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(54)发明名称

一种4-1BB结合蛋白及其应用

(57)摘要

本发明公开了一种4-1BB结合蛋白及其应用。所述4-1BB结合蛋白,其包括重链可变区;所述的重链可变区包含HCDR1、HCDR2和HCDR3。本发明的4-1BB结合蛋白为全人源抗体,其具有与人4-1BB和食蟹猴4-1BB结合的活性,部分4-1BB结合蛋白的大小只有传统IgG抗体的一半,可很好地用于双特异性抗体。

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1.一种4-1BB结合蛋白,其特征在于,其包括重链可变区;

所述的重链可变区包含HCDR1、HCDR2和HCDR3,所述HCDR1、HCDR2和HCDR3分别如序列表中SEQ ID NO: 20、SEQ ID NO: 69和SEQ ID NO: 115所示,或者分别如SEQ ID NO: 20、SEQ ID NO: 71和SEQ ID NO: 115所示,或者分别如SEQ ID NO: 19、SEQ ID NO: 57和SEQ ID NO: 101所示,或者分别如SEQ ID NO: 15、SEQ ID NO: 58和SEQ ID NO: 102所示,或者分别如SEQ ID NO: 20、SEQ ID NO: 59和SEQ ID NO: 103所示,或者分别如SEQ ID NO: 20、SEQ ID NO: 60和SEQ ID NO: 104所示,或者分别如SEQ ID NO: 15、SEQ ID NO: 61和SEQ ID NO: 105所示,或者分别如SEQ ID NO: 15、SEQ ID NO: 60和SEQ ID NO: 106所示,或者分别如SEQ ID NO: 20、SEQ ID NO: 63和SEQ ID NO: 108所示,或者分别如SEQ ID NO: 20、SEQ ID NO: 60和SEQ ID NO: 108所示,或者分别如SEQ ID NO: 22、SEQ ID NO: 64和SEQ ID NO: 109所示,或者分别如SEQ ID NO: 15、SEQ ID NO: 60和SEQ ID NO: 110所示,或者分别如SEQ ID NO: 15、SEQ ID NO: 65和SEQ ID NO: 111所示,或者分别如SEQ ID NO: 22、SEQ ID NO: 66和SEQ ID NO: 112所示,或者分别如SEQ ID NO: 15、SEQ ID NO: 49和SEQ ID NO: 113所示,或者分别如SEQ ID NO: 20、SEQ ID NO: 60和SEQ ID NO: 103所示,或者分别如SEQ ID NO: 15、SEQ ID NO: 63和SEQ ID NO: 104所示,或者分别如SEQ ID NO: 15、SEQ ID NO: 60和SEQ ID NO: 114所示,或者分别如SEQ ID NO: 23、SEQ ID NO: 67和SEQ ID NO: 105所示,或者分别如SEQ ID NO: 24、SEQ ID NO: 68和SEQ ID NO: 103所示,或者分别如SEQ ID NO: 15、SEQ ID NO: 60和SEQ ID NO: 105所示,或者分别如SEQ ID NO: 15、SEQ ID NO: 70和SEQ ID NO: 116所示,或者分别如SEQ ID NO: 300、SEQ ID NO: 308和SEQ ID NO: 326所示的序列,或者分别如SEQ ID NO: 300、SEQ ID NO: 309和SEQ ID NO: 327所示的序列,或者分别如SEQ ID NO: 300、SEQ ID NO: 310和SEQ ID NO: 328所示的序列,或者分别如SEQ ID NO: 300、SEQ ID NO: 308和SEQ ID NO: 329所示的序列,或者分别如SEQ ID NO: 300、SEQ ID NO: 311和SEQ ID NO: 330所示的序列,或者分别如SEQ ID NO: 300、SEQ ID NO: 312和SEQ ID NO: 331所示的序列,或者分别如SEQ ID NO: 300、SEQ ID NO: 308和SEQ ID NO: 332所示的序列,或者分别如SEQ ID NO: 300、SEQ ID NO: 313和SEQ ID NO: 330所示的序列,或者分别如SEQ ID NO: 300、SEQ ID NO: 314和SEQ ID NO: 329所示的序列,或者分别如SEQ ID NO: 300、SEQ ID NO: 315和SEQ ID NO: 331所示的序列,或者分别如SEQ ID NO: 300、SEQ ID NO: 314和SEQ ID NO: 327所示的序列,或者分别如SEQ ID NO: 300、SEQ ID NO: 316和SEQ ID NO: 331所示的序列,或者分别如SEQ ID NO: 300、SEQ ID NO: 308和SEQ ID NO: 333所示的序列,或者分别如SEQ ID NO: 300、SEQ ID NO: 317和SEQ ID NO: 334所示的序列。

2.如权利要求1所述的4-1BB结合蛋白,其特征在于,编码所述重链可变区的FR的基因来源于胚系V基因IGHV4-34、IGHV3-23、IGHV3-11或者IGHV3-74。

3.如权利要求1所述的4-1BB结合蛋白,其特征在于,所述的重链可变区包含如序列表中SEQ ID NO: 175-180、SEQ ID NO: 182-196、SEQ ID NO: 337-352以及SEQ ID NO: 198中的任一个所示的序列。

4.一种4-1BB结合蛋白,其特征在于,所述的4-1BB结合蛋白包括重链可变区和轻链可变区,所述的重链可变区包含HCDR1、HCDR2和HCDR3,所述的轻链可变区包含LCDR1、LCDR2和LCDR3,所述的HCDR1、HCDR2和HCDR3分别如SEQ ID NO: 16、SEQ ID NO: 50和SEQ ID NO:

96所示,或者分别如SEQ ID NO: 16、SEQ ID NO: 53和SEQ ID NO: 96所示,或者分别如SEQ ID NO: 16、SEQ ID NO: 54和SEQ ID NO: 96所示;所述的LCDR1如SEQ ID NO: 133所示,所述的LCDR2如SEQ ID NO: 145所示,所述的LCDR3如SEQ ID NO: 158所示。

5.如权利要求4所述的4-1BB结合蛋白,其特征在于,编码所述轻链可变区的FR的基因来源于胚系V基因IGKV3-15;其中:LFWR1包含如SEQ ID NO: 126或者SEQ ID NO: 128所示的氨基酸序列,LFWR2包含如SEQ ID NO: 140所示的氨基酸序列,LFWR3包含如SEQ ID NO: 151所示的氨基酸序列,LFWR4包含如SEQ ID NO: 164所示的氨基酸序列。

6.如权利要求4所述的4-1BB结合蛋白,其特征在于,所述的重链可变区的氨基酸序列如SEQ ID NO: 168所示,且所述的轻链可变区的氨基酸序列如SEQ ID NO: 201所示;或者,所述的重链可变区的氨基酸序列如SEQ ID NO: 171所示,且所述的轻链可变区的氨基酸序列如SEQ ID NO: 204所示;或者,所述的重链可变区的氨基酸序列如SEQ ID NO: 172所示,且所述的轻链可变区的氨基酸序列如SEQ ID NO: 204所示。

7.如权利要求1-6任一项所述的4-1BB结合蛋白,其特征在于,所述4-1BB结合蛋白还包含重链恒定区和/或轻链恒定区;所述重链恒定区选自hIgG1、hIgG2、hIgG3或hIgG4或其变体,所述轻链恒定区选自κ链或者λ链或其突变;所述hIgG1的变体的突变选自L234A、L235A、E345R和P329G中的一个或多个;所述hIgG4的变体的突变为S228P。

8.如权利要求7所述的4-1BB结合蛋白,其特征在于,所述hIgG1的变体的突变为E345R,或者L234A、L235A和E345R的组合,或者L234A、L235A和P329G的组合。

9.如权利要求4所述的4-1BB结合蛋白,其特征在于,所述4-1BB结合蛋白包含重链和轻链,所述重链的氨基酸序列如SEQ ID NO: 209所示,且所述轻链的氨基酸序列如SEQ ID NO: 243所示;或者,所述重链的氨基酸序列如SEQ ID NO: 212所示,且所述轻链的氨基酸序列如SEQ ID NO: 246所示;或者,所述重链的氨基酸序列如SEQ ID NO: 213所示,且所述轻链的氨基酸序列如SEQ ID NO: 246所示;或者,所述重链的氨基酸序列如SEQ ID NO: 216所示,且所述轻链的氨基酸序列如SEQ ID NO: 246所示。

10.如权利要求1所述的4-1BB结合蛋白,其特征在于,其为全长抗体、双特异性抗体、多特异性抗体、重链抗体、单域抗体或单区抗体的形式,或为由上述抗体制得的单克隆抗体。

11.如权利要求4所述的4-1BB结合蛋白,其特征在于,其为全长抗体、Fab、Fab'、$F(ab')_2$、Fv、scFv、双特异性抗体、多特异性抗体的形式,或为由上述抗体制得的单克隆抗体。

12.如权利要求11所述的4-1BB结合蛋白,其特征在于,所述全长抗体的重链包含如SEQ ID NO: 209所示的序列,且轻链包含如SEQ ID NO: 243所示的序列;或者包含如SEQ ID NO: 212所示的序列,且轻链包含如SEQ ID NO: 246所示的序列,或者包含如SEQ ID NO: 213所示的序列,且轻链包含如SEQ ID NO: 246所示的序列,或者包含SEQ ID NO: 216所示的序列,且轻链包含如SEQ ID NO: 246所示的序列。

13.一种双特异性抗体,其特征在于,所述的双特异性抗体包含第一蛋白功能区和第二蛋白功能区,所述的第一蛋白功能区为如权利要求1-12任一项所述的4-1BB结合蛋白,所述的第二蛋白功能区靶向肿瘤抗原。

14.如权利要求13所述的双特异性抗体,其特征在于,所述第二蛋白功能区为HER2抗体或者PD-L1抗体。

15.如权利要求14所述的双特异性抗体，其特征在于，所述的HER2抗体为trastuzumab或者pertuzumab，所述的PD-L1抗体为atezolizumab或者PR000265，所述PR000265的重链如SEQ ID NO: 211所示，轻链如SEQ ID NO: 245所示。

16.如权利要求13所述的双特异性抗体，其特征在于，所述的第一蛋白功能区或者所述的第二蛋白功能区为scFv、VHH、免疫球蛋白、Fab、Fab'、$F(ab')_2$或者重链可变区的形式。

17.如权利要求16所述的双特异性抗体，其特征在于，所述的第一蛋白功能区为Fab，所述的第二蛋白功能区为VHH；或者，所述第一蛋白功能区为Fab，所述的第二蛋白功能区为免疫球蛋白；或者，所述的第一蛋白功能区为免疫球蛋白，所述的第二蛋白功能区为重链可变区。

18.如权利要求17所述的双特异性抗体，其特征在于，所述第一蛋白功能区和所述第二蛋白功能区之间和/或所述scFv的重链可变区和轻链可变区之间通过连接子连接，所述连接子的氨基酸序列为GS或者如序列表中SEQ ID NO: 273-293任一个所示。

19.如权利要求13-18任一项所述的双特异性抗体，其特征在于，所述的双特异性抗体包含多肽链1和多肽链2；或者包含多肽链1、多肽链2和多肽链3；

所述多肽链1的氨基酸序列如SEQ ID NO: 244所示，且所述多肽链2的氨基酸序列如SEQ ID NO: 251-265中任一个所示；或者所述多肽链1的氨基酸序列如SEQ ID NO: 245所示，且所述多肽链2的氨基酸序列如SEQ ID NO: 271所示；或者所述多肽链1的氨基酸序列如SEQ ID NO: 249所示，且所述多肽链2的氨基酸序列如SEQ ID NO: 272所示；或者所述多肽链1的氨基酸序列如SEQ ID NO: 245所示，且所述多肽链2的氨基酸序列如SEQ ID NO: 270所示；或者所述多肽链1的氨基酸序列如SEQ ID NO: 245所示，且所述多肽链2的氨基酸序列如SEQ ID NO: 269所示；或者所述多肽链1的氨基酸序列如SEQ ID NO: 245所示，且所述多肽链2的氨基酸序列如SEQ ID NO: 268所示；或者所述多肽链1的氨基酸序列如SEQ ID NO: 245所示，且所述多肽链2的氨基酸序列如SEQ ID NO: 369-382中任一个所示；或者所述多肽链1的氨基酸序列如SEQ ID NO: 267所示，所述多肽链2的氨基酸序列如SEQ ID NO: 266所示，且所述多肽链3的氨基酸序列如SEQ ID NO: 246所示；或者所述多肽链1的氨基酸序列如SEQ ID NO: 250所示，且所述多肽链2的氨基酸序列如SEQ ID NO: 249所示，且所述多肽链3的氨基酸序列如SEQ ID NO: 246所示。

20.一种分离的核酸，其编码如权利要求1-12任一项所述的4-1BB结合蛋白或如权利要求13-19任一项所述的双特异性抗体。

21.一种包含如权利要求20所述的分离的核酸的表达载体。

22.一种宿主细胞，其包含如权利要求21所述的表达载体；所述宿主细胞为原核细胞或真核细胞。

23.一种4-1BB结合蛋白的制备方法，其包含培养如权利要求22所述的宿主细胞，从培养物中获得所述4-1BB结合蛋白。

24.一种嵌合抗原受体，其包含如权利要求1-12任一项所述的4-1BB结合蛋白或如权利要求13-19任一项所述的双特异性抗体。

25.一种抗体药物偶联物，其包含细胞毒性剂，以及如权利要求1-12任一项所述的4-1BB结合蛋白或如权利要求13-19任一项所述的双特异性抗体。

26.如权利要求25所述的抗体药物偶联物，其特征在于，所述细胞毒性剂为MMAF或

MMAE。

27.一种药物组合物，其包含如权利要求1-12任一项所述的4-1BB结合蛋白、如权利要求13-19任一项所述的双特异性抗体和/或如权利要求25-26任一项所述的抗体药物偶联物。

28.如权利要求1-12任一项所述的4-1BB结合蛋白、如权利要求13-19任一项所述的双特异性抗体和如权利要求27所述的药物组合物在制备治疗癌症的药物中的应用。

29.如权利要求28所述的应用，其特征在于，所述癌症为与HER2、PD-L1以及4-1BB中的一种或多种相关的癌症，所述癌症为乳腺癌、黑色素瘤、肺癌、胃癌、肝癌、食管癌、宫颈癌、头颈部肿瘤或者结直肠癌。

30.试剂盒，其包括如权利要求1-12任一项所述的4-1BB结合蛋白、如权利要求13-19任一项所述的双特异性抗体、如权利要求24所述的嵌合抗原受体、如权利要求25-26任一项所述的抗体药物偶联物和/或如权利要求27所述的药物组合物。

