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro		
[2669]	50 55 60		
[2670]	Asn Leu Leu Ile Tyr Thr Ala Ser Thr Leu Gln Ser Gly Val Pro Ser		
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[2672]	Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser		
[2673]	85 90 95		
[2674]	Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn		
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[2676]	Ile Phe Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg		
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[2680]	Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr		
[2681]	145 150 155 160		
[2682]	Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser		
[2683]	165 170 175		
[2684]	Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr		
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[2686]	Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys		
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[2705]	Ser Thr Leu Met His Trp Tyr Gln Gln Lys Pro Gly Gln Gln Pro Lys	
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[2807]	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp			

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[2813]	Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu		
[2814]	325	330	335
[2815]	Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Glu Glu Lys		
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[2817]	Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr		
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[2821]	Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu		
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[2825]	Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys		
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[2858]	Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp			
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[2860]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu			
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[2874]	Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr			
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[2876]	Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val			
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[2880]	Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Glu Glu Lys Thr Ile Ser			
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[2882]	Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro			
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[2888]	Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
[2889]	405 410 415
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[2892]	Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
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[2908]	35 40 45
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[2919]	Val Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
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[2921]	Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
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[2925]	Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
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[2927]	Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
[2928]	195 200 205
[2929]	Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro
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[2931]	Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu
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[2939]	Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
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[2941]	Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
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[2952]	385 390 395 400
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[2997]	225					230					235					240
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[3006]	Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val		
[3007]	305	310	315
[3008]	Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys		
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[3011]	340	345	350
[3012]	Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro		
[3013]	355	360	365
[3014]	Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val		
[3015]	370	375	380
[3016]	Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly		
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[3019]	405	410	415
[3020]	Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp		
[3021]	420	425	430
[3022]	Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His		
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[3039]	Ala Gly Gly Tyr Trp Trp Thr Trp Ile Arg Gln Phe Pro Gly Gln Lys		
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[3041]	Leu Glu Trp Met Gly Tyr Ile Tyr Ser Ser Gly Ser Thr Asn Tyr Asn		

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[3043]	Pro Ser Ile Lys Ser Arg Ile Ser Ile Thr Arg Asp Thr Ala Lys Asn			
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[3045]	Gln Phe Phe Leu Gln Leu Asn Ser Val Thr Thr Glu Glu Asp Thr Ala			
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[3049]	Ser Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Thr Thr Lys			
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[3055]	Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr			
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[3057]	Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val			
[3058]		195	200	205
[3059]	Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn			
[3060]		210	215	220
[3061]	Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro			
[3062]	225	230	235	240
[3063]	Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu			
[3064]		245	250	255
[3065]	Leu Leu Ala Gly Pro Asp Val Phe Leu Phe Pro Pro Lys Pro Lys Asp			
[3066]		260	265	270
[3067]	Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp			
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[3069]	Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly			
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[3071]	Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn			
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[3073]	Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp			
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[3075]	Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro			
[3076]		340	345	350
[3077]	Leu Pro Glu Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu			
[3078]		355	360	365
[3079]	Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn			
[3080]		370	375	380

[3081]	Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
[3082]	385 390 395 400
[3083]	Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
[3084]	405 410 415
[3085]	Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
[3086]	420 425 430
[3087]	Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
[3088]	435 440 445
[3089]	Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
[3090]	450 455 460
[3091]	Ser Leu Ser Pro Gly Lys
[3092]	465 470

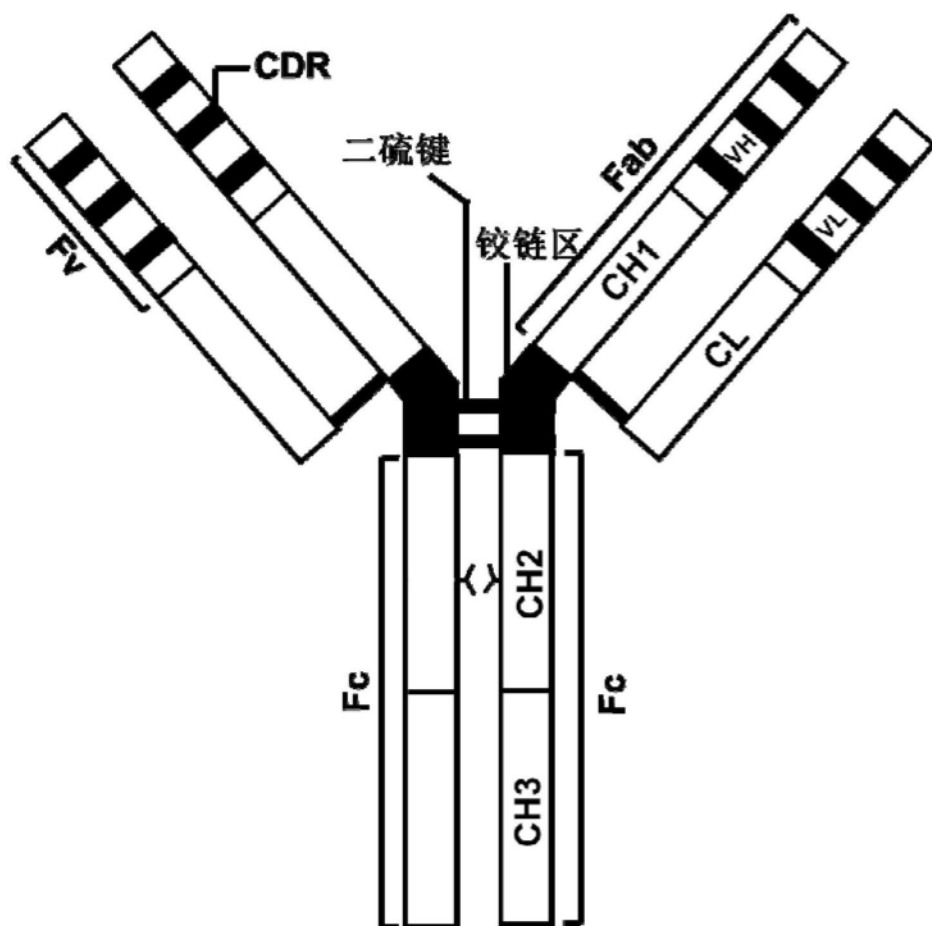


图1

Section 1									
	(1)	1	10	20	30	40	50	60	
EU 指数		118	-----CH1-----						
G1	(1)	ASTKGPSVFPLAPSSKSTSGGT AAL GCL VKDYF PEPVT VSWNS GAL TSGVHTF PAVL QSS							
G2	(1)	ASTKGPSVFPLAPCSRSTSESTAAL GCL VKDYF PEPVT VSWNS GAL TSGVHTF PAVL QSS							
G3	(1)	ASTKGPSVFPLAPCSRSTSGGT AAL GCL VKDYF PEPVT VSWNS GAL TSGVHTF PAVL QSS							
G4	(1)	ASTKGPSVFPLAPCSRSTSESTAAL GCL VKDYF PEPVT VSWNS GAL TSGVHTF PAVL QSS							
Consensus	(1)	ASTKGPSVFPLAPCSRSTSGSTAALGCLVKDYFPEPVT VSWNS GAL TSGVHTF PAVL QSS							
Section 2									
	(61)	61	70	80	90	100	110	120	
EU 指数		----->215 216<-----							
G1	(61)	GLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKRVE-----							
G2	(61)	GLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVR-----							
G3	(61)	GLYSLSSVVTVPSSSLGTQTYTCNVNHKPSNTKVDKRVELKTPLGDTTHTCPRCPEPKSC							
G4	(61)	GLYSLSSVVTVPSSSLGTQTYTCNVDHKPSNTKVDKRVES-----							
Consensus	(61)	GLYSLSSVVTVPSSSLGTQTYTCNVNHKPSNTKVDKRVE							
Section 3									
	(121)	121	130	140	150	160	170	180	
EU 指数		-----Hinge----->230 231<-----							
G1	(100)	-----PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT							
G2	(101)	-----KCCVECPPCPAPPVAG-PSVFLFPPKPKDT							
G3	(121)	DTPPPCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCPAPELLGGPSVFLFPPKPKDT							
G4	(101)	-----KYGPPCPCPAPEFLGGPSVFLFPPKPKDT							
Consensus	(121)	PKSCKPPCPPCPAPELLGGPSVFLFPPKPKDT							
Section 4									
	(181)	181	190	200	210	220	230	240	
EU 指数		-----CH2-----							
G1	(134)	LMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH							
G2	(130)	LMI SRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVH							
G3	(181)	LMI SRTPEVTCVVVDVSHEDPEVQFKWYVDGVEVHNAKTKPREEQYNSTFRVVSVLTVLH							
G4	(131)	LMI SRTPEVTCVVVDVSEQDEPVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLH							
Consensus	(181)	LMI SRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVLH							
Section 5									
	(241)	241	250	260	270	280	290	300	
EU 指数		----->340 341<-----							
G1	(194)	QDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK							
G2	(190)	QDWLNGKEYKCKVSNKGLPAPIEKTI SKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVK							
G3	(241)	QDWLNGKEYKCKVSNKALPAPIEKTI SKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVK							
G4	(191)	QDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVK							
Consensus	(241)	QDWLNGKEYKCKVSNKALPAPIEKTI SKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVK							
Section 6									
	(301)	301	310	320	330	340	350	360	
EU 指数		-----CH3-----							
G1	(254)	GFYPSDI AVEWESNGQPENNYKTTPPVLDSGDSFFLYSKLTVDKSRWQQGNVFC SVMHE							
G2	(250)	GFYPSDI AVEWESNGQPENNYKTTPPMLDSGDSFFLYSKLTVDKSRWQQGNVFC SVMHE							
G3	(301)	GFYPSDI AVEWESSGQPENNYNTTPMLDSGDSFFLYSKLTVDKSRWQQGNI FSC SVMHE							
G4	(251)	GFYPSDI AVEWESNGQPENNYKTTPPVLDSGDSFFLYSRLTVDKSRWQEGNVFC SVMHE							
Consensus	(301)	GFYPSDIAVEWESNGQPENNYKTTPPMLDSGDSFFLYSKLTVDKSRWQQGNVFC SVMHE							
Section 7									
	(361)	361	378						
EU 指数		----->447							
G1	(314)	ALHNHYTQKSLSLSPGK-							
G2	(310)	ALHNHYTQKSLSLSPGK-							
G3	(361)	ALHNRFTQKSLSLSPGK-							
G4	(311)	ALHNHYTQKSLSLSLGK-							
Consensus	(361)	ALHNHYTQKSLSLSPGK							