31.如权利要求30所述的试剂盒，其特征在于，所述试剂盒还包括(i)施用抗体或其抗原结合片段或抗体药物偶联物或药物组合物的装置;和/或(ii)使用说明。

32.一种套装药盒，其包含药盒A和药盒B，其中：

所述药盒A含有如权利要求1-12任一项所述的4-1BB结合蛋白、如权利要求13-19任一项所述的双特异性抗体、如权利要求24所述的嵌合抗原受体、如权利要求25-26任一项所述的抗体药物偶联物和/或如权利要求27所述的药物组合物；

所述药盒B含有其他抗肿瘤抗体或者包含所述其他抗肿瘤抗体的药物组合物，和/或由激素制剂、靶向小分子制剂、蛋白酶体抑制剂、成像剂、诊断剂、化疗剂、溶瘤药物、细胞毒性剂、细胞因子、共刺激分子的激活剂、抑制性分子的抑制剂以及疫苗组成的群组中的一种或多种。

33.一种免疫检测或者测定4-1BB的方法，其包括使用如权利要求1-12任一项所述的4-1BB结合蛋白、如权利要求13-19任一项所述的双特异性抗体、如权利要求24所述的嵌合抗原受体、如权利要求25-26任一项所述的抗体药物偶联物或如权利要求27所述的药物组合物;所述检测为非诊断和/或治疗目的的。

一种4-1BB结合蛋白及其应用

[0001] 本申请要求申请日为2020/6/30的中国专利申请202010619500.9的优先权。本申请引用上述中国专利申请的全文。

技术领域

[0002] 本申请涉及生物医药领域,具体的涉及一种4-1BB结合蛋白及其应用。

背景技术

[0003] 4-1BB,也称为CD137、肿瘤坏死因子受体超家族成员9(TNFRSF9),是一种激活诱导型的共刺激受体分子。4-1BB主要在淋巴细胞系上表达,如活化的T细胞,活化的自然杀伤(NK)细胞,活化的胸腺细胞以及皮内淋巴细胞。此外,4-1BB也在树突细胞,单核细胞、中心粒细胞以及嗜酸性细胞上表达。T细胞的激活除了需要T细胞表面的抗原识别受体(TCR)与MHC分子抗原肽的特异性结合之外,还需要抗原呈递细胞(APC)表面的共刺激分子与T细胞表面相应受体结合所提供的共刺激信号。4-1BB和其配体4-1BBL的结合能提供共刺激信号激活T细胞,加强细胞因子和免疫功能。4-1BB也被证明可以促进中枢记忆T细胞反应,这点可能支持4-1BB激动剂治疗的患者对肿瘤特异性T细胞的治疗持久性和对力竭的抵抗[1,2]。肿瘤上过表达抗4-1BB单链抗体片段(scFv)导致CD4+T细胞和NK细胞依赖的肿瘤清除消除[3,4,5]。小鼠模型全身性注射抗4-1BB抗体也被证明可导致肿瘤生长的延迟[6]。

[0004] 有研究证明,激活性4-1BB抗体可以代替其配体激活4-1BB下游通路。目前,临床上正在研究的激活性4-1BB抗体有Urelumab(BMS-663513)和Utomilumab(PF-05082566)。Utomilumab是一种配体阻断的IgG2抗体,Urelumab是一种非配体阻断的IgG4抗体。Utomilumab和Urelumab在体内体外都能增强T细胞功能,促进抗肿瘤作用。但是临床试验表明,在Urelumab使用剂量大于1mg/kg时,部分患者出现肺炎毒性(参见NCT00309023,NCT00612664,NCT01471210)。相比Urelumab,Utomilumab的安全性较高,但是激活4-1BB的活性较低。因此,急需研发更加安全有效的靶向4-1BB的新型疗法。

[0005] 为解决现有技术中缺乏抗肿瘤疗效,并解决安全性等技术问题,本发明提供一种靶向4-1BB的全人源抗体,以及基于该抗体和肿瘤特异性靶点的双特异性抗体及其应用。本申请提供了一种抗4-1BB抗原结合蛋白,其具有下述性质中的一种或多种:1)能够结合源自人和猴的4-1BB蛋白;2)能够刺激免疫细胞分泌IFN-γ,IL2和/或TNFα;3)能够抑制肿瘤生长和/或肿瘤细胞增殖;4)能够激活4-1BB信号通路。本申请还提供了所述抗原结合蛋白在预防和治疗肿瘤中的应用。

发明内容

[0006] 本发明所要解决的技术问题是为克服现有技术中抗体药物缺乏抗肿瘤疗效,以及安全性欠佳等缺陷,提供一种靶向4-1BB结合蛋白及其应用,特别是靶向4-1BB的全人源抗体,以及基于该抗体和肿瘤特异性靶点的双特异性抗体及其应用。

[0007] 本发明的第一方面提供一种4-1BB结合蛋白,其包括重链可变区;所述的重链可变

区包含HCDR1、HCDR2和HCDR3，所述的HCDR1包含如SEQ ID NO:15或其变体1、或者SEQ ID NO:16所示的序列，所述的HCDR2包含选自如SEQ ID NO:60或其变体2、或者SEQ ID NO:50或其变体4所示的序列，所述的HCDR3包含如SEQ ID NO:103或其变体3、SEQ ID NO:333或其变体5、SEQ ID NO:110、SEQ ID NO:111、SEQ ID NO:116、SEQ ID NO:326、SEQ ID NO:331、SEQ ID NO:334或者SEQ ID NO:96所示的序列；

[0008] 其中：

[0009] 所述的变体1的突变包括T3I、S6N/G/R以及Y7F中的一个或多个；较佳地，所述变体1的序列优选如序列表中SEQ ID NO:19、SEQ ID NO:20、SEQ ID NO:22、SEQ ID NO:23、SEQ ID NO:300或者SEQ ID NO:24所示；

[0010] 所述变体2的突变包括S1G/N/D、G2S/A、S3D、G5D/N/F/S/V以及S6T/N/D中的一个或多个；所述变体2的序列优选如序列表中SEQ ID NO:57-59、SEQ ID NO:61、SEQ ID NO:49、SEQ ID NO:308-317以及SEQ ID NO:63-71中的任一个序列所示；

[0011] 所述的变体3的突变包括G2R/D/A/K、S3A/T、S4G/N/A/T/H、E5T/V/M/G、T6A、D7G/S、H9Y/S/N、Y10H、Y11F、N12G/D以及V13I/M/T中的一个或多个；所述变体3的氨基酸序列优选如序列表中SEQ ID NO:101、SEQ ID NO:102、SEQ ID NO:104-106、SEQ ID NO:108、SEQ ID NO:109以及SEQ ID NO:112-115中的任一个序列所示；

[0012] 所述变体4的突变包括N1I或者N1Q；所述变体4的氨基酸序列优选如序列表中SEQ ID NO:53或54所示；

[0013] 所述变体5的突变包括E4A/P和/或N13Y；所述变体5的氨基酸序列优选如序列表中SEQ ID NO:327-330所示；

[0014] 所述变体1、变体2、变体3、变体5以及变体4至少包含突变前序列的功能。

[0015] 较佳地，如上所述HCDR1、HCDR2和HCDR3包含分别如序列表中SEQ ID NO:16、SEQ ID NO:50和SEQ ID NO:96所示，或者分别如SEQ ID NO:16、SEQ ID NO:53和SEQ ID NO:96所示，或者分别如SEQ ID NO:16、SEQ ID NO:54和SEQ ID NO:96所示，或者分别如SEQ ID NO:19、SEQ ID NO:57和SEQ ID NO:101所示，或者分别如SEQ ID NO:15、SEQ ID NO:58和SEQ ID NO:102所示，或者分别如SEQ ID NO:20、SEQ ID NO:59和SEQ ID NO:103所示，或者分别如SEQ ID NO:20、SEQ ID NO:60和SEQ ID NO:104所示，或者分别如SEQ ID NO:15、SEQ ID NO:61和SEQ ID NO:105所示，或者分别如SEQ ID NO:15、SEQ ID NO:60和SEQ ID NO:106所示，或者分别如SEQ ID NO:20、SEQ ID NO:63和SEQ ID NO:108所示，或者分别如SEQ ID NO:20、SEQ ID NO:60和SEQ ID NO:108所示，或者分别如SEQ ID NO:22、SEQ ID NO:64和SEQ ID NO:109所示，或者分别如SEQ ID NO:15、SEQ ID NO:60和SEQ ID NO:110所示，或者分别如SEQ ID NO:15、SEQ ID NO:65和SEQ ID NO:111所示，或者分别如SEQ ID NO:22、SEQ ID NO:66和SEQ ID NO:112所示，或者分别如SEQ ID NO:15、SEQ ID NO:49和SEQ ID NO:113所示，或者分别如SEQ ID NO:20、SEQ ID NO:60和SEQ ID NO:103所示，或者分别如SEQ ID NO:15、SEQ ID NO:63和SEQ ID NO:104所示，或者分别如SEQ ID NO:15、SEQ ID NO:60和SEQ ID NO:114所示，或者分别如SEQ ID NO:23、SEQ ID NO:67和SEQ ID NO:105所示，或者分别如SEQ ID NO:24、SEQ ID NO:68和SEQ ID NO:103所示，或者分别如SEQ ID NO:15、SEQ ID NO:60和SEQ ID NO:105所示，或者分别如SEQ ID NO:20、SEQ ID NO:69和SEQ ID NO:115所示，或者分别如SEQ ID NO:15、SEQ ID NO:70和SEQ ID NO:116所示，或者

分别如SEQ ID NO:20、SEQ ID NO:71和SEQ ID NO:115所示的序列,或者分别如SEQ ID NO:300、SEQ ID NO:308和SEQ ID NO:326所示的序列,或者分别如SEQ ID NO:300、SEQ ID NO:309和SEQ ID NO:327所示的序列,或者分别如SEQ ID NO:300、SEQ ID NO:310和SEQ ID NO:328所示的序列,或者分别如SEQ ID NO:300、SEQ ID NO:308和SEQ ID NO:329所示的序列,或者分别如SEQ ID NO:300、SEQ ID NO:311和SEQ ID NO:330所示的序列,或者分别如SEQ ID NO:300、SEQ ID NO:312和SEQ ID NO:331所示的序列,或者分别如SEQ ID NO:300、SEQ ID NO:308和SEQ ID NO:332所示的序列,或者分别如SEQ ID NO:300、SEQ ID NO:313和SEQ ID NO:330所示的序列,或者分别如SEQ ID NO:300、SEQ ID NO:314和SEQ ID NO:329所示的序列,或者分别如SEQ ID NO:300、SEQ ID NO:315和SEQ ID NO:331所示的序列,或者分别如SEQ ID NO:300、SEQ ID NO:314和SEQ ID NO:327所示的序列,或者分别如SEQ ID NO:300、SEQ ID NO:316和SEQ ID NO:331所示的序列,或者分别如SEQ ID NO:300、SEQ ID NO:308和SEQ ID NO:333所示的序列,或者分别如SEQ ID NO:300、SEQ ID NO:317和SEQ ID NO:334所示的序列。见下表1。

[0016] 表1

[0017]

抗体编号	HCDR1 SEQ ID NOs:	HCDR1 序列	HCDR2 SEQ ID NOs:	HCDR2 序列	HCDR3 SEQ ID NOs:	HCDR3 序列
PR000197	16	GGSFSGY	50	NHSGS	96	LTGPFDY
PR000447	16	GGSFSGY	53	IHSGS	96	LTGPFDY
PR000448	16	GGSFSGY	54	QHSGS	96	LTGPFDY
PR000980	16	GGSFSGY	54	QHSGS	96	LTGPFDY
PR001758	19	GFTFSRY	57	SGSGDD	101	EKAGTTGDYYYNVDV
PR001759	15	GFTFSSY	58	GGSGGD	102	EGSNGTDDNYYDVDV
PR001760	20	GFTFSNY	59	SGSGVS	103	EGSSETDDHYYNVDV
PR001763	20	GFTFSNY	60	SGSGGS	104	EGSNGTDDYHYDIDV
PR001764	15	GFTFSSY	61	SGGGGS	105	EGTTETDDYHYNMDV
PR001766	15	GFTFSSY	60	SGSGGS	106	EKTGTTGDYYYDMDV
PR001768	20	GFTFSNY	63	SGSGDS	108	EGTGTTSDYYYNVDV
PR001771	20	GFTFSNY	60	SGSGGS	108	EGTGTTSDYYYNVDV
PR001774	22	GFTFSSF	64	SGSGDT	109	EATAMASDYYYGVDV
PR001775	15	GFTFSSY	60	SGSGGS	110	ERAYDYSNYVDFDY
PR001776	15	GFTFSSY	65	SSSGGS	111	DGVTTPSYYYYYDMDV
PR001780	22	GFTFSSF	66	SGSGDN	112	EDTAVASDYYYNIDV
PR001781	15	GFTFSSY	49	SGSGGN	113	ERTGTTGDYYYNVDV
PR001830	20	GFTFSNY	60	SGSGGS	103	EGSSETDDHYYNVDV
PR001831	15	GFTFSSY	63	SGSGDS	104	EGSNGTDDYHYDIDV
PR001833	15	GFTFSSY	60	SGSGGS	114	EGATETDDYHFNTDV
PR001834	23	GFTFSGY	67	SGSGNN	105	EGTTETDDYHYNMDV
PR001836	24	GFIFSNF	68	NGSGFN	103	EGSSETDDHYYNVDV
PR001837	15	GFTFSSY	60	SGSGGS	105	EGTTETDDYHYNMDV
PR001838	20	GFTFSNY	69	DGSGGD	115	EGSHGTDDSHYDVDV

[0018]

PR001840	15	GFTFSSY	70	NSDGSS	116	KGSSSYYHYSIEDD
PR004469	20	GFTFSNY	71	DASGGD	115	EGSHGTDDSHYDVDV
PR007286	300	GFTFSDY	308	SSSGST	326	VKPVAGTWDWFDP
PR007287	300	GFTFSDY	309	SSSGSI	327	EREAVAGTLDFDN
PR007288	300	GFTFSDY	310	SGSGSI	328	EREAVAGTLDFDY
PR007289	300	GFTFSDY	308	SSSGST	329	EREPVAGTLDFDN
PR007290	300	GFTFSDY	311	SSSGTT	330	EREEVAGTLDFDY
PR007291	300	GFTFSDY	312	SGNGST	331	VRPGGSGNYWDWFDP
PR007292	300	GFTFSDY	308	SSSGST	332	EREEVAGTLDYDN
PR007293	300	GFTFSDY	313	NSSGST	330	EREEVAGTLDFDY
PR007294	300	GFTFSDY	314	SGSGTT	329	EREPVAGTLDFDN
PR007295	300	GFTFSDY	315	SNNGST	331	VRPGGSGNYWDWFDP
PR007296	300	GFTFSDY	314	SGSGTT	327	EREAVAGTLDFDN
PR007297	300	GFTFSDY	316	SRSGST	331	VRPGGSGNYWDWFDP
PR007298	300	GFTFSDY	308	SSSGST	333	EREEVAGTLDFDN
PR007299	300	GFTFSDY	317	SSSGRT	334	EGRFF
PR007300	300	GFTFSDY	315	SNNGST	331	VRPGGSGNYWDWFDP
PR007381	20	GFTFSNY	71	DASGGD	115	EGSHGTDDSHYDVDV