图2

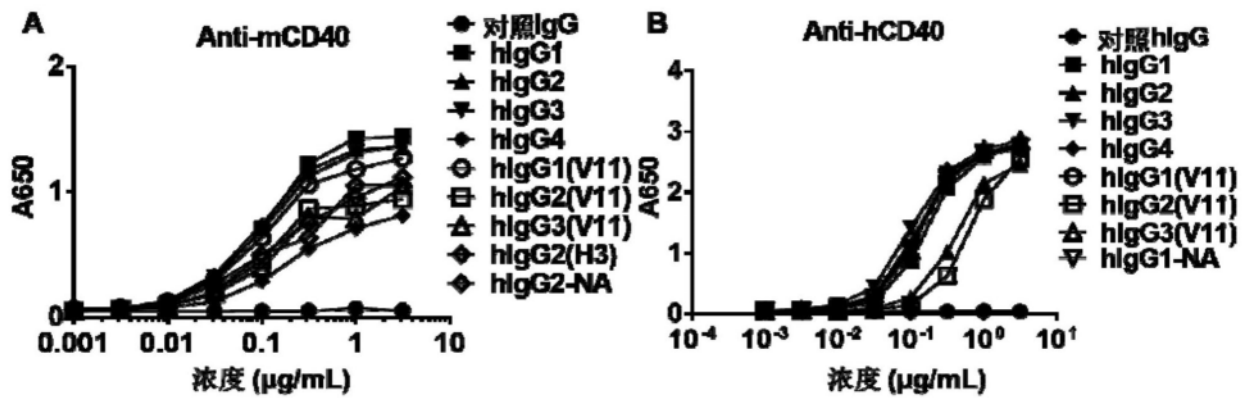


图3

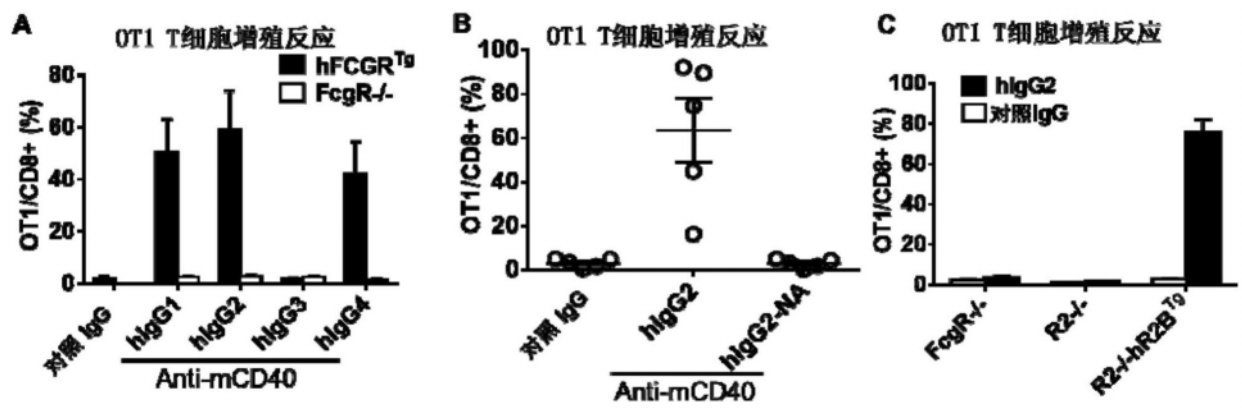


图4

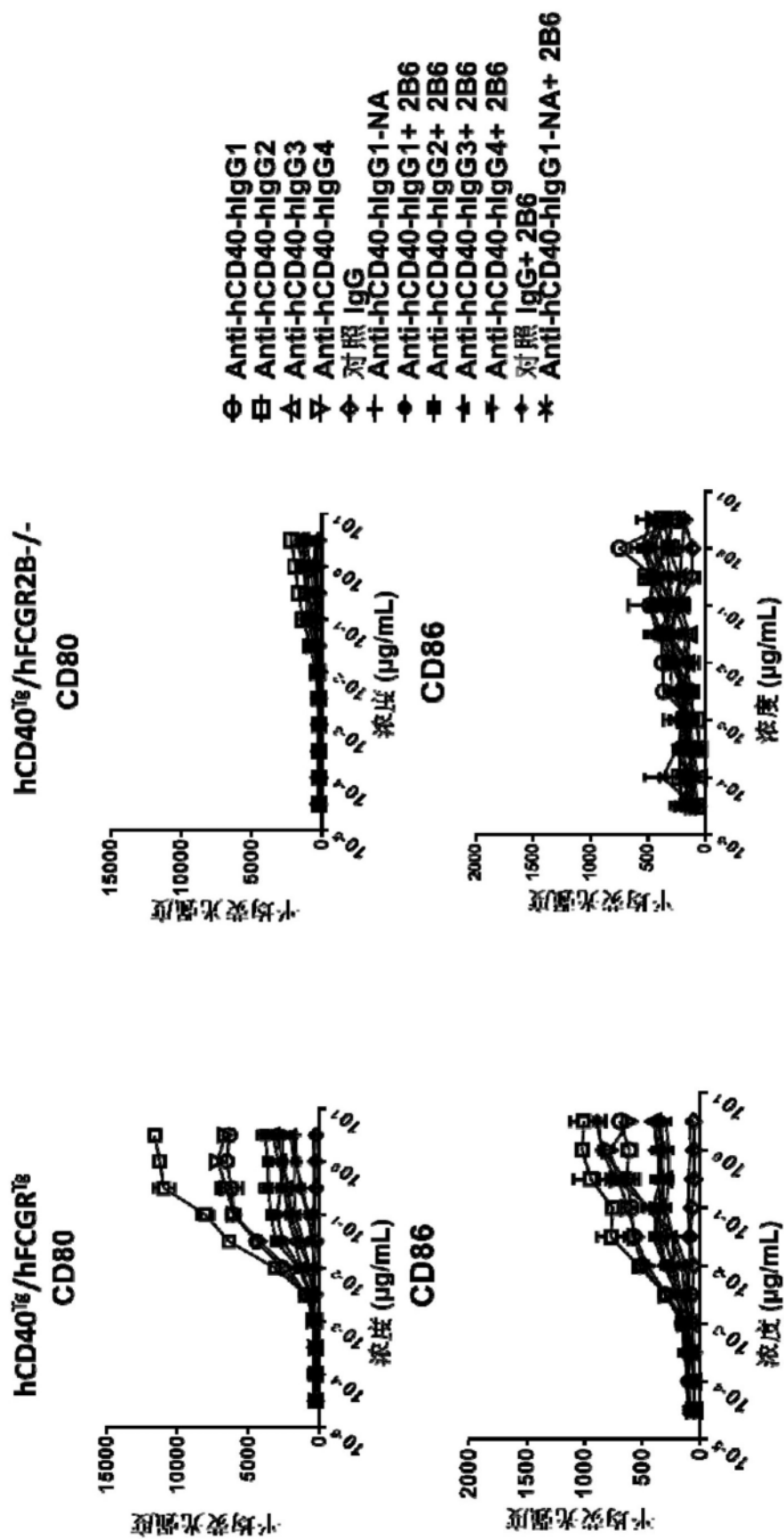


图5

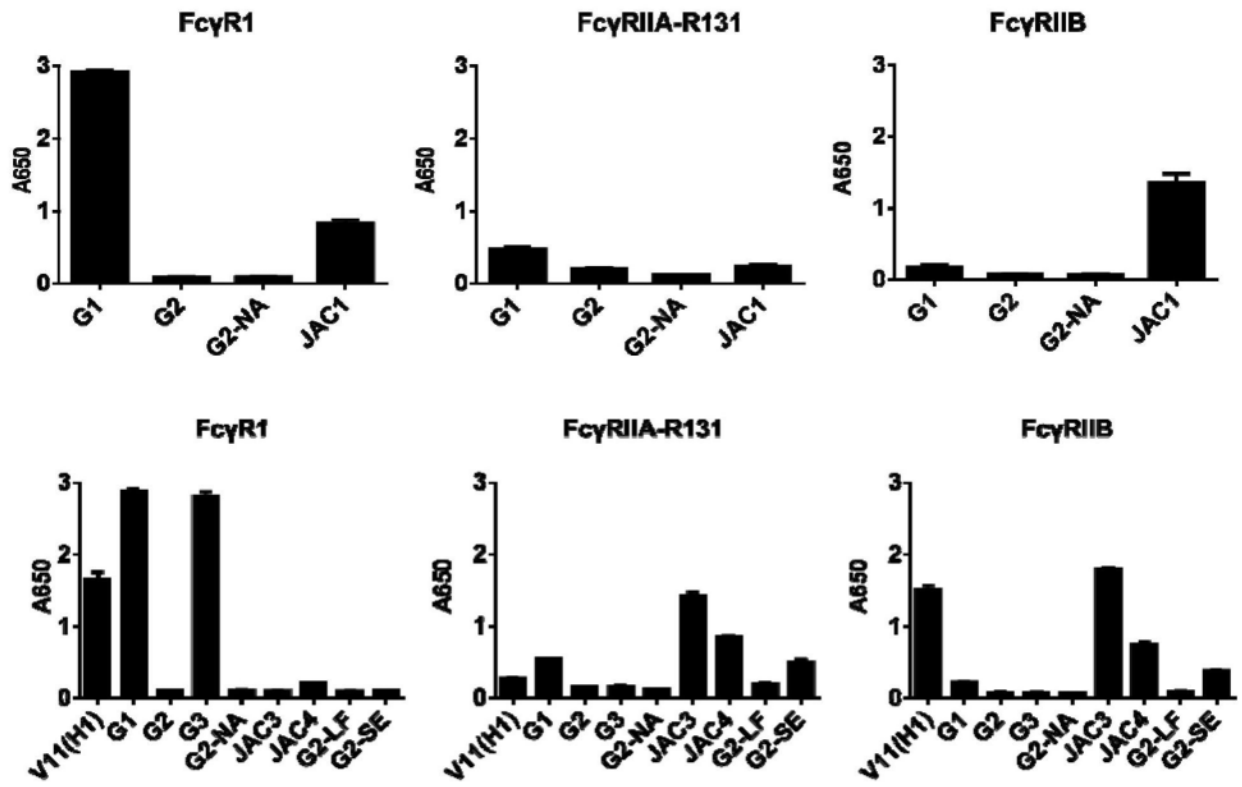


图6

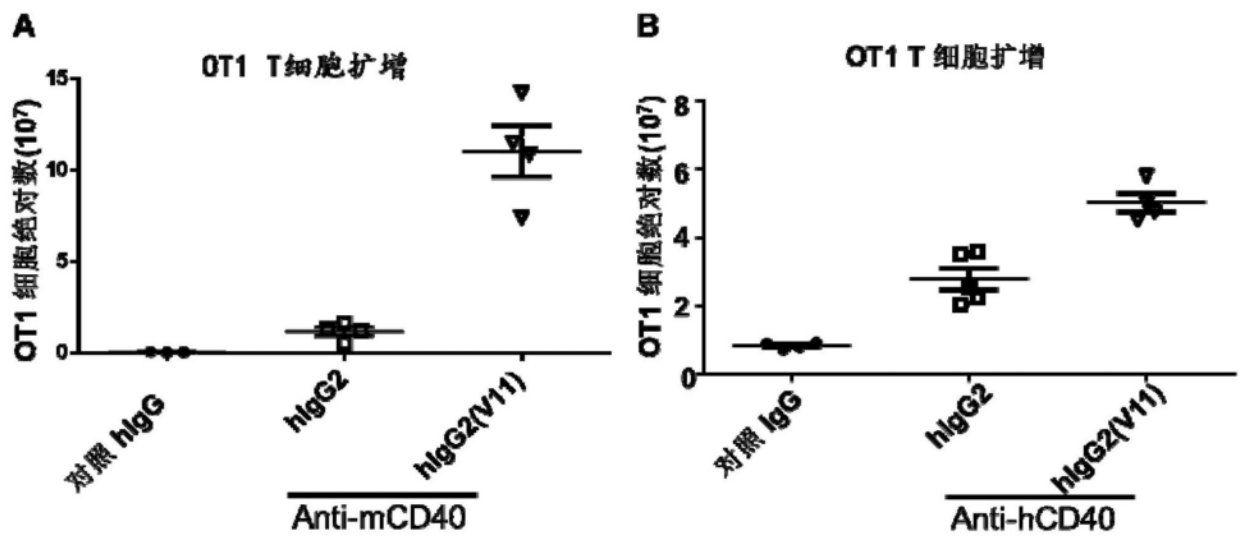


图7

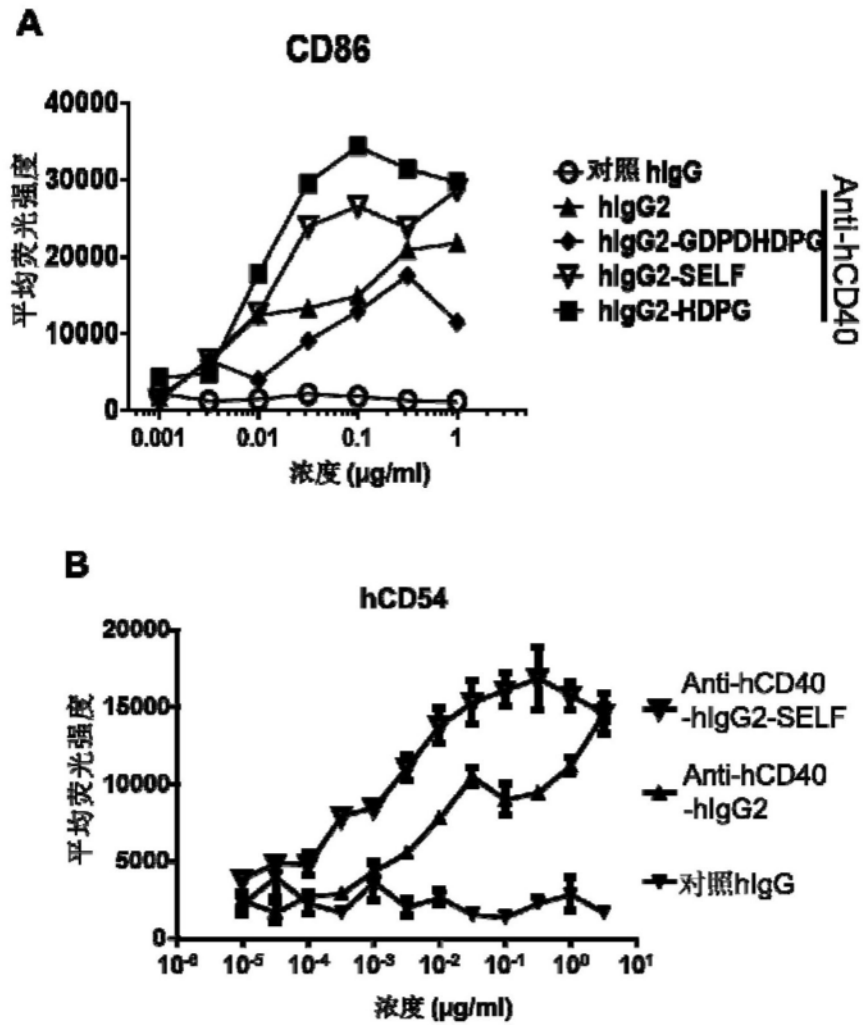


图8