[0019] 编码所述重链可变区的FR的基因较佳地来源于胚系V基因IGHV4-34、IGHV3-23、IGHV3-11或者IGHV3-74;其中:HFWR1优选包含如SEQ ID NO:1、SEQ ID NO:3、SEQ ID NO:5-8、SEQ ID NO:294-299以及SEQ ID NO:10-13中任一个所示的氨基酸序列,HFWR2优选包含如SEQ ID NO:27、SEQ ID NO:32-36、SEQ ID NO:301-307以及SEQ ID NO:38-46中任一个所示的氨基酸序列,HFWR3优选包含如SEQ ID NO:74、SEQ ID NO:79-83、SEQ ID NO:318-325以及SEQ ID NO:85-92中任一个所示的氨基酸序列,HFWR4优选包含如SEQ ID NO:118、SEQ ID NO:119、SEQ ID NO:335、SEQ ID NO:336或者SEQ ID NO:123所示的氨基酸序列。较佳地,所述HFWR1的氨基酸序列如SEQ ID NO:3所示、所述HFWR2的氨基酸序列如SEQ ID NO:27所示、所述HFWR3的氨基酸序列如SEQ ID NO:74所示且所述HFWR4的氨基酸序列如SEQ ID NO:118所示,所述HFWR1的氨基酸序列如SEQ ID NO:5所示、所述HFWR2的氨基酸序列如SEQ ID NO:32所示、所述HFWR3的氨基酸序列如SEQ ID NO:79所示且所述HFWR4的氨基酸序列如SEQ ID NO:119所示,所述HFWR1的氨基酸序列如SEQ ID NO:6所示、所述HFWR2的氨基酸序列如SEQ ID NO:33所示、所述HFWR3的氨基酸序列如SEQ ID NO:80所示且所述HFWR4的氨基酸序列如SEQ ID NO:119所示,或者所述HFWR1的氨基酸序列如SEQ ID NO:7所示、所述HFWR2的氨基酸序列如SEQ ID NO:32所示、所述HFWR3的氨基酸序列如SEQ ID NO:81所示且所述HFWR4的氨基酸序列如SEQ ID NO:119所示,所述HFWR1的氨基酸序列如SEQ ID NO:8所示、所述HFWR2的氨基酸序列如SEQ ID NO:34所示、所述HFWR3的氨基酸序列如SEQ ID NO:82所示且所述HFWR4的氨基酸序列如SEQ ID NO:119所示,所述HFWR1的氨基酸序列如SEQ

ID NO:6所示、所述HFWR2的氨基酸序列如SEQ ID NO:35所示、所述HFWR3的氨基酸序列如SEQ ID NO:83所示且所述HFWR4的氨基酸序列如SEQ ID NO:119所示，所述HFWR1的氨基酸序列如SEQ ID NO:6所示、所述HFWR2的氨基酸序列如SEQ ID NO:36所示、所述HFWR3的氨基酸序列如SEQ ID NO:80所示且所述HFWR4的氨基酸序列如SEQ ID NO:119所示，所述HFWR1的氨基酸序列如SEQ ID NO:6所示、所述HFWR2的氨基酸序列如SEQ ID NO:38所示、所述HFWR3的氨基酸序列如SEQ ID NO:80所示且所述HFWR4的氨基酸序列如SEQ ID NO:119所示，所述HFWR1的氨基酸序列如SEQ ID NO:6所示、所述HFWR2的氨基酸序列如SEQ ID NO:39所示、所述HFWR3的氨基酸序列如SEQ ID NO:80所示且所述HFWR4的氨基酸序列如SEQ ID NO:119所示，所述HFWR1的氨基酸序列如SEQ ID NO:1所示、所述HFWR2的氨基酸序列如SEQ ID NO:40所示、所述HFWR3的氨基酸序列如SEQ ID NO:85所示且所述HFWR4的氨基酸序列如SEQ ID NO:119所示，所述HFWR1的氨基酸序列如SEQ ID NO:10所示、所述HFWR2的氨基酸序列如SEQ ID NO:41所示、所述HFWR3的氨基酸序列如SEQ ID NO:86所示且所述HFWR4的氨基酸序列如SEQ ID NO:118所示，所述HFWR1的氨基酸序列如SEQ ID NO:6所示、所述HFWR2的氨基酸序列如SEQ ID NO:35所示、所述HFWR3的氨基酸序列如SEQ ID NO:80所示且所述HFWR4的氨基酸序列如SEQ ID NO:119所示，所述HFWR1的氨基酸序列如SEQ ID NO:11所示、所述HFWR2的氨基酸序列如SEQ ID NO:42所示、所述HFWR3的氨基酸序列如SEQ ID NO:87所示且所述HFWR4的氨基酸序列如SEQ ID NO:119所示，所述HFWR1的氨基酸序列如SEQ ID NO:5所示、所述HFWR2的氨基酸序列如SEQ ID NO:32所示、所述HFWR3的氨基酸序列如SEQ ID NO:80所示且所述HFWR4的氨基酸序列如SEQ ID NO:119所示，所述HFWR1的氨基酸序列如SEQ ID NO:8所示、所述HFWR2的氨基酸序列如SEQ ID NO:34所示、所述HFWR3的氨基酸序列如SEQ ID NO:88所示且所述HFWR4的氨基酸序列如SEQ ID NO:119所示，所述HFWR1的氨基酸序列如SEQ ID NO:12所示、所述HFWR2的氨基酸序列如SEQ ID NO:34所示、所述HFWR3的氨基酸序列如SEQ ID NO:89所示且所述HFWR4的氨基酸序列如SEQ ID NO:123所示，所述HFWR1的氨基酸序列如SEQ ID NO:6所示、所述HFWR2的氨基酸序列如SEQ ID NO:34所示、所述HFWR3的氨基酸序列如SEQ ID NO:88所示且所述HFWR4的氨基酸序列如SEQ ID NO:119所示，所述HFWR1的氨基酸序列如SEQ ID NO:6所示、所述HFWR2的氨基酸序列如SEQ ID NO:43所示、所述HFWR3的氨基酸序列如SEQ ID NO:90所示且所述HFWR4的氨基酸序列如SEQ ID NO:119所示，所述HFWR1的氨基酸序列如SEQ ID NO:6所示、所述HFWR2的氨基酸序列如SEQ ID NO:44所示、所述HFWR3的氨基酸序列如SEQ ID NO:91所示且所述HFWR4的氨基酸序列如SEQ ID NO:119所示，所述HFWR1的氨基酸序列如SEQ ID NO:13所示、所述HFWR2的氨基酸序列如SEQ ID NO:34所示、所述HFWR3的氨基酸序列如SEQ ID NO:90所示且所述HFWR4的氨基酸序列如SEQ ID NO:119所示，所述HFWR1的氨基酸序列如SEQ ID NO:6所示、所述HFWR2的氨基酸序列如SEQ ID NO:45所示、所述HFWR3的氨基酸序列如SEQ ID NO:80所示且所述HFWR4的氨基酸序列如SEQ ID NO:119所示，或者所述HFWR1的氨基酸序列如SEQ ID NO:1所示、所述HFWR2的氨基酸序列如SEQ ID NO:46所示、所述HFWR3的氨基酸序列如SEQ ID NO:92所示且所述HFWR4的氨基酸序列如SEQ ID NO:118所示，或者所述HFWR1的氨基酸序列如SEQ ID NO:294所示、所述HFWR2的氨基酸序列如SEQ ID NO:301所示、所述HFWR3的氨基酸序列如SEQ ID NO:318所示且所述HFWR4的氨基酸序列如SEQ ID NO:335所示，或者所述HFWR1的氨基酸序列如SEQ ID NO:295所示、所述HFWR2的氨基酸序列如SEQ ID NO:302所

示、所述HFWR3的氨基酸序列如SEQ ID NO:319所示且所述HFWR4的氨基酸序列如SEQ ID NO:118所示，或者所述HFWR1的氨基酸序列如SEQ ID NO:294所示、所述HFWR2的氨基酸序列如SEQ ID NO:302所示、所述HFWR3的氨基酸序列如SEQ ID NO:320所示且所述HFWR4的氨基酸序列如SEQ ID NO:118所示，或者所述HFWR1的氨基酸序列如SEQ ID NO:294所示、所述HFWR2的氨基酸序列如SEQ ID NO:302所示、所述HFWR3的氨基酸序列如SEQ ID NO:321所示且所述HFWR4的氨基酸序列如SEQ ID NO:335所示，或者所述HFWR1的氨基酸序列如SEQ ID NO:296所示、所述HFWR2的氨基酸序列如SEQ ID NO:302所示、所述HFWR3的氨基酸序列如SEQ ID NO:322所示且所述HFWR4的氨基酸序列如SEQ ID NO:335所示，或者所述HFWR1的氨基酸序列如SEQ ID NO:297所示、所述HFWR2的氨基酸序列如SEQ ID NO:303所示、所述HFWR3的氨基酸序列如SEQ ID NO:318所示且所述HFWR4的氨基酸序列如SEQ ID NO:335所示，或者所述HFWR1的氨基酸序列如SEQ ID NO:294所示、所述HFWR2的氨基酸序列如SEQ ID NO:301所示、所述HFWR3的氨基酸序列如SEQ ID NO:322所示且所述HFWR4的氨基酸序列如SEQ ID NO:118所示，或者所述HFWR1的氨基酸序列如SEQ ID NO:294所示、所述HFWR2的氨基酸序列如SEQ ID NO:302所示、所述HFWR3的氨基酸序列如SEQ ID NO:323所示且所述HFWR4的氨基酸序列如SEQ ID NO:118所示，或者所述HFWR1的氨基酸序列如SEQ ID NO:298所示、所述HFWR2的氨基酸序列如SEQ ID NO:302所示、所述HFWR3的氨基酸序列如SEQ ID NO:322所示且所述HFWR4的氨基酸序列如SEQ ID NO:118所示，或者所述HFWR1的氨基酸序列如SEQ ID NO:294所示、所述HFWR2的氨基酸序列如SEQ ID NO:301所示、所述HFWR3的氨基酸序列如SEQ ID NO:318所示且所述HFWR4的氨基酸序列如SEQ ID NO:120所示，或者所述HFWR1的氨基酸序列如SEQ ID NO:298所示、所述HFWR2的氨基酸序列如SEQ ID NO:302所示、所述HFWR3的氨基酸序列如SEQ ID NO:322所示且所述HFWR4的氨基酸序列如SEQ ID NO:335所示，或者所述HFWR1的氨基酸序列如SEQ ID NO:294所示、所述HFWR2的氨基酸序列如SEQ ID NO:301所示、所述HFWR3的氨基酸序列如SEQ ID NO:318所示且所述HFWR4的氨基酸序列如SEQ ID NO:118所示，或者所述HFWR1的氨基酸序列如SEQ ID NO:294所示、所述HFWR2的氨基酸序列如SEQ ID NO:304所示、所述HFWR3的氨基酸序列如SEQ ID NO:324所示且所述HFWR4的氨基酸序列如SEQ ID NO:118所示，或者所述HFWR1的氨基酸序列如SEQ ID NO:294所示、所述HFWR2的氨基酸序列如SEQ ID NO:305所示、所述HFWR3的氨基酸序列如SEQ ID NO:325所示且所述HFWR4的氨基酸序列如SEQ ID NO:336所示，或者所述HFWR1的氨基酸序列如SEQ ID NO:299所示、所述HFWR2的氨基酸序列如SEQ ID NO:306所示、所述HFWR3的氨基酸序列如SEQ ID NO:318所示且所述HFWR4的氨基酸序列如SEQ ID NO:335所示，或者所述HFWR1的氨基酸序列如SEQ ID NO:6所示、所述HFWR2的氨基酸序列如SEQ ID NO:307所示、所述HFWR3的氨基酸序列如SEQ ID NO:80所示且所述HFWR4的氨基酸序列如SEQ ID NO:119所示。详见下表2。

[0020] 表2

[0021]

抗体编号	HFWR1 SEQ ID NOs:	HFWR2 SEQ ID NOs:	HFWR3 SEQ ID NOs:	HFWR4 SEQ ID NOs:
PR000197	3	27	74	118

[0022]

PR000447	3	27	74	118
PR000448	3	27	74	118
PR000980	3	27	74	118
PR001758	5	32	79	119
PR001759	6	33	80	119
PR001760	7	32	81	119
PR001763	8	34	82	119
PR001764	6	35	83	119
PR001766	6	36	80	119
PR001768	6	38	80	119
PR001771	6	39	80	119
PR001774	1	40	85	119
PR001775	10	41	86	118
PR001776	6	35	80	119
PR001780	11	42	87	119
PR001781	5	32	80	119
PR001830	8	34	88	119
PR001831	12	34	89	123
PR001833	6	34	88	119
PR001834	6	43	90	119
PR001836	6	44	91	119
PR001837	13	34	90	119
PR001838	6	45	80	119
PR001840	1	46	92	118
PR004469	6	45	80	119
PR007286	294	301	318	335
PR007287	295	302	319	118
PR007288	294	302	320	118
PR007289	294	302	321	335
PR007290	296	302	322	335
PR007291	297	303	318	335

[0023]

PR007292	294	301	322	118
PR007293	294	302	323	118
PR007294	298	302	322	118
PR007295	294	301	318	120
PR007296	298	302	322	335
PR007297	294	301	318	118
PR007298	294	304	324	118
PR007299	294	305	325	336
PR007300	299	306	318	335
PR007381	6	307	80	119

[0024] 本发明中,所述的重链可变区较佳地包含如序列表中SEQ ID NO:168、SEQ ID NO:171、SEQ ID NO:172、SEQ ID NO:175-180、SEQ ID NO:182-196、SEQ ID NO:337-352以及SEQ ID NO:198中的任一个所示的氨基酸序列。