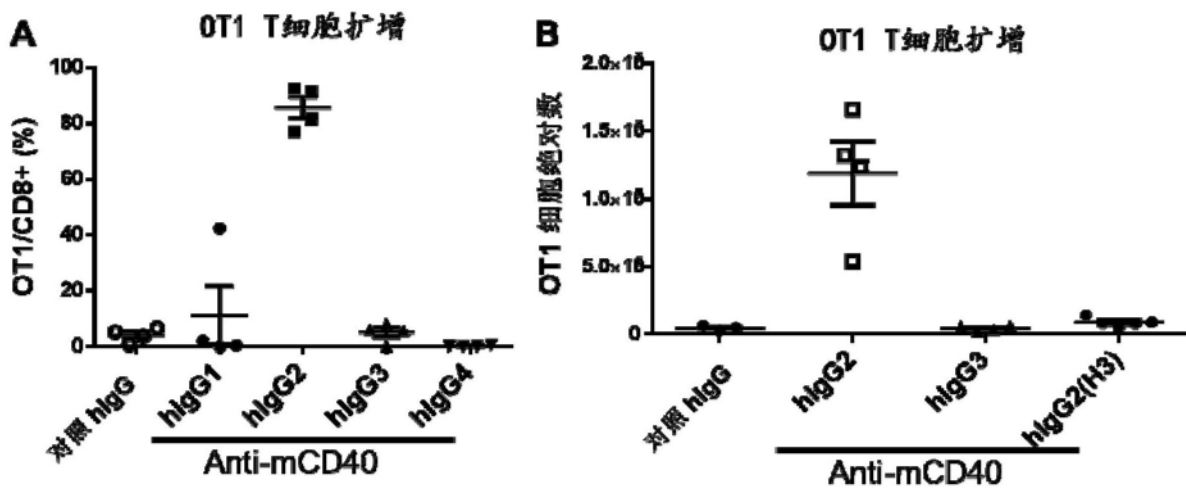


图9

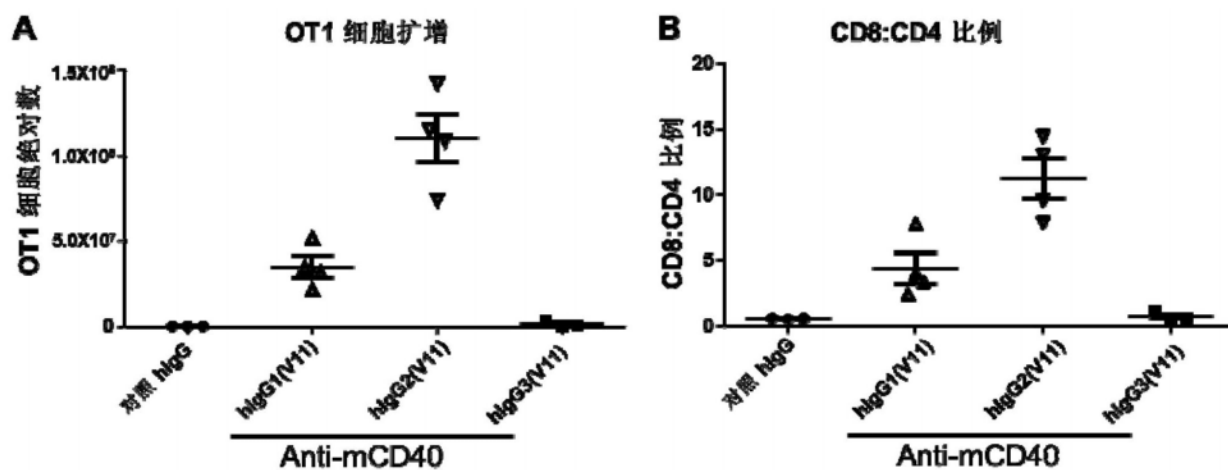


图10

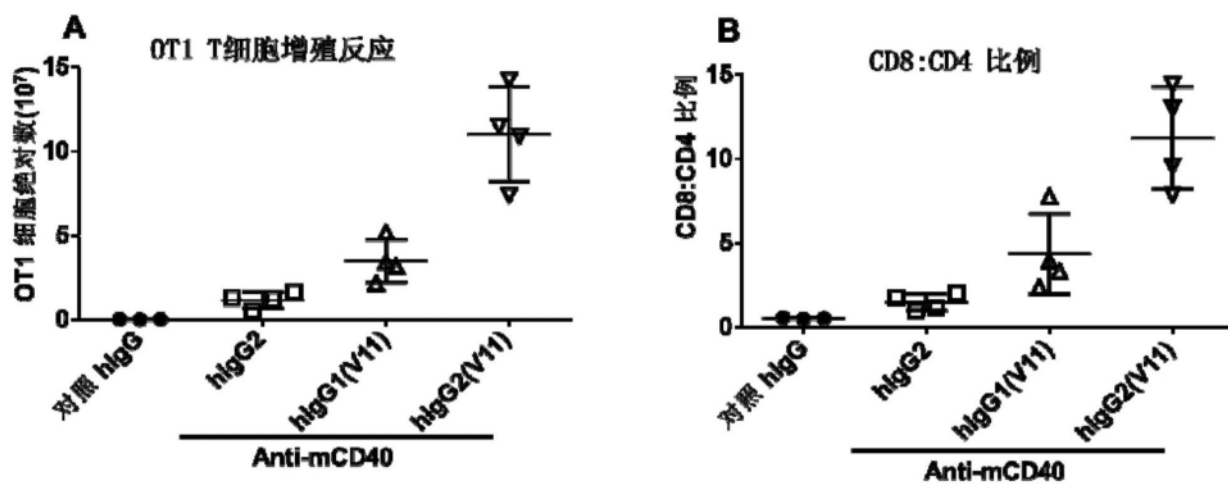


图11