[0025] 基于如上所述,本发明中所述的4-1BB结合蛋白还含有轻链可变区,所述的轻链可变区包含LCDR1、LCDR2和LCDR3,所述的LCDR1包含如SEQ ID NO:133所示的序列,所述的LCDR2包含如SEQ ID NO:145所示的序列,所述的LCDR3包含如SEQ ID NO:158所示的序列。较佳地,编码所述轻链可变区的FR的基因来源于胚系V基因IGKV3-15;其中:LFWR1优选包含如SEQ ID NO:126或者SEQ ID NO:128所示的氨基酸序列,LFWR2优选包含如SEQ ID NO:140所示的氨基酸序列,LFWR3优选包含如SEQ ID NO:151所示的氨基酸序列,LFWR4优选包含如SEQ ID NO:164所示的氨基酸序列;更佳地,所述的轻链可变区包含如序列表中SEQ ID NO:201所示的序列或其变体,所述的变体基于如SEQ ID NO:201所示的序列发生一个或者多个氨基酸残基突变;突变后所得轻链可变区的序列优选如SEQ ID NO:204所示。

[0026] 在本发明一具体实施方案中,所述的重链可变区的氨基酸序列如SEQ ID NO:168所示,且所述的轻链可变区的氨基酸序列如SEQ ID NO:201所示;或者,所述的重链可变区的氨基酸序列如SEQ ID NO:171所示,且所述的轻链可变区的氨基酸序列如SEQ ID NO:204所示;或者,所述的重链可变区的氨基酸序列如SEQ ID NO:172所示,且所述的轻链可变区的氨基酸序列如SEQ ID NO:204所示。详见下表3。

[0027] 表3

[0028]

抗体编号	VL	VH
PR000197	201	168

[0029]

PR000447	204	171
PR000448	204	172
PR000980	204	172

[0030] 另外,本发明所述的4-1BB结合蛋白还可包含重链恒定区和/或轻链恒定区;较佳

地，所述重链恒定区选自hIgG1、hIgG2、hIgG3或hIgG4或其变体，所述轻链恒定区选自κ链或者λ链或其突变。

[0031] 其中，所述hIgG1的变体的突变优选L234A、L235A、E345R和P329G中的一个或多个，更优选E345R，或者L234A、L235A和E345R的组合，或者L234A、L235A和P329G的组合；所述hIgG4的变体的突变优选S228P。

[0032] 在本发明一较佳实施例中，所述的4-1BB结合蛋白的重链包含如序列表中SEQ ID NO:209、SEQ ID NO:212、SEQ ID NO:213、SEQ ID NO:216-222、SEQ ID NO:224-238、SEQ ID NO:353-368以及SEQ ID NO:240中的任一个所示的序列，和/或其轻链包含如序列表中SEQ ID NO:246或者SEQ ID NO:243所示的序列。例如：所述重链的氨基酸序列如SEQ ID NO:209所示，且所述轻链的氨基酸序列如SEQ ID NO:243所示；或者，所述重链的氨基酸序列如SEQ ID NO:212所示，且所述轻链的氨基酸序列如SEQ ID NO:246所示；或者，所述重链的氨基酸序列如SEQ ID NO:213所示，且所述轻链的氨基酸序列如SEQ ID NO:246所示；或者，所述重链的氨基酸序列如SEQ ID NO:216所示，且所述轻链的氨基酸序列如SEQ ID NO:246所示。如下表4所示。

[0033] 表4

[0034]

抗体编号	轻链	重链
PR000197	243	209
PR000447	246	212
PR000448	246	213
PR000980	246	216

[0035] 本发明中如上所述的4-1BB结合蛋白，其可为全长抗体、Fab、Fab'、$F(ab')_2$、Fv、scFv、双特异性抗体、多特异性抗体、重链抗体、单域抗体或单区抗体的形式，或为由上述抗体制得的单克隆抗体或多克隆抗体。

[0036] 当所述4-1BB结合蛋白为全长抗体时，其重链包含如SEQ ID NO:209所示的序列，且轻链包含如SEQ ID NO:243所示的序列；或者包含如SEQ ID NO:212所示的序列，且轻链包含如SEQ ID NO:246所示的序列，或者包含如SEQ ID NO:213所示的序列，且轻链包含如SEQ ID NO:246所示的序列，或者包含SEQ ID NO:216所示的序列，且轻链包含如SEQ ID NO:246所示的序列。

[0037] 本发明的第二方面提供一种双特异性抗体，其包含第一蛋白功能区和第二蛋白功能区，所述的第一蛋白功能区为如上所述的4-1BB结合蛋白，所述的第二蛋白功能区靶向肿瘤抗原；较佳地为HER2抗体或者PD-L1抗体；其中，所述的HER2抗体优选trastuzumab或者pertuzumab，所述的PD-L1抗体优选atezolizumab或者PR000265，所述PR000265的重链如SEQ ID NO:211所示，轻链如SEQ ID NO:245所示。其中，所述PR000265的详细信息见申请CN201910944996.4。

[0038] 具体来说，所述的第一蛋白功能区或者所述的第二蛋白功能区可为scFv、VHH、免疫球蛋白、Fab、Fab'、$F(ab')_2$或者重链可变区的形式；例如，所述的第一蛋白功能区为Fab，所述的第二蛋白功能区为VHH；或者，所述第一蛋白功能区为Fab，所述的第二蛋白功能区为免疫球蛋白；或者，所述的第一蛋白功能区为免疫球蛋白，所述的第二蛋白功能区为重链可变区。

[0039] 较佳地，所述第一蛋白功能区和所述第二蛋白功能区之间和/或所述scFv的重链可变区和轻链可变区之间通过连接子连接，所述连接子的氨基酸序列为GS或者如序列表中SEQ ID NO:273-293中任一个所示。

[0040] 在本发明的具体实施方案中，所述的双特异性抗体包含多肽链1和多肽链2，任选地还包含多肽链3；较佳地：

[0041] 所述多肽链1的氨基酸序列如SEQ ID NO:244所示，且所述多肽链2的氨基酸序列如SEQ ID NO:251-265中任一个所示；或者所述多肽链1的氨基酸序列如SEQ ID NO:245所示，且所述多肽链2的氨基酸序列如SEQ ID NO:271所示；或者所述多肽链1的氨基酸序列如SEQ ID NO:249所示，且所述多肽链2的氨基酸序列如SEQ ID NO:272所示；或者所述多肽链1的氨基酸序列如SEQ ID NO:245所示，且所述多肽链2的氨基酸序列如SEQ ID NO:270所示；或者所述多肽链1的氨基酸序列如SEQ ID NO:245所示，且所述多肽链2的氨基酸序列如SEQ ID NO:269所示；或者所述多肽链1的氨基酸序列如SEQ ID NO:245所示，且所述多肽链2的氨基酸序列如SEQ ID NO:268所示；或者所述多肽链1的氨基酸序列如SEQ ID NO:245所示，且所述多肽链2的氨基酸序列如SEQ ID NO:369-382中任一个所示；或者所述多肽链1的氨基酸序列如SEQ ID NO:267所示，所述多肽链2的氨基酸序列如SEQ ID NO:266所示，且所述多肽链3的氨基酸序列如SEQ ID NO:246所示；或者所述多肽链1的氨基酸序列如SEQ ID NO:250所示，且所述多肽链2的氨基酸序列如SEQ ID NO:249所示，且所述多肽链3的氨基酸序列如SEQ ID NO:246所示。

[0042] 本发明的第三方面提供一种分离的核酸，其编码如本发明第一方面所述的4-1BB结合蛋白或如本发明的第二方面所述的双特异性抗体。

[0043] 本发明的第四方面提供一种包含如第三方面所述的分离的核酸的表达载体。

[0044] 本发明的第五方面提供一种宿主细胞，其包含本发明第四方面所述的表达载体；优选地，所述宿主细胞为原核细胞或真核细胞。其中，所述的真核细胞优选哺乳动物细胞。

[0045] 本发明的第六方面提供一种4-1BB结合蛋白的制备方法，其包含培养如第五方面的宿主细胞，从培养物中获得所述4-1BB结合蛋白。

[0046] 本发明的第七方面提供一种嵌合抗原受体，其包含如本发明第一方面所述的4-1BB结合蛋白或如本发明的第二方面所述的双特异性抗体。

[0047] 本发明的第八方面提供一种抗体药物偶联物，其包含细胞毒性剂，以及如本发明第一方面所述的4-1BB结合蛋白或如本发明的第二方面所述的双特异性抗体。

[0048] 所述细胞毒剂优选细胞毒素、化学治疗剂、放射性同位素、治疗性核酸、免疫调节剂、抗血管生成剂、抗增殖促凋亡剂或细胞溶解酶。更优选地，所述细胞毒剂为微管蛋白合成酶抑制剂——甲基奥瑞他汀F(MMAF)，或者为甲基奥瑞他汀E(MMAE)。

[0049] 所述的抗体药物偶联物的制备方法可为本领域常规，较佳地采用Doronina，2006，Bioconjugate Chem.17，114-124所记载的制备方法。优选地，所述的制备方法产生具有最低限度的低偶联级分(LCF)小于10％的抗体药物偶联物。

[0050] 所述的抗体药物偶联物能够以本领域所知的任何物理形态而存在，较佳地为澄清溶液。

[0051] 本发明的第九方面提供一种药物组合物，其包含如本发明第一方面所述的4-1BB结合蛋白、如本发明的第二方面所述的双特异性抗体和/或如本发明第八方面所述的抗体

药物偶联物,和药学上可接受的载体。

[0052] 所述的药物组合物较佳地还包括其他抗肿瘤抗体作为活性成分,和/或含有由激素制剂、靶向小分子制剂、蛋白酶体抑制剂、成像剂、诊断剂、化疗剂、溶瘤药物、细胞毒性剂、细胞因子、共刺激分子的激活剂、抑制性分子的抑制剂以及疫苗组成的群组中的一种或多种。

[0053] 所述的药学上可接受的载体可为本领域常规的载体,所述的载体可以为任意合适的生理学或药学上可接受的药物辅料。所述的药物辅料为本领域常规的药物辅料,较佳地包括药学上可接受的赋形剂、填充剂、稳定剂或稀释剂等。更佳地,所述的药物组合物包括0.01-99.99%的上述蛋白质和/或上述的抗体药物偶联物,和0.01-99.99%的药用载体,所述百分比为占所述药物组合物的质量百分比。

[0054] 较佳地,所述的药物组合物是抗肿瘤的药物。更佳地为治疗胃癌、食管癌、肺癌、卵巢癌、黑素瘤、肾癌、乳腺癌、结肠直肠癌、肝癌、胰腺癌、膀胱癌、头颈癌、支气管癌、神经胶质瘤和/或白血病的药物。

[0055] 本发明所述的药物组合物的给药途径较佳地为肠胃外施用、注射给药或口服给药。所述注射给药较佳地包括静脉注射、肌肉注射、腹腔注射、皮内注射或皮下注射等途径。所述的药物组合物为本领域常规的各种剂型,较佳地为固体、半固体或液体的形式,即可以为水溶液、非水溶液或混悬液,更佳的为片剂、胶囊、颗粒剂、注射剂或输注剂等。更佳地为经由血管内、皮下、腹膜内或肌内施用。较佳地,所述药物组合物还可以作为气雾剂或粗喷雾剂施用,即经鼻施用;或者,鞘内、髓内或心室内施用。更佳地,所述的药物组合物还可以透皮、经皮、局部、肠内、阴道内、舌下或经直肠施用。

[0056] 本发明所述的药物组合物的给药剂量水平可以根据达到所需诊断或治疗结果的组合物量而调整。施用方案也可以为单次注射或多次注射,或进行调整。所选择的剂量水平和方案依赖于包括所述药物组合物的活性和稳定性(即,半衰期)、制剂、施用途径、与其他药物或治疗的组合、待检测和/或治疗的疾病或病症、以及待治疗的受试者的健康状况和先前医疗史等各种因素而进行合理地调整。

[0057] 对于本发明的所述药物组合物的治疗有效剂量可以最初在细胞培养实验或动物模型例如啮齿类动物、兔、犬、猪和/或灵长类动物中进行估计。动物模型也可以用于测定合适的施用浓度范围和途径。随后可以用于确定在人中施用的有用剂量和途径。一般地,施用有效量或剂量的确定和调整以及何时和如何进行此类调整的评估为本领域技术人员已知。

[0058] 对于组合疗法,上述4-1BB结合蛋白、上述抗体药物偶联物和/或另外的治疗或诊断剂可以各自作为单一药剂,在适合于执行预期治疗或诊断的任何时间范围内进行使用。因此,这些单一药剂可以基本上同时(即作为单一制剂或在数分钟或数小时内)或以按顺序连续施用。例如,这些单一药剂可以在一年内,或10、8、6、4或2个月内,或4、3、2、或1周内,或5、4、3、2或1天内施用。

[0059] 关于制剂、剂量、施用方案和可测量的治疗结果的另外指导,参见Berkow等人(2000)The Merck Manual of Medical Information(Merck医学信息手册)和Merck& Co.Inc.,Whitehouse Station,New Jersey;Ebadi(1998)CRC Desk Reference of Clinical Pharmacology(临床药理学手册)等著作。

[0060] 本发明的第十方面如第一方面所述的4-1BB结合蛋白、如本发明的第二方面所述

的双特异性抗体和如第七方面所述的药物组合物在制备治疗和/或预防癌症的药物中的应用;所述癌症优选与HER2、PD-L1以及4-1BB中的一种或多种相关的癌症,如乳腺癌、黑色素瘤、肺癌、胃癌、肝癌、食管癌、宫颈癌、头颈部肿瘤或者结直肠癌。

[0061] 在一些方面,本公开提供与HER2、PD-L1以及4-1BB中的一种或多种相关的疾病的治疗方法,所述方法包括向受试者施用药物有效量的如前所述的4-1BB结合蛋白,或包含如前所述的药物组合物,或如前所述的核酸分子,以治疗与HER2、PD-L1以及4-1BB中的一种或多种相关的疾病,其中所述疾病优选为肿瘤或癌症。