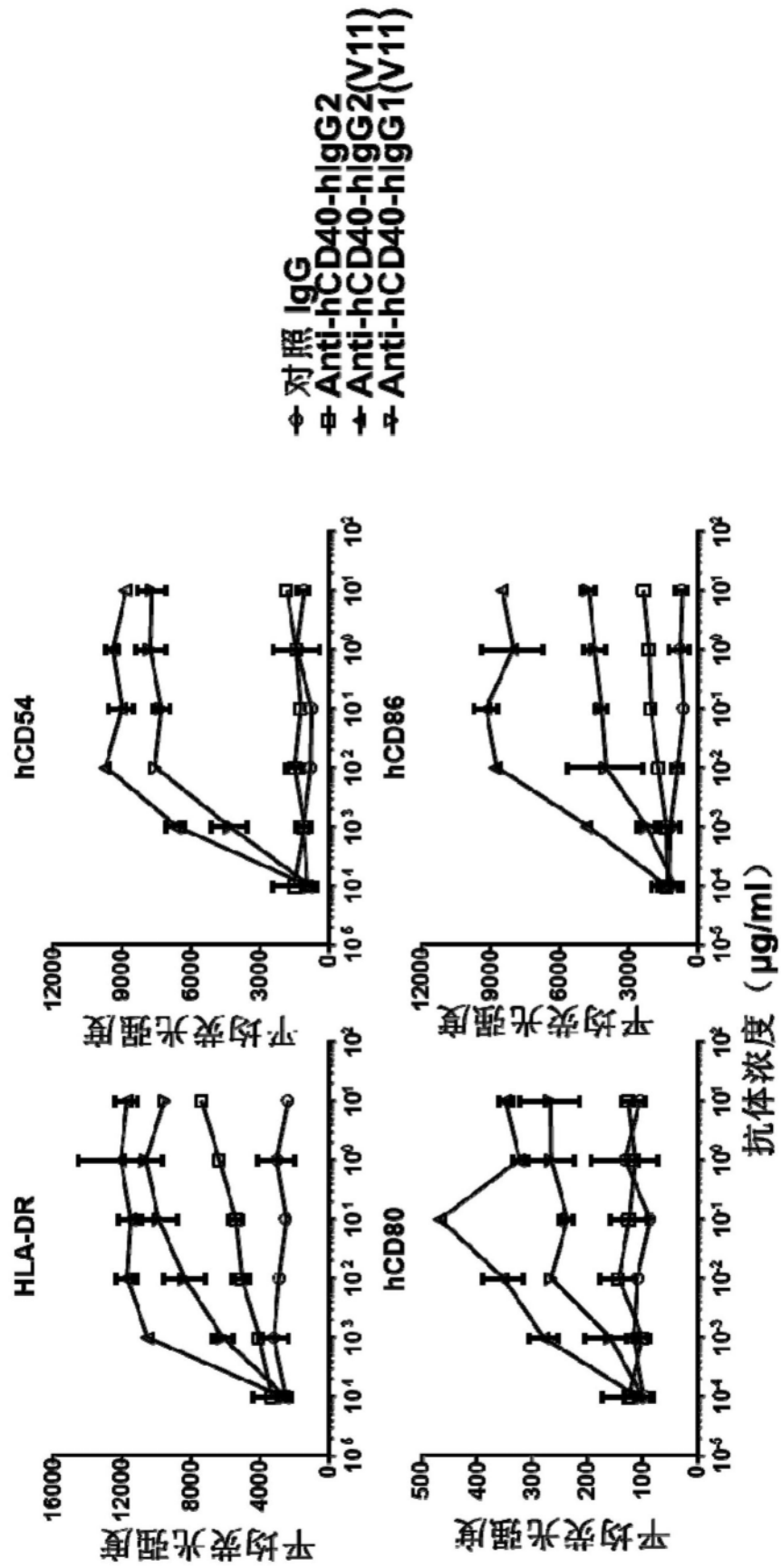


图12

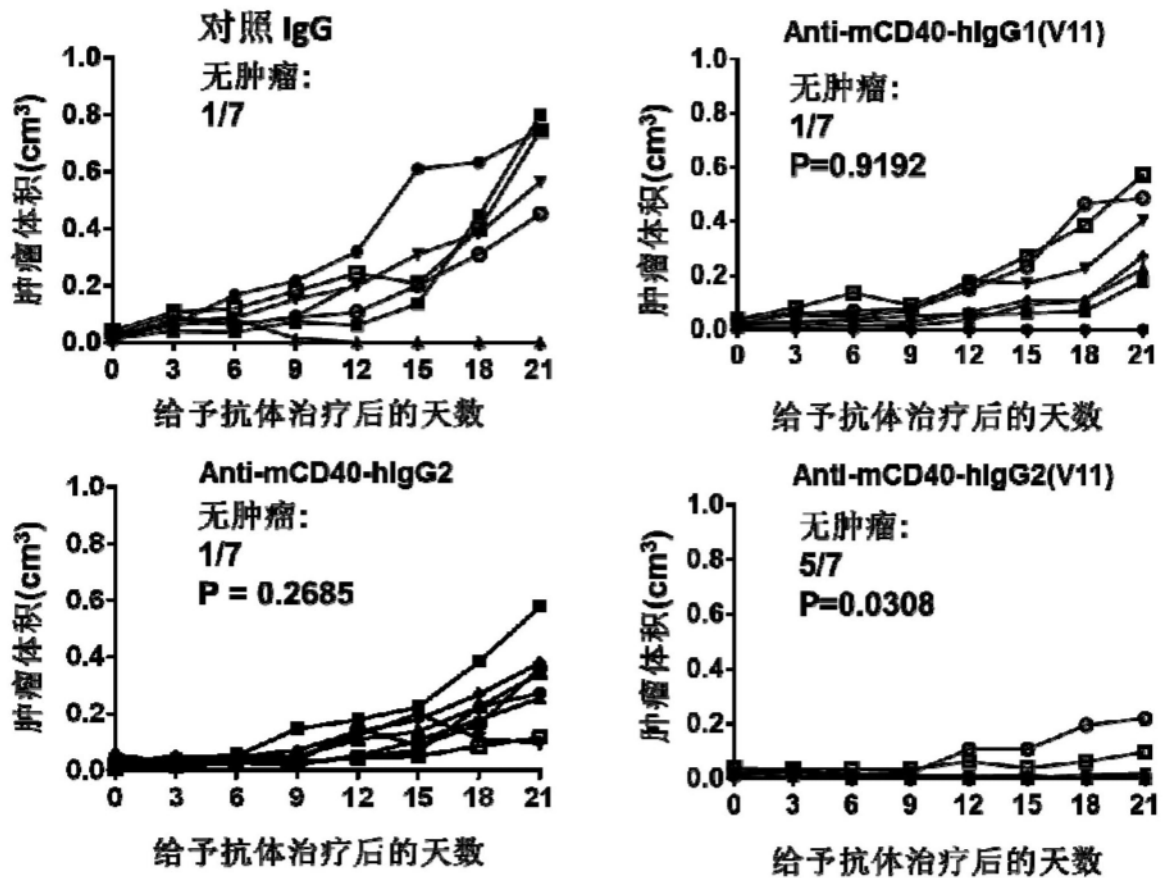


图13

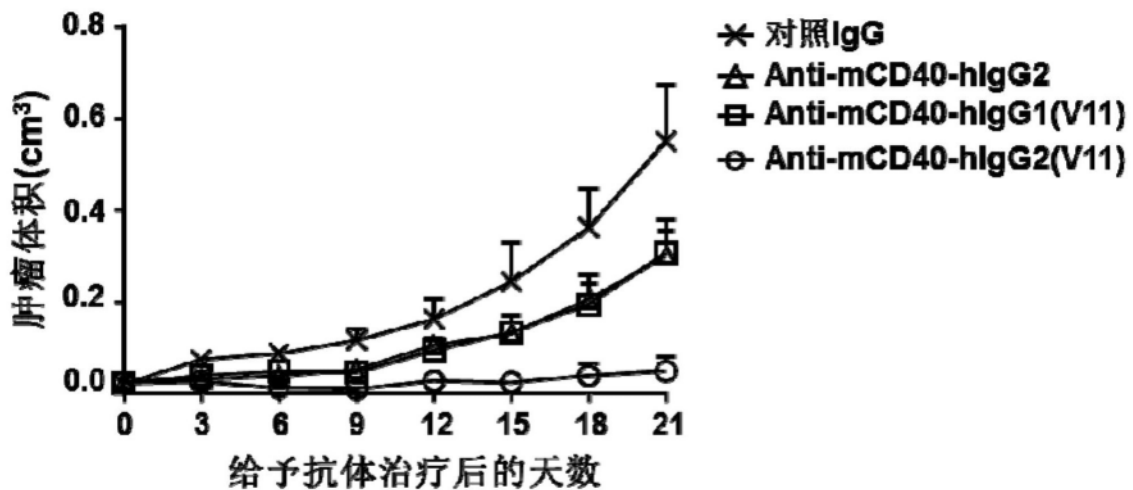


图14