[0062] 其中,所述的肿瘤或者癌症即为本领域中常规的HER2、PD-L1以及4-1BB中的一种或多种表达异常的肿瘤或者癌症,例如:鳞状细胞癌、骨髓瘤、小细胞肺癌、非小细胞肺癌(NSCLC)、头和颈鳞状细胞癌(HNSCC)、神经胶质瘤、何杰金淋巴瘤、非何杰金淋巴瘤、弥漫性大B-细胞淋巴瘤(DLBCL)、滤泡性淋巴瘤、急性成淋巴细胞性白血病(ALL)、急性髓细胞样白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性髓细胞样白血病(CML)、原发性纵隔大B-细胞淋巴瘤、套细胞淋巴瘤(MCL)、小淋巴细胞性淋巴瘤(SLL)、富含T-细胞/组织细胞的大B-细胞淋巴瘤、多发性骨髓瘤、髓样细胞白血病-1蛋白(Mcl-1)、骨髓异常增生综合征(MDS)、胃肠(道)癌、肾癌、卵巢癌、肝癌、成淋巴细胞性白血病、淋巴细胞白血病、结肠直肠癌、子宫内膜癌、肾癌、前列腺癌、甲状腺癌、黑素瘤、软骨肉瘤、神经母细胞瘤、胰腺癌、多形性成胶质细胞瘤、胃癌、骨癌、尤因氏肉瘤、子宫颈癌、脑癌、胃癌、膀胱癌、肝细胞瘤、乳腺癌、结肠癌、肝细胞癌(HCC)、透明细胞肾细胞癌(RCC)、头和颈癌、咽喉癌、肝胆癌(hepatobiliary cancer)、中枢神经系统癌、食管癌、恶性胸膜间皮瘤、全身性轻链淀粉样变性、淋巴浆细胞性淋巴瘤(lymphoplasmacytic lymphoma)、骨髓异常增生综合征、骨髓增生性肿瘤、神经内分泌肿瘤、梅克尔细胞癌、睾丸癌和皮肤癌,最优选为PD-L1阳性的鳞状细胞癌、骨髓瘤、小细胞肺癌、非小细胞肺癌(NSCLC)、头和颈鳞状细胞癌(HNSCC)、神经胶质瘤、何杰金淋巴瘤、非何杰金淋巴瘤、弥漫性大B-细胞淋巴瘤(DLBCL)、滤泡性淋巴瘤、急性成淋巴细胞性白血病(ALL)、急性髓细胞样白血病(AML)、慢性淋巴细胞性白血病(CLL)、慢性髓细胞样白血病(CML)、原发性纵隔大B-细胞淋巴瘤、套细胞淋巴瘤(MCL)、小淋巴细胞性淋巴瘤(SLL)、富含T-细胞/组织细胞的大B-细胞淋巴瘤、多发性骨髓瘤、髓样细胞白血病-1蛋白(Mcl-1)、骨髓异常增生综合征(MDS)、胃肠(道)癌、肾癌、卵巢癌、肝癌、成淋巴细胞性白血病、淋巴细胞白血病、结肠直肠癌、子宫内膜癌、肾癌、前列腺癌、甲状腺癌、黑素瘤、软骨肉瘤、神经母细胞瘤、胰腺癌、多形性成胶质细胞瘤、胃癌、骨癌、尤因氏肉瘤、子宫颈癌、脑癌、胃癌、膀胱癌、肝细胞瘤、乳腺癌、结肠癌、肝细胞癌(HCC)、透明细胞肾细胞癌(RCC)、头和颈癌、咽喉癌、肝胆癌(hepatobiliary cancer)、中枢神经系统癌、食管癌、恶性胸膜间皮瘤、全身性轻链淀粉样变性、淋巴浆细胞性淋巴瘤(lymphoplasmacytic lymphoma)、骨髓异常增生综合征、骨髓增生性肿瘤、神经内分泌肿瘤、梅克尔细胞癌、睾丸癌和皮肤癌。

[0063] 本发明的第十一方面提供试剂盒,其包括如本发明第一方面所述的4-1BB结合蛋白、如本发明的第二方面所述的双特异性抗体、如本发明第七方面所述的嵌合抗原受体、如本发明第八方面所述的抗体药物偶联物和/或如本发明第九方面所述的药物组合物。

[0064] 优选地,所述试剂盒还包括(i)施用抗体或其抗原结合片段或抗体药物偶联物或药物组合物的装置;和/或(ii)使用说明。

[0065] 本发明的第十二方面提供一种套装药盒,其包含药盒A和药盒B,其中:

[0066] 所述药盒A含有如本发明第一方面所述的4-1BB结合蛋白、如本发明的第二方面所述的双特异性抗体、如本发明第七方面所述的嵌合抗原受体、如本发明第八方面所述的抗体药物偶联物和/或如本发明第九方面所述的药物组合物；

[0067] 所述药盒B含有其他抗肿瘤抗体或者包含所述其他抗肿瘤抗体的药物组合物，和/或由激素制剂、靶向小分子制剂、蛋白酶体抑制剂、成像剂、诊断剂、化疗剂、溶瘤药物、细胞毒性剂、细胞因子、共刺激分子的激活剂、抑制性分子的抑制剂以及疫苗组成的群组中的一种或多种。

[0068] 为了解决上述技术问题，如本发明第一方面所述的4-1BB结合蛋白、如本发明的第二方面所述的双特异性抗体、如本发明第七方面所述的嵌合抗原受体、本发明第八方面所述的抗体药物偶联物和/或如本发明第九方面所述的药物组合物还可以与其他药物进行联合用药，例如可以与激素制剂、靶向小分子制剂、蛋白酶体抑制剂、成像剂、诊断剂、化疗剂、溶瘤药物、细胞毒性剂、细胞因子、共刺激分子的激活剂、抑制性分子的抑制剂、疫苗等和/或其他抗肿瘤抗体(或者包含所述其他抗肿瘤抗体的药物组合物)进行联合用药。

[0069] 本发明的第十三方面提供一种诊断、治疗和/或预防4-1BB介导的疾病或病症的方法，所述方法包括向有需要的患者施用治疗有效量的如本发明第一方面所述的4-1BB结合蛋白、如本发明的第二方面所述的双特异性抗体、如本发明第七方面所述的嵌合抗原受体、如本发明第八方面所述的抗体药物偶联物或如本发明第九方面所述的药物组合物，或者使用如本发明第十二方面所述的套装药盒治疗有需要的患者。

[0070] 较佳地，所述的疾病或病症为肿瘤，优选4-1BB阳性肿瘤，更优选胃癌、食管癌、肺癌、卵巢癌、黑素瘤、肾癌、乳腺癌、结肠直肠癌、肝癌、胰腺癌、膀胱癌、头颈癌、支气管癌、神经胶质瘤和/或白血病。

[0071] 本发明的第十四方面提供一种免疫检测或者测定4-1BB的方法，其包括使用如本发明第一方面所述的4-1BB结合蛋白、如本发明的第二方面所述的双特异性抗体、如本发明第七方面所述的嵌合抗原受体、如本发明第八方面所述的抗体药物偶联物或如本发明第九方面所述的药物组合物；优选地，所述检测为非诊断和/或治疗目的的。

[0072] 本发明的第十五方面提供一种联合疗法，其包括分别向有需要的患者施用如本发明第一方面所述的4-1BB结合蛋白、如本发明的第二方面所述的双特异性抗体、如本发明第七方面所述的嵌合抗原受体、如本发明第八方面所述的抗体药物偶联物或如本发明第九方面所述的药物组合物，和第二治疗剂；所述第二治疗剂较佳地包含其他抗肿瘤抗体或者包含所述其他抗肿瘤抗体的药物组合物，和/或由激素制剂、靶向小分子制剂、蛋白酶体抑制剂、成像剂、诊断剂、化疗剂、溶瘤药物、细胞毒性剂、细胞因子、共刺激分子的激活剂、抑制性分子的抑制剂以及疫苗组成的群组中的一种或多种。

[0073] 在符合本领域常识的基础上，上述各优选条件，可任意组合，即得本发明各较佳实例。

[0074] 本发明所用试剂和原料均市售可得。

[0075] 本发明的积极进步效果在于：

[0076] 1.本申请提供了一种抗4-1BB结合蛋白的全人源抗体，其具有至少一种下述性质1)本发明的抗4-1BB结合蛋白的全人源抗体包括一种全长抗体，和一种全新的仅含“重链”的全人抗体，具有与人4-1BB和食蟹猴4-1BB结合的活性；其中该4-1BB结合蛋白的重链抗体

的大小只有传统IgG抗体的一半，由于不含轻链的这一特点，使得该抗体可以用于双特异性抗体，并解决了轻链错配和异源二聚化的问题。能够结合源自人和猴的4-1BB蛋白；2)结合表位与Urelumab不同；3)能够激活4-1BB信号通路，刺激免疫细胞分泌IFN-γ，IL2和/或TNFα，抑制肿瘤生长和/或肿瘤细胞增殖；活性显著强于Utomilumab。

[0077] 2.本发明提供的PD-L1×4-1BB双特异性抗体，通过一个或者多个作用机制来提高抗肿瘤效果和安全性。第一，PD-L1×4-1BB双抗可以通过阻断PD-1/PD-L1信号通路来激活T细胞。第二，高表达于肿瘤细胞表面的PD-L1分子可以利用双抗分子促进T细胞表面的4-1BB分子的交联和三聚化并激活下游信号传导通路，进而促进T细胞的活化和增殖，其激活T细胞的能力甚至优于Urelumab。第三，PD-L1×4-1BB双抗对T细胞激活作用是特异性依赖PD-L1的表达，双抗分子介导的T细胞激活仅限于肿瘤微环境内。相比于现有技术中依赖于交联的抗4-1BB的HCAb单抗不能直接激活T细胞，本发明利用HCAb单抗构建的PD-L1×4-1BB双抗在高表达PD-L1的细胞存在时则可以特异性地激活T细胞，这样可以避免类似Urelumab的单抗在正常组织中过度激活T细胞所带来的毒副作用。第四，本实施例利用抗PD-L1的IgG抗体的抗原结合结构域Fab和抗4-1BB的HCAb抗体的抗原结合结构域VH，构建了多种结构的抗PD-L1×4-1BB的双特异性抗体分子。展现出了基于HCAb构建双特异性抗体分子结构的灵活性，通过不同的结构类型、相对位置、结合价数等参数来调节激活T细胞的功能活性。基于HCAb的双抗结构，尤其是IgG-VH四价对称结构的双抗分子和Fab-HCAb结构的双抗分子，一方面保留了PD-L1端的活性，在MLR实验中体现出比对应的抗PD-L1亲本单抗更强的T细胞激活能力；另一方面靶细胞上高表达的PD-L1分子可以介导4-1BB的交联和三聚化以传递T细胞活化信号，其激活T细胞的能力甚至优于Urelumab。而且IgG-VH四价对称结构和Fab-HCAb对称结构的双抗分子显示出比FIT-Ig结构的双抗分子拥有更强的T细胞激活能力。

[0078] 3.本发明提供的HER2×4-1BB双特异性抗体，通过一个或者多个作用机制来提高抗肿瘤效果和安全性。第一，HER2×4-1BB双抗保留了原有的HER2抑制剂的作用机制(阻止HER2二聚化，促进HER2的内化和降解，抑制下游磷酸化信号)。第二，高表达于肿瘤细胞表面的HER2分子可以利用双抗分子促进T细胞表面的4-1BB分子的交联和三聚化并激活下游信号传导通路，进而促进T细胞的活化和增殖，其激活T细胞的能力甚至优于Urelumab。第三，HER2×4-1BB双抗对T细胞激活作用是特异性依赖HER2的表达，双抗分子介导的T细胞激活仅限于肿瘤微环境内。不同于现有技术中依赖于交联的抗4-1BB的HCAb单抗不能直接激活T细胞，本发明中利用HCAb单抗构建的HER2×4-1BB双抗在高表达HER2的细胞存在时则可以特异地激活T细胞这样可以避免类似Urelumab的单抗在正常组织中过度激活T细胞所带来的毒副作用。第四，本实施例构建了IgG-VH和IgG-scFv两种结构的抗HER2×4-1BB的双特异性抗体分子，通过不同的结构类型、相对位置、结合价数等参数来调节激活T细胞的功能活性。同时展现出了基于HCAb构建双特异性抗体分子结构的灵活性。

附图说明

[0079] 图1A-图1B：FACS检测4-1BB H2L2抗体与过表达人或食蟹猴4-1BB的CHO-K1细胞的结合。

[0080] 图2：FACS检测4-1BB H2L2抗体阻断4-1BB配体与CHO-K1/人4-1BB细胞结。

[0081] 图3A-图3B：利用HEK293/4-1BB/NF-kb报告基因细胞检测4-1BB H2L2抗体对4-1BB

信号通路的激活。

[0082] 图4:4-1BB H2L2抗体体外激活4-1BB通路,并诱导激活T细胞分泌IFN-γ。

[0083] 图5A-图5B:4-1BB H2L2抗体体外激活4-1BB通路,并诱导激活CD8+T细胞,CD4+T细胞分泌IFN-γ。

[0084] 图6A-图6C:4-1BB H2L2抗体PR000448在B6-h4-1BB转基因小鼠MC38皮下结肠癌模型中的抑制肿瘤生长活性。

[0085] 图7:PR000448在C57BL/6J小鼠体内的药代动力学。

[0086] 图8A-图8C:PR000980抗体体外激活4-1BB通路,并诱导激活T细胞分泌IFN-γ、TNF-α和IL-2。

[0087] 图9A-图9D:BIACORE检测4-1BB H2L2抗体与人4-1BB蛋白或猴4-1BB蛋白的亲和力。

[0088] 图10A-图10B:4-1BB H2L2抗体PR000980在B6-h4-1BB转基因小鼠MC38皮下结肠癌模型中的抑制肿瘤生长活性。

[0089] 图11A-图11M:FACS检测4-1BB HCAb抗体与过表达人4-1BB的CHO-K1细胞的结合。

[0090] 图12A-图12L:FACS检测4-1BB HCAb抗体与过表达食蟹猴4-1BB的CHO-K1细胞的结合。

[0091] 图13A-图13J:利用HEK293/4-1BB/NF-kb报告基因细胞检测4-1BB HCAb抗体对4-1BB信号通路的激活。

[0092] 图14A-图14K:FACS检测4-1BB HCAb抗体阻断4-1BB配体与CHO-K1/人4-1BB细胞结合。

[0093] 图15A-图15D:4-1BB HCAb抗体体外激活4-1BB通路,并诱导激活T细胞分泌IFN-γ。

[0094] 图16A-图16B:在CHO-K1/CD32b交联或者没有CHO-K1/CD32b交联的情况下,4-1BB HCAb抗体体外激活4-1BB通路,并诱导激活T细胞分泌IFN-γ。

[0095] 图17A-图17D:FACS检测4-1BB HCAb抗体与CHO-K1/人4-1BB细胞的特异性结合。

[0096] 图18A-图18C:HER2×4-1BB双特异性抗体的结构示意图。

[0097] 图19A-图19C:FACS检测HER2×4-1BB双特异性抗体与SK-BR-3细胞的结合。

[0098] 图20A-图20E:FACS检测HER2×4-1BB双特异性抗体与过表达人4-1BB的CHO-K1细胞的结合。

[0099] 图21A-图21B:FACS检测HER2×4-1BB双特异性抗体与过表达食蟹猴4-1BB的CHO-K1细胞的结合。

[0100] 图22A-图22D:HER2×4-1BB双特异性抗体在SK-BR-3细胞的交联下,体外激活4-1BB通路,并诱导激活T细胞分泌IFN-γ。

[0101] 图23A-图23E:PD-L1×4-1BB双特异性抗体的结构示意图。

[0102] 图24A-图24E:FACS检测PD-L1×4-1BB双特异性抗体与CHO-K1/hPD-L1细胞的结合。

[0103] 图25A-图25E:FACS检测PD-L1×4-1BB双特异性抗体与过表达人4-1BB的CHO-K1细胞的结合。

[0104] 图26A-图26B:FACS检测PD-L1×4-1BB双特异性抗体与过表达食蟹猴4-1BB的CHO-

K1细胞的结合。

[0105] 图27A-图27I:PD-L1×4-1BB双特异性抗体在CHO-K1/hPD-L1或MDA-MB-231细胞的交联下,体外激活4-1BB通路,并诱导激活T细胞分泌IFN-γ。

[0106] 图28A-图28K:利用混合淋巴细胞反应(MLR)来研究PD-L1 x 4-1BB双抗分子对T细胞的激活作用。

[0107] 图29:PD-L1×4-1BB双特异性抗体在C57BL/6J小鼠体内的药代动力学。

具体实施方式

[0108] 以下具体定义了某些技术和科学术语。除显而易见在本文件中的它处另有明确定义,否则本文使用的所有其它技术和科学术语都具有本发明所属领域的一般技术人员通常理解的含义。

[0109] 所用氨基酸三字母代码和单字母代码如J.Biol.Chem,243,p3558(1968)中所述。

[0110] 术语“抗体”指免疫球蛋白,是由两条相同的重链和两条相同的轻链通过链间二硫键连接而成的四肽链结构。免疫球蛋白重链恒定区的氨基酸组成和排列顺序不同,故其抗原性也不同。据此,可将免疫球蛋白分为五类,或称为免疫球蛋白的同种型,即IgM,IgD,IgG,IgA和IgE,其相应的重链分别为μ链,δ链,γ链,α链和ε链。同一类Ig根据其铰链区氨基酸组成和重链二硫键的数目和位置的差别,又可分为不同的亚类,如IgG可分为IgG1,IgG2,IgG3,IgG4。轻链通过恒定区的不同分为κ链或λ链。五类Ig中第每类Ig都可以有κ链或λ链。

[0111] 抗体轻链抗体可进一步包含轻链恒定区,所述的轻链恒定区可包含人源的κ、λ链或其变体。

[0112] 抗体重链抗体可进一步包含重链恒定区,所述的重链恒定区可包含人源的IgG1,2,3,4或其变体。

[0113] 抗体重链和轻链靠近N端的氨基酸的序列变化很大,为可变区(V区);靠近C端的其余氨基酸序列相对稳定,为恒定区(C区)。轻重链可变区分别由110个左右氨基酸组成其中有些区域的氨基酸残基变化较可变区其他部位更大,如轻链第24-34、50-56、89-97位和重链第31-35、50-65、95-102位。这些区域称为高变区(hypervariable region,HVR),由于高变区是抗体与抗原表位直接接触的部位,因此又称为互补决定区(complementarity-region,CDR)。可变区中的非高变区,其氨基酸组成与序列变化相对较少,这些氨基酸残基组成可变区稳定的立体结构,即框架结构或支架结构(framework region,FR)。可变区包括3个高变区(HVR)和4个序列相对保守的骨架区(FR)。每条轻链可变区(VL)和重链可变区(VH)由3个CDR区4个FR区组成,从氨基端到羧基端依次排列的顺序为:FR1,CDR1,FR2,CDR2,FR3,CDR3,FR4。轻链的3个CDR区指LCDR1,LCDR2,和LCDR3;重链的3个CDR区指HCDR1,HCDR2和HCDR3。本申请采用Chothia定义规则划分。但是,本领域人员公知,在本领域中可以通过多种方法来定义抗体的CDR,例如基于序列可变性的Kabat定义规则(参见,Kabat等人,免疫学的蛋白质序列,第五版,美国国立卫生研究院,贝塞斯达,马里兰州(1991))和基于结构环区域位置的Chothia定义规则(参见JMol Biol 273:927-48,1997)。在本发明的技术方案中,还可以使用包含了Kabat定义和Chothia定义的Combined定义规则来确定可变结构域序列中的氨基酸残基。其中Combined定义规则即是将Kabat定义和Chothia定义的范围相结合。本领域技术人员应当理解的是,除非另有规定,否则术语给定抗体或其区(例如可变区)

的“CDR”及“互补决定区”应了解为涵盖如通过本发明描述的上述已知方案中的任何一种界定的互补决定区。虽然本发明中请求保护的范围是基于Chothia定义规则所示出的序列,但是根据其他CDR的定义规则所对应的氨基酸序列也应当落在本发明的保护范围中。

[0114] 在本申请中,术语“全人源抗体”通常是指将人类编码抗体的基因全部转移至基因工程改造的抗体基因缺失动物中,使动物表达的抗体。抗体所有部分(包括抗体的可变区和恒定区)均由人类来源的基因所编码。全人源抗体可以大大减少异源抗体对人体造成的免疫副反应。本领域获得全人源抗体的方法可以有噬菌体展示技术、转基因小鼠技术等。

[0115] 术语“单链抗体”是由抗体的重链可变区(VH)和轻链可变区(VL)通过一段连接肽连接而成的单链重组蛋白,它是具有完全抗原结合位点的最小抗体片段。

[0116] 术语“表位”是指抗原上与免疫球蛋白或抗体特异性结合的位点。表位可以由相邻的氨基酸、或通过蛋白质的三级折叠而并列的不相邻的氨基酸形成。由相邻的氨基酸形成的表位通常在暴露于变性溶剂后保持,而通过三级折叠形成的表位通常在变性溶剂处理后丧失。表位通常以独特的空间构象包括至少3-15个氨基酸。确定什么表位由给定的抗体结合的方法在本领域中是熟知的,包括免疫印迹和免疫沉淀检测分析等。确定表位的空间构象的方法包括本领域中的技术和本文所述的技术,例如X射线晶体分析法和二维核磁共振等。

[0117] 术语“核酸”是指DNA分子和RNA分子。其可以是单链或双链的,但优选是双链DNA。当将核酸与另一个核酸序列置于功能关系中时,核酸是“有效连接的”。例如,如果启动子或增强子影响编码序列的转录,那么启动子或增强子有效地连接至所述编码序列。

[0118] 在本申请中,术语“特异性结合”通常是指抗体通过其抗原结合域与表位结合,并且该结合需要抗原结合域和表位之间的一些互补性。根据该定义,当抗体相比于其将结合随机的,不相关的表位而言更容易通过其抗原结合域与表位结合时,抗体被称为“特异性结合”该抗原。

[0119] 在本申请中,术语“Fab”通常指常规抗体(例如IgG)中与抗原结合的部分,包括抗体的重链可变区VH、轻链可变区VL和重链恒定区结构域CH1以及轻链恒定区CL。在常规抗体中,VH的C端与CH1的N端联结形成重链Fd片段,VL的C端与CL的N端联结形成轻链,CH1的C端又进一步与重链的铰链区和其他恒定区结构域联结形成重链。在一些实施例中,“Fab”也指Fab的变体结构。例如,在某些实施例中,VH的C端与CL的N端联结形成一个多肽链,VL的C端与CH1的N端联结形成另一个多肽链,形成Fab(cross VH/VL)的结构;在某些实施例中,Fab的CH1不与铰链区联结,而是CL的C端与重链的铰链区联结,形成Fab(cross Fd/LC)的结构。

[0120] 在本申请中,术语“VH”通常指抗体的重链可变区VH结构域,即可以是人或者其他动物的常规抗体(H2L2结构)的重链可变区VH,也可以是骆驼科等动物的重链抗体(HCAb结构)的重链可变区VHH,还可以是利用Harbour HCAb转基因小鼠产生的全人源重链抗体(HCAb结构)的重链可变区VH。

[0121] 实施例1.全人源4-1BB H2L2抗体的获得

[0122] 实施例1.1.单克隆抗体的制备

[0123] Harbour H2L2小鼠(Harbour Antibodies BV)是一种携带人免疫球蛋白免疫库的转基因小鼠,其产生的抗体具有完整的人的抗体可变结构域和大鼠恒定结构域。用可溶的重组人4-1BB-Fc融合蛋白对Harbour H2L2小鼠进行多轮免疫。当检测小鼠血清中4-1BB特

异的抗体滴度达到一定的水平后,将小鼠的脾细胞取出并与骨髓瘤细胞系融合得到杂交瘤细胞;对杂交瘤细胞经过多轮筛选和克隆之后,分离出2个表达抗4-1BB单克隆抗体分子的杂交瘤细胞株65D4G5G11和79B10G8D4。利用常规的杂交瘤测序手段获得编码抗体分子可变结构域的核苷酸序列以及对应的氨基酸序列。在本实施例中,从免疫的Harbour H2L2小鼠得到的单克隆抗体分子可变结构域的序列是人源抗体序列。抗体可变结构域的CDR序列可以通过Kabat、Chothia或者结合了Kabat定义和Chothia定义的称为Combined定义规则进行分析。本申请实施例中的CDR序列根据Chothia定义规则划分。

[0124] 实施例1.2.重组全人源抗体的制备

[0125] 在得到编码抗体分子的轻、重链可变结构域序列以后,可以采用常规的重组DNA技术,将轻、重链可变结构域序列和相应的人的抗体轻、重链恒定结构域序列进行融合表达,得到重组抗体分子。

[0126] 65D4G5G11克隆的抗体编号为PR000196,79B10G8D4克隆的抗体编号为PR000197。

[0127] 同时,本申请生产制备了抗4-1BB的阳性对照抗体Urelumab和Utomilumab类似物,Urelumab对应的抗体编号为PR000628,Utomilumab对应的抗体编号为PR000483。其相应的氨基酸序列来源于IMGT数据库。

[0128] 在本实施例中,抗体轻链可变结构域序列(VL)通过基因合成并克隆到编码人抗体κ轻链恒定结构域序列的哺乳动物细胞表达质粒载体中,以编码产生抗体的全长轻链。在本实施例中,抗体重链可变结构域序列(VH)通过基因合成并克隆到编码人IgG4抗体重链恒定结构域序列的哺乳动物细胞表达质粒载体中,以编码产生IgG4抗体的全长重链,并且在该IgG4重链恒定区引入S228P突变(根据EU编号,第228位丝氨酸取代成脯氨酸)以增加IgG4抗体的稳定性。在本实施例中,抗体重链可变结构域序列(VH)通过基因合成并克隆到编码人IgG1或者人IgG2抗体重链恒定结构域序列的哺乳动物细胞表达质粒载体中,以编码产生IgG1或者IgG2抗体的全长重链。在本实施例中,由于从免疫的Harbour H2L2小鼠得到的单克隆抗体分子可变结构域的序列是人源抗体序列,因而本实施例也得到全人源的抗4-1BB重组抗体。

[0129] 将编码抗体重链的质粒和编码抗体轻链的质粒同时转染哺乳动物宿主细胞(如人胚肾细胞HEK293),利用常规的重组蛋白表达和纯化技术,可以得到轻重链正确配对组装的纯化的重组抗体。具体说来,将HEK293细胞在FreeStyle™F17 Expression Medium培养基(Thermo,A1383504)扩培。瞬时转染开始之前,调节细胞浓度至6-8×10^5细胞/ml,于37℃ 8%CO_2摇床中培养24小时,细胞浓度在1.2×10^6细胞/ml。准备30ml培养的细胞。将上述编码抗体重链的质粒和编码抗体轻链的质粒以2:3的比例混合共计30μg质粒溶解于1.5ml Opti-MEM减血清培养基(Thermo,31985088),并用0.22μm滤膜过滤除菌。再取1.5ml Opti-MEM溶入1mg/ml PEI(Polysciences Inc,23966-2)120μl,静置5分钟。把PEI缓慢加入质粒中,室温孵育10分钟,边摇晃培养瓶边缓慢滴入质粒PEI混合溶液,于37℃ 8%CO_2摇床中培养5天。5天后观测细胞活率。收集培养物,以3300G转速离心10分钟后取上清;然后将上清高速离心去除杂质。用PBS(pH7.4)平衡含有MabSelectTM(GE Healthcare Life Science,71-5020-91AE)的重力柱(Bio-Rad,7311550),2-5倍柱体积冲洗。将上清样品过柱。用5-10倍柱体积的PBS冲洗柱子。再用pH3.5的0.1M甘氨酸洗脱目的蛋白,后用pH 8.0的Tris-HCl调节至中性,最后用超滤管(Millipore,UFC901024)浓缩换液至PBS缓冲液,得到纯化的抗体溶

液。然后用NanoDrop(Thermo Scientific™NanoDrop™One)测定浓度,分装、存储备用。

[0130] 实施例1.3.抗体的序列分析和优化

[0131] 抗体的重链可变结构域序列来源于染色体上重链基因群的胚系基因V、D、J基因片段的基因重排和体细胞高频突变等事件;轻链可变结构域序列来源于κ或λ轻链基因群的胚系基因V、J基因片段的基因重排和体细胞高频突变等事件。基因重排和体细胞高频突变是增加抗体多样性的主要因素。来源于相同胚系V基因片段的抗体也可能产生不同的序列,但总体上相似性较高。利用一些算法,例如IMGT/DomainGapAlign(http://imgt.org/3Dstructure-DB/cgi/DomainGapAlign.cgi)或者NCBI/IgBLAST(https://www.ncbi.nlm.nih.gov/igblast/)可以从抗体的可变结构域序列推测出其发生基因重排时可能的胚系基因片段。将实施例1.1得到的抗体序列进行分析,其重链可变结构域(VH)和轻链可变结构域(VL)的胚系基因V基因片段列于表5。

[0132] 蛋白质或多肽氨基酸链在细胞中翻译合成后有时会引入化学修饰,称为翻译后修饰(PTM)。对于抗体而言,一些PTM的位点是非常保守的,例如,在人的IgG1抗体的恒定结构域的第297位(EU编号)的保守的氨基酸天冬酰胺Asn通常会发生糖基化修饰形成糖链,而该糖链结构对于抗体结构和相关的效应子功能是至关重要的。但是,如果在抗体的可变结构域尤其是抗原结合区域(如CDR)中存在PTM,那么这些PTM的存在有可能会对抗原的结合有较大的影响,也可能对抗体的物理化学性质带来变化。例如,糖基化、脱酰胺、异构化、氧化等都可能增加抗体分子的不稳定性或异质性,从而增加抗体开发的难度和风险。因而避免一些潜在的PTM对于治疗性抗体的开发是非常重要的。随着经验的积累,人们发现一些PTM是和氨基酸序列的组成尤其是相邻氨基酸组成的“模式”是高度相关的,这样使得可以从蛋白质的一级氨基酸序列预测出潜在的PTM。例如,N-x-S/T(第一位是天冬酰胺,第二位是非脯氨酸以外的任意氨基酸,第三位是丝氨酸或者苏氨酸)的序列模式预测出N-连接糖基化位点。引起PTM的氨基酸序列模式有可能来源于胚系基因序列,例如人胚系基因片段IGHV3-33天然地在FR3区域存在糖基化模式NST;也可能来源于体细胞高频突变。表5列出了实施例1.1的抗体的可变结构域VH和VL的预测的PTM。具体说来,NHS可能是糖基化位点,NG可能是脱酰胺位点。