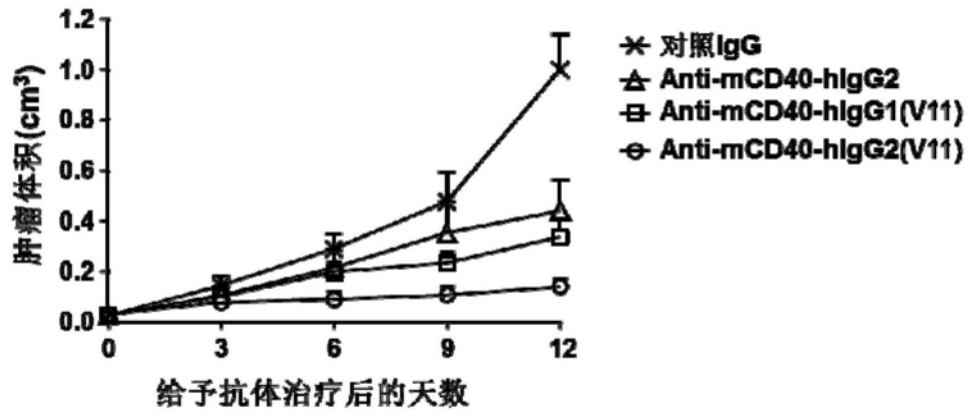


图15

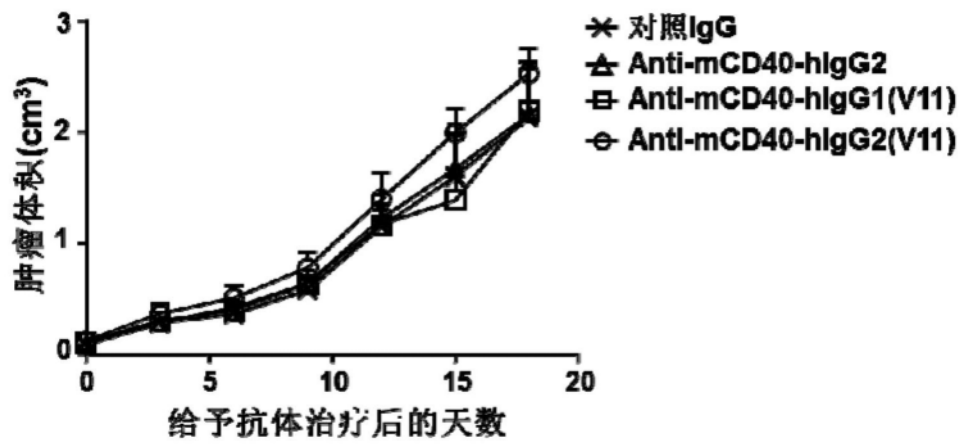


图16

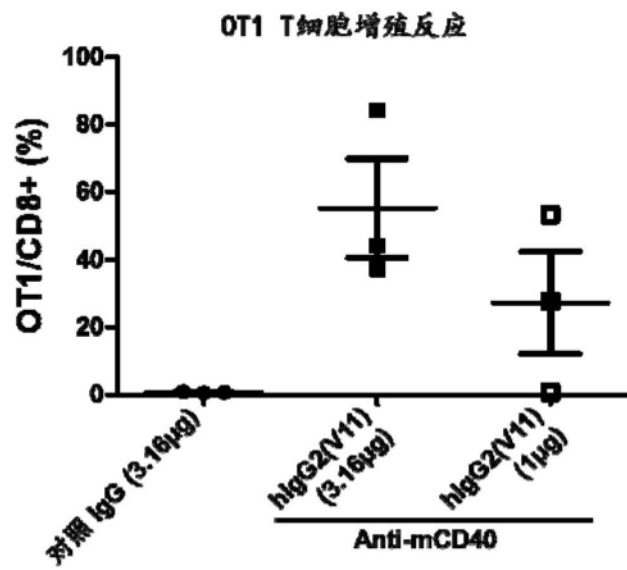


图17