[0133] 表5杂交瘤单克隆抗体序列的胚系基因分析和翻译后修饰位点(PTM)分析

[0134]

克隆号	重组抗体	VH胚系V基因	VL胚系V基因	VH PTM	VL PTM
65D4G5G11	PR000196	IGHV3-23	IGKV2-28	/	NG (LCDR1)
79B10G8D4	PR000197	IGHV4-34	IGKV3-15	NHS (HCDR2)	/

[0135] 可以通过氨基酸突变来破坏PTM的氨基酸序列模式,从而降低或者去除特定PTM的形成。根据抗体序列和PTM序列模式的不同,有不同的突变设计方法。一种方法是将“热点”氨基酸(如NG模式中的N或G)替换成物理化学性质相似的氨基酸(如把N突变为Q)。如果PTM序列模式来源于体细胞高频突变,而并不存在于胚系基因序列中,那么另一种方法可以是把该序列模式替换成对应的胚系基因序列。实际操作中,对同一个PTM序列模式可能采用多种突变设计方法。

[0136] 抗体Fc结构域介导的效应子功能如ADCC和CDC也有非常重要的生物学功能,不同

的IgG亚型有着不同的ADCC或CDC功能，例如IgG1和IgG3有较强的ADCC和CDC作用，而IgG2和IgG4的作用相对较弱。另外，通过氨基酸突变或者修饰来改变Fc与Fc受体的结合能力也可以调节Fc原有的效应子功能。例如，IgG1中的“LALA”双突变体(L234A/L235A)能够显著降低与Fcγ RIIIA(CD16A)的亲和力，进而降低ADCC作用。在本实施例中，来源于同一个抗体的可变区可以重组成为不同的IgG亚型或者突变体，以调节效应子功能，例如，人IgG4(S228P)、人IgG2、人IgG1(LALA)。

[0137] D.Zhang等人发现在人IgG的Fc的E345位点引入突变E345R可以有效地增加激动型OX40抗体的激活作用(The Journal of Biological Chemistry,291:27134-27146,2016)。

[0138] 本申请也发现该E345R突变可以有效地增加激动型4-1BB抗体的激活作用。在本实施例中，通过IgG亚型变换、可变区突变和Fc突变对表5的抗4-1BB杂交瘤单克隆抗体进行序列优化，得到一系列的重组抗体或其变体(见表6)。表7、表8和表1列出了本实施例中得到的重组抗体的轻、重链可变结构域氨基酸序列，轻链全长氨基酸序列，重链全长氨基酸序列，和根据Chothia定义规则定义的CDR的氨基酸序列。

[0139] 表6通过IgG亚型变换、可变区突变和Fc突变得到的重组抗体

[0140]

初始抗体	重组抗体（变体）	可变区突变	IgG 亚型	Fc 突变
65D4G5G11	PR000196		人 IgG4	S228P
79B10G8D4	PR000197		人 IgG4	S228P
PR000197	PR000447	VH:N52I; VL:F2I	人 IgG4	S228P
PR000197	PR000448	VH:N52Q; VL:F2I	人 IgG4	S228P
PR000448	PR000980	VH:N52Q; VL:F2I	人 IgG1	L234A, L235A, E345R

[0141]

[0142] 表7抗原结合蛋白序列编号表

[0143]

抗体编号	轻链	重链	VL	VH	LCDR1	LCDR2	LCDR3	HCDR1	HCDR2	HCDR3
PR000483	247	214	205	173	136	147	161	18	55	99
PR000628	248	215	206	174	137	148	162	16	56	100
PR000196	242	208	200	167	132	144	157	15	49	95
PR000197	243	209	201	168	133	145	158	16	50	96
PR000447	246	212	204	171	133	145	158	16	53	96
PR000448	246	213	204	172	133	145	158	16	54	96
PR000980	246	216	204	172	133	145	158	16	54	96

[0144] 表8CDR序列编号对应具体序列

[0145]

HCDR 1 SEQ ID NO:	具体序列	HCDR 2 SEQ ID NO:	具体序列	HCDR 3 SEQ ID NO:	具体序列
15	GFTFSSY	49	SGSGGN	95	EAYHYGSGSYYDDYYYGMDV
16	GGSFSGY	50	NHSGS	96	LTGPFDY
18	GYSFSTY	53	IHSGS	99	GYGIFDY
		54	QHSGS	100	DYGPGNYDWYFDL
		55	YPGDSY		
		56	NHGGY		
LCDR 1 SEQ ID NO:	具体序列	LCDR 2 SEQ ID NO:	具体序列	LCDR 3 SEQ ID NO:	具体序列
132	RSSQSLLHSNGYNYLD	144	LGSNRAS	157	MQALQTPLT
133	RASQSISSILA	145	GASTRAT	158	QQYYNWPLT
136	SGDNIGDQYAH	147	QDKNRPS	161	ATYTGFGSLAV
137	RASQSVSSYLA	148	DASNRAT	162	QQRSNWPPALT

[0146] 实施例1.4.4-1BB H2L2抗体与细胞表面的4-1BB结合

[0147] 将表达人4-1BB的CHO-K1细胞和表达食蟹猴4-1BB的CHO-K1细胞扩增培养后,PBS洗涤3次,按3×10^5/孔铺96孔板(Corning,#3799)。然后加入100μl待测抗原结合蛋白或者阳性对照抗体Utomilumab或者Urelumab,最高浓度200nM,5倍稀释,4℃培育一小时。用FACS缓冲液清洗两次,加入1:1000稀释的羊抗人IgG的AF488偶联抗体(Life Technologies,#A11013),4℃培育1小时。用FACS缓冲液清洗两次,100μl PBS重悬,进行FACS(BD Biosciences,CantoⅡ)测试,读取荧光信号。根据测定结果计算半数最大结合效应浓度(EC50),作为相对结合活性的评价依据。

[0148] 结果如图1及下表9所示。图1A显示的是抗原结合蛋白与人4-1BB结合活性,图1B显示的是抗原结合蛋白与猴4-1BB结合活性。PR000447和PR000448均能结合人和食蟹猴的4-1BB,结合活性优于阳性对照Urelumab。Urelumab不能交叉结合食蟹猴4-1BB。

[0149] 表9抗原结合蛋白与表达人或猴4-1BB的细胞的结合

[0150]

EC50(nM)	PR000447	PR000448	Urelumab	Utomilumab
人4-1BB	1.007	0.9473	1.114	0.6271
食蟹猴4-1BB	1.285	1.064	不结合	0.9293

[0151] 实施例1.5.4-1BB H2L2抗体阻断4-1BB配体与4-1BB结合

[0152] 为了研究人4-1BB结合蛋白体外阻断人4-1BB与人4-1BBL结合的活性。采用过表达人4-1BB的CHO-K1细胞株(CHO-K1/hu4-1BB)进行细胞水平的人4-1BB/人4-1BBL结合阻断实验。简言之,消化CHO-K1/hu4-1BB细胞,并用F-12K完全培养基重悬,将细胞密度调整为1×10^6细胞/mL。以100μL细胞/孔接种于96孔V底板(Corning,#3894),随后加入100μL/孔,2倍

于终浓度的3倍浓度梯度稀释的待测抗原结合蛋白，混合均匀，其中抗原结合蛋白最高终浓度为100nM，共8个浓度，hIgG1作为对照。将细胞放置于4℃，避光孵育1小时。之后，4℃下离心5分钟，弃上清，随后加入50μL/孔，1μg/mL浓度的生物素标记的人4-1BBL蛋白(Acro，#41L-H82F9)，4℃，避光孵育30分钟。加入100μL/孔预冷PBS漂洗细胞两次，于500g，4℃下离心5分钟，弃上清。加入100μL/孔荧光二抗(PE Streptavidin，BD，#554061，1:200)，4℃，避光孵育30分钟。用200μL/孔预冷PBS洗涤细胞两次，于500g，4℃下离心5分钟，弃上清。最后，200μL/孔预冷PBS重悬细胞，使用BD FACS CANTOII读取荧光发光信号值，计算IC50，抑制率%＝1-MFI(4-1BB Ab)/MFI(iso)。

[0153] 结果如图2所示。PR000448可阻断4-1BB配体与4-1BB结合，并且阻断效果与Utomilumab相似。

[0154] 实施例1.6.利用报告基因细胞系检测对4-1BB信号通路的刺激作用

[0155] 将表达CD32b的CHO-K1细胞CHO-K1/CD32b(Genscript，#M00587)或CHO-K1(ATCC，#CCL-61)铺到96孔板(Perkin Elmer，#6005225)上，细胞量为1.5×10^4/孔，100μL/孔。37℃在5%CO_2环境下孵育过夜。去除上清液，加入40μL/孔的2倍的待测抗原结合蛋白稀释液，起始终浓度浓度为200nM，5倍浓度稀释，hIgG1为对照组。加入4.5×10^4/孔的可持续表达4-1BB和NF-Kb反应元件的荧光素酶报告基因的HEK293报告细胞(HEK293/4-1BB/NF-kb报告细胞，BPS Biosciences，#79289)40μL/孔。37℃在5%CO_2环境下培养6小时。加入ONE-Glo™荧光素酶试剂(Promega，#E6110)，室温孵育5分钟，酶标仪检测发光值。

[0156] 如图3A、图3B以及下表10所示，本申请所述4-1BB抗原结合蛋白PR000448是CHO-K1/CD32b交联依赖型。如图3A所示，在CHO-K1/CD32b交联下，本申请所述的PR000448对4-1BB介导的NF-Kb信号通路的促进作用与其浓度成正相关关系递增。与参照抗体(Utomilumab)相比，该抗体的EC50比参照抗体更低，且最大发光值也比参照抗体更高，说明该抗体能以较低的浓度促进NF-Kb的激活。如图3B所示，而参照抗体Urelumab对4-1BB信号通路的激活不依赖交联，在没有CHO-K1/CD32b交联，同样能激活4-1BB介导的NF-Kb信号通路。而PR000448在没有CHO-K1/CD32b交联不能激活4-1BB介导的NF-Kb信号通路。

[0157] 表10报告基因系统检测4-1BB抗体对4-1BB信号通路的激活

[0158]

抗体	EC50(nM)	最大值
PR000448	0.6632	86095
Utomilumab	1.489	40042
Urelumab	0.2728	101148

[0159] 实施例1.7.4-1BB H2L2抗体的体外功能检测

[0160] 实施例1.7.1.4-1BB H2L2抗体体外激活4-1BB通路

[0161] 使用10μg/ml的丝裂霉素(北京中生瑞泰科技，10107409001)处理CHO-K1-CD32b(过表达人CD32b的CHO-K1细胞)的细胞，37℃放置30分钟。然后用10%FBS的F-12K培养液，洗涤4次。把处理过的细胞放入96孔板里，每孔1.5×10^4个，37℃保温箱培养过夜。第二天，使用MACS试剂盒(Miltenyi Biotec，#130-096-535)从人PBMC里分离人CD3阳性T细胞。首先确定细胞数量，然后根据细胞数量加入相应量的MACS缓冲液和Pan-T细胞生物素抗体，混匀，4℃静置5分钟。然后加入相应量微磁珠，4℃静置10分钟。通过LS柱的是CD3阳性的T细胞。将前一天96孔板的培养液洗掉，加入纯化的T细胞，每孔1×10^5个。然后加入相应浓度的

4-1BB抗原结合蛋白体或者对照抗体Utomilumab、PR000196，加入OKT3(eBiosciences，#16-0037-85)并且使其最终浓度达到0.3μg/ml。37℃保温箱培养72小时。72小时后，收取上清液，使用ELISA试剂盒(Invitrogen，#88-7316-88)来检测IFN-γ的含量。在96平底板里加入包被抗体，4℃过夜。第二天加入ELISA缓冲液，室温1小时。加入收取的上清液，室温培养2小时。洗板2次，加入检测抗体，室温1小时。洗板两次，加入HRP-链霉亲和素，室温孵育1小时。然后加入TMB底物，稍后加入ELISA终止液(BBI，#E661006-0200)。酶标仪(PerkinElemer Enspire)读取450nm和570nm吸光度值，用OD450-OD570计算IFN-γ浓度。

[0162] 结果如图4所示，PR000197、PR000447和PR000448抗体都能激活4-1BB通路，并诱导激活T细胞分泌IFN-γ。且其激活作用都比Utomilumab、PR000196更强。

[0163] 实施例1.7.2.4-1BB H2L2抗体诱导CD4+和CD8+T细胞的活性

[0164] 按照实施例1.7.1的方法处理CHO-K1或CHO-K1/CD32b的细胞，铺板，37℃保温箱培养过夜。第二天，使用分选的试剂(Miltenyi Biotec，#130-096-495，#130-096-533)来分选CD8+和CD4+T细胞。然后加入相应浓度的4-1BB抗体或者是对照抗体，加入OKT3(eBiosciences，#16-0037-85)并且使其最终浓度达到0.3μg/ml。37℃保温箱培养72小时。72小时后，收取上清液，使用ELISA试剂盒(Invitrogen，#88-7316-88)来检测IFN-γ的含量。

[0165] CD8+T细胞诱导如图5A，CD4+T细胞诱导如图5B。

[0166] 结果显示，PR000447和PR000448显著激活CD8+T细胞分泌IFN-γ，但是对CD4+T细胞激活功能不显著。这可能是因为4-1BB在CD8+T细胞上的表达比CD4+T细胞高的缘故。

[0167] 实施例1.8.4-1BB H2L2抗体抑制体内肿瘤生长的活性

[0168] 建立B6-h4-1BB转基因小鼠(北京百奥赛图基因生物技术有限公司，#110004)MC38皮下结肠癌模型。首先复苏小鼠结肠癌细胞MC38(Kerafast，ENH204-FP)复苏。培养条件：RPMI-1640培养基(Gibco，22400089)+100U/mL青霉素(AMRESCO®，#0242-100MU)+100μg/mL链霉素(AMRESCO®，#0382)+10％FBS(GIBCO® InvitrogenTM，#10099)；37℃，饱和湿度，5％CO_2。收集对数生长期的MC38细胞(记录传代次数)，去除培养液并用PBS洗两次后接种(荷瘤前细胞活率：98.9％、荷瘤后细胞存活率：92％)，接种量：5×10^5/100μl/只(不添加基质胶)，接种位置：右侧皮下。按照分组标准将小鼠分为5组，每组6只，各组均值相近，且均值的范围为80-120mm^3，入组标准：各组内单只小鼠肿瘤体积尽量不超过150mm^3，且组内SEM尽量不超过均值的1/10。分组当天定义为第0天，并于分组当天第0天开始给药。

[0169] 待测样品用PBS配制，给药方式为腹腔注射，剂量体积为10μl/g，给药剂量为5mg/kg，给药频率2次/周，给药3周，共给药6次。给药当日测量小鼠体重和肿瘤体积，每周测量2次直至肿瘤平均体积达到700-800mm^3；当肿瘤平均体积超过700-800mm^3，改为一周测量3次肿瘤体积。肿瘤体积计算方式为：肿瘤体积(mm^3)＝0.5×肿瘤长径×肿瘤短径^2。

[0170] 小鼠体重监测如图6A所示，肿瘤体积监测如图6B所示，27天后安乐死小鼠，取出肿瘤拍照，肿瘤大小如图6C所示。

[0171] 结果显示，PR000448有明显肿瘤抑制效果，在实验过程中，各组动物体重均出现增长，表明动物对受试品耐受良好。未对动物产生明显毒性作用，安全性较好。

[0172] 实施例1.9.药代动力学试验

[0173] 评价PR000448在雌性C57BL/6J小鼠体内的药代动力学。将PR000448和Utomilumab

以5mg/kg静脉内单次给予小鼠(n＝5)，在注射前和注射后1天、2天、4天、7天、10天、14天进行采血。采集的血液立即以4℃、15,000rpm离心15分钟，获得血浆，保存在-20℃以下的冰箱中。采用ELISA法测定血浆中待测抗体的浓度。PR000448和Utomilumab在血浆中浓度的变化如图7所示。通过药物动力分析软件WinNolin，对所得血浆中浓度变化数据进行分析，计算药物半衰期($t_{1/2}$)。$t_{1/2}$是由最终三点或软件自动设定的最终相血浆中浓度计算。所得末端$t_{1/2}$如图7和下表11所示。

[0174] 结果显示，与Utomilumab相比，PR000448具有较长的血液半衰期。

[0175] 表11抗原结合蛋白的药代动力学参数

[0176]

	PR000448	Utomilumab
末端$t_{1/2}$(天数)	16.9	12.1

[0177] 实施例1.10.Fc点突变4-1BB H2L2抗体的体外激活功能

[0178] 为了评价Fc突变抗体PR000980对4-1BB通路的激活效果，按照实施例1.6.1的方法，使用ELISA试剂盒(Invitrogen#88-7316-88，Invitrogen#88-7346-88，Invitrogen#88-7025-77)检测IFN-γ，TNF-α和IL-2的含量。Utomilumab、IgG1、IgG2、IgG4作为对照。

[0179] 结果如图8A、图8B和图8C所示，待测抗原结合蛋白均能刺激活化的T细胞分泌细胞因子，强于Utomilumab。且Fc突变后的PR000980保留了亲本抗体PR000448刺激T细胞分泌细胞因子(IFN-γ、TNF-α、IL-2)的能力。

[0180] 实施例1.11.抗原结合蛋白的表位鉴定

[0181] 使用ForteBio Octet平台对实施例1得到的4-1BB H2L2抗体(PR000448和PR000980)和Utomilumab、Urelumab进行表位鉴定。其中，Urelumab为Bristol-Myers Squibb的抗4-1BB抗体BMS-663513(CAS:934823-49-1)，按照实施例1.2的方法表达纯化得到。第一步，用传感器捕获组氨酸标记的4-1BB抗原后，将传感器浸入抗体中，获取该抗体的100％信号。第二步，将第一抗体负载至多个AHC尖端上，随后在测定缓冲液pH 7.5中获得60秒基线。然后将尖端暴露于组氨酸标记的4-1BB持续180秒，以允许抗原结合。将尖端转移至含有测定缓冲液中的第二抗体的孔持续90秒，将最终信号记录为该第二抗体的信号。抑制率通过下式计算：抑制率(％)＝(A-B)/A*100，A：某抗体的100％信号(从第一步中获得)，B：该抗体作为第二抗体的信号(从第二步获得)。

[0182] 如果第二抗体表现出明显结合(即抑制率小于40％)，那么就将它视为非竞争剂(即，在与第一抗体不同的表位区间中)。如果第二抗体不表现明显结合(即抑制率大于等于40％)，那么就将它视为竞争剂(即，在与第一抗体相同的表位区间中)。通过比较第二抗体在第一抗体存在下与4-1BB的结合与第一抗体阻断本身来进行结合测定。

[0183] 结果如下表12所示，PR000448和PR000980与Utomilumab在4-1BB的结合位点重叠性高，但是与Urelumab的结合位点重叠性低。

[0184] 表12本申请抗原结合蛋白与临床抗体的表位鉴定

[0185]

抑制率（%）		第二抗体			
		PR000448	PR000980	Urelumab	Utomilumab
第一抗体	PR000448	98.4	90.2	18.3	90.6
	PR000980	101.6	98.5	21.0	95.1
	Urelumab	32.5	18.5	95.1	34.8
	Utomilumab	82.8	69.3	21.8	94.9

[0186] 实施例1.12.4-1BB H2L2抗体与人或猴4-1BB蛋白的亲和力测试

[0187] 使用Biacore平台对实施例1得到的4-1BB H2L2抗体(PR000448和PR000980)和Utomilumab、Urelumab进行亲和力鉴定。测试中使用HBS-EP+(10mM HEPES,150mM NaCl,3mM EDTA和0.05％P20,pH7.4,GE Healthcare,BR-1006-69)作为运行缓冲液,系列S CM5(GE Healthcare,BR-1005-30)为实验芯片。先设置流速10μl/min通过以下程序在CM5的4个通道上偶联Protein A:1)设置注入时间800s,将50mM NHS和200mM EDC以1:1体积比新鲜混合后注入4个通道;2)用pH4.5的醋酸钠(GE Healthcare,BR-1003-50)将Protein A稀释至20μg/ml,注入各通道800s;3)注入1M pH8.5乙醇胺800s,以封闭芯片表面剩余的活性羧基。封闭后继续用1×HBS-EP+缓冲液平衡仪器两小时,Protein A最终偶联量约为2000RU。再设置多循环动力学模式进行抗体与蛋白的亲和力测定,每个循环包括抗体的捕获、分析物的结合以及芯片的再生。将抗体均稀释至1μg/ml,以10μl/min的流速注入2、3、4通道30s,由预先偶联的Protein A捕获各抗体,捕获量约为120RU。将人的4-1BB或食蟹猴4-1BB依次按照0nM、0.391nM、0.781nM、1.5625nM、3.125nM、6.25nM、12.5nM、25nM的浓度梯度注入四个通道,流速为30μl/min,对PR000448、PR000980设置解离时间600s,对Uremulab、Utomilumab设置解离时间80s,注入时间均设为120s。最后为了从表面除去测试的抗体,以同样流速注入10mM甘氨酸-盐酸pH1.5(GE Life Sciences,BR-1003-54)30s,来再生芯片。使用Biacore T200分析软件2.0对实验结果进行分析,1通道作为参比通道扣除,分析模型选用1:1动力学拟合模型。

[0188] 结果如表13和图9A-图9D所示,4-1BB H2L2抗体与组氨酸标记的人4-1BB蛋白和组氨酸标记的猴4-1BB蛋白的亲和力结果。结果显示不管是与人还是猴的4-1BB蛋白的结合亲和力上,抗体PR000448和PR000980的结合亲和力均高于Uremulab和Utomilumab,而Urelumab不结合猴的4-1BB蛋白。

[0189] 表13 BIACORE测定的4-1BB抗体的与人或猴4-1BB蛋白的结合亲和力

[0190]

抗原结合蛋白	人 4-1BB 蛋白抗原（组氨酸标记）			猴 4-1BB 蛋白抗原（组氨酸标记）		
	k_a (1/Ms)	k_d (1/s)	K_D (M)	k_a (1/Ms)	k_d (1/s)	K_D (M)
PR000448	1.42E+06	2.20E-04	1.55E-10	1.19E+06	8.92E-04	7.51E-10
PR000980	1.43E+06	2.50E-04	1.74E-10	1.17E+06	8.40E-04	7.16E-10
Uremulab	1.09E+06	1.50E-03	1.38E-09	NA	NA	NA
Utomilumab	1.43E+06	1.50E-02	1.05E-08	1.09E+06	1.74E-02	1.59E-08

[0191] 实施例1.13.Fc点突变抗体抑制体内肿瘤生长的活性

[0192] 按照实施例5的方法建立B6-h4-1BB转基因小鼠MC38皮下结肠癌模型。平均肿瘤体积达到99.14mm^3时,小鼠根据肿瘤体积随机分组,每组6只。分组当天定义为第0天,并于分组当天第0天开始给药。待测样品用PBS配制,给药方式为腹腔注射,给药剂量为2mg/kg。开始给药后,每周称量体重两次。每周测量瘤体积两次,瘤体积计算方式为:肿瘤体积(mm^3)＝0.5×肿瘤长径×肿瘤短径^2。

[0193] 小鼠体重和肿瘤体积变化如图10A、图10B结果显示,给药29天后测量,PR000448的Fc变体PR000980具有更强的抑制肿瘤生长的活性。

[0194] 小结

[0195] 本申请提供了一种抗4-1BB抗原结合蛋白,其具有下述性质中的一种或多种:1)能

够结合源自人和猴的4-1BB蛋白;2)能够刺激免疫细胞分泌IFN-γ,IL2和/或TNFα;3)能够抑制肿瘤生长和/或肿瘤细胞增殖;4)能够激活4-1BB信号通路。本申请还提供了所述抗原结合蛋白在预防和治疗肿瘤中的应用。

[0196] 实施例2.全人源4-1BB HCAB抗体的获得

[0197] 实施例2.1.全人源HCAb小鼠的免疫和4-1BB抗体的获得

[0198] Harbour HCAb小鼠(Harbour Antibodies BV,WO 2002/085945 A3)是一种携带人免疫球蛋白免疫库的转基因小鼠,能够产生全新的仅"重链"抗体,该抗体的大小只有传统IgG抗体的一半。其产生的抗体仅具有人的抗体"重链"可变结构域和小鼠Fc恒定结构域。由于不含轻链的这一特点,该抗体几乎解决了轻链错配和异源二聚化的问题,使得这一技术平台能够开发出传统抗体平台难以实现的产品。

[0199] 实施例2.1.1.免疫HCAb小鼠

[0200] 6～8周龄Harbour人源抗体转基因小鼠采用了2组免疫方案对Harbour HCAb小鼠进行多轮免疫。免疫方案1,用重组的人4-1BB-ECD-Fc(ChemPartner,Shanghai)抗原蛋白进行免疫。每只小鼠每次免疫时通过皮下经腹股沟注射或通过腹腔注射接受的总注射剂量是100微升。在首轮免疫中,每只小鼠接受用50微克抗原蛋白与完全弗氏佐剂(Sigma,#F5881)以体积比1:1混合配制的免疫原试剂的免疫。在随后的每轮增强免疫中,每只小鼠接受用25微克抗原蛋白与Ribi佐剂(Sigma Adjuvant System,Sigma,#S6322)混合配制的免疫原试剂的免疫。免疫方案2,用过表达人4-1BB的NIH3T3-h4-1BB(ChemPartner,Shanghai)稳定细胞系进行免疫。每只小鼠每次免疫时腹腔注射2×10^6细胞悬液。每轮增强免疫的间隔时间至少为两周,通常不超过五轮增强免疫。免疫时间为第0、14、28、42、56、70天;并且在第49、77天,检测小鼠血清抗体滴度。在进行HCAb小鼠脾B细胞分离前5天,以每只小鼠25微克抗原蛋白的剂量进行最后一次增强免疫。

[0201] 实施例2.1.2.获得抗4-1BB的HCAb抗体序列

[0202] 采集小鼠血液,对血液进行10倍稀释取6个浓度(1:100、1:1000、1:10000、1:100000、1:1000000),在包被有人4-1BB-ECD-Fc(Chempartner,Shanghai)的ELISA板进行ELISA检测来确定小鼠血液中抗人4-1BB的滴度,并经流式细胞术检测2个浓度的小鼠血液

[0203] (1:100、1:1000)对4-1BB高表达的CHO-K1/h4-1BB细胞(Chempartner,Shanghai)和CHO-K1母细胞的特异反应性。空白对照组(PB)为免疫前老鼠的血清。当检测小鼠血清中4-1BB特异的抗体滴度达到一定的水平后,将小鼠的脾细胞取出分离B细胞,用BD FACS AriaII Cell Sorter分选CD138阳性的浆细胞和人4-1BB抗原阳性的B细胞群。提取B细胞的RNA,反转录cDNA(SuperScript IV First-Strand synthesis system,Invitrogen,18091200),然后用特异性的引物PCR扩增人VH基因。PCR引物5'-GGTGTCCAGTGTSAGGTGCAGCTG-3',5'-AATCCCTGGGCACTGAAGAGACGGTGACC-3'。将扩增的VH基因片段构建到编码人IgG1抗体重链Fc结构域序列的哺乳动物细胞表达质粒pCAG载体中。

[0204] 构建好的质粒转染哺乳动物宿主细胞(如人胚肾细胞HEK293)进行表达获得HCAb的抗体。检测表达HCAb的上清与过表达人4-1BB的CHO-K1/hu 4-1BB(ChemPartner,Shanghai)稳定细胞系的结合,同时用CHO-K1细胞作为阴性对照,进行Acumen筛选。获得的阳性单克隆抗体进一步检测与过表达食蟹猴4-1BB的CHO-K1/cyno 4-1BB(ChemPartner,Shanghai)稳定细胞系的结合交叉结合活性。获得683个结合CHO-K1/hu4-1BB和CHO-K1/

cyno 4-1BB的单克隆的表达上清进行NF-kb功能试验，同时利用常规的测序手段获得编码抗体分子可变结构域的核苷酸序列以及对应的氨基酸序列。去除重复序列后得到323个同时结合CHO-K1/hu 4-1BB和CHO-K1/cyno 4-1BB的功能性的具有独特序列的全人源4-1BB单克隆抗体。根据人猴细胞结合能力及NF-Kb功能试验结果，选择综合排名靠前的38个抗体进行重组表达，信息见表14。

[0205] 表14 HCAb抗体序列的胚系基因分析和翻译后修饰位点(PTM)分析

[0206]

序号	克隆号1	重组抗体	VH胚系V基因	VH PTM
1	1016P0010B11	PR001758	IGHV3-23	
2	1016P0010D7	PR001759	IGHV3-23	NxS/T (HCDR