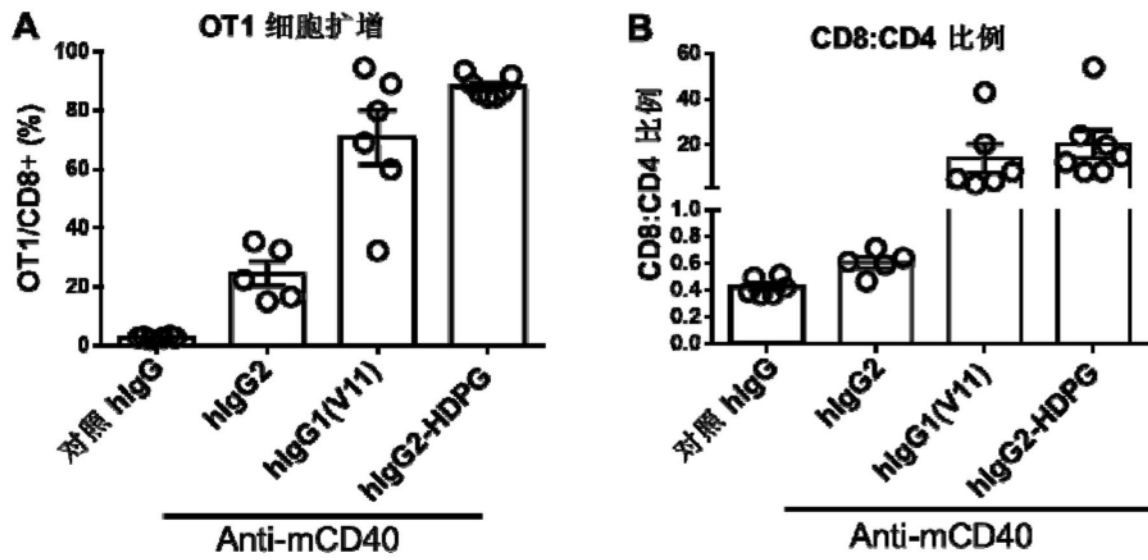


图18

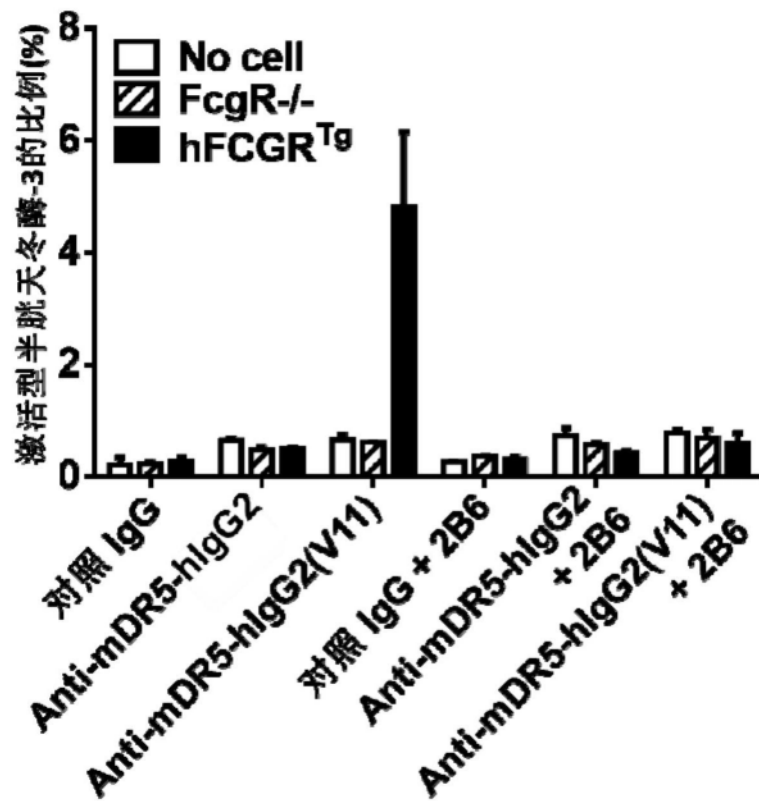


图19

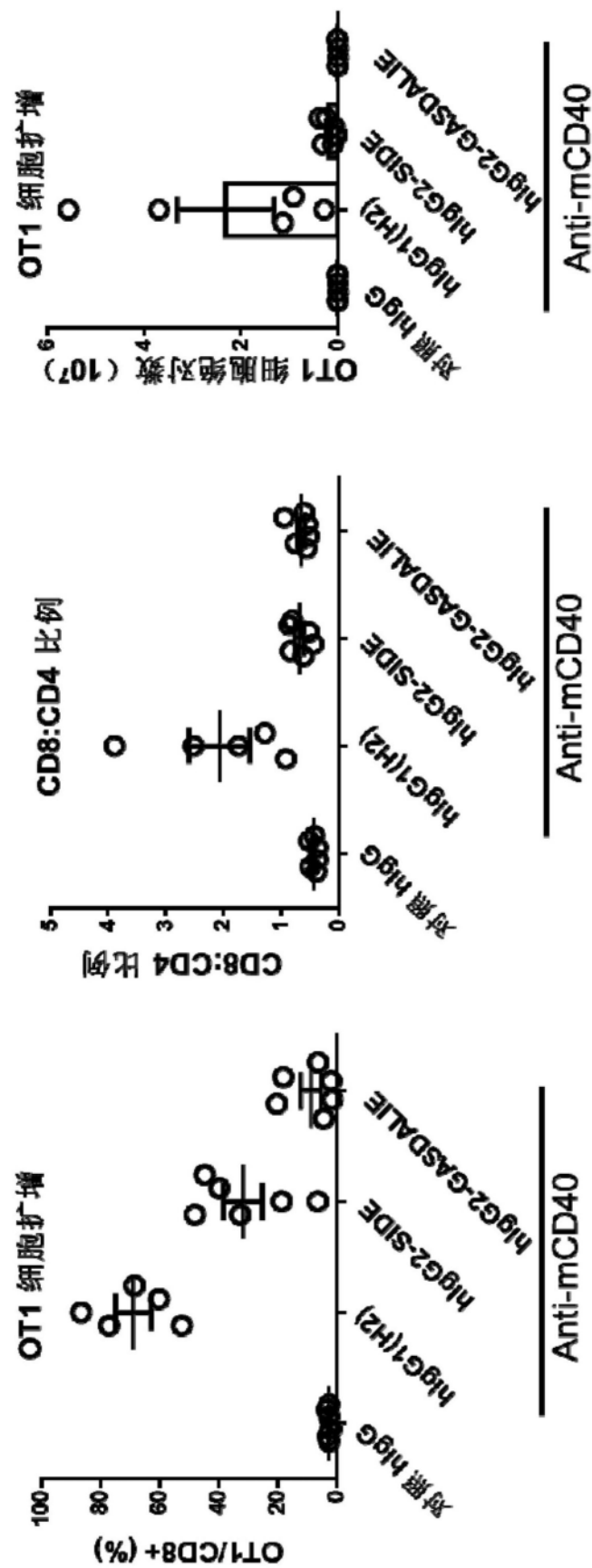


图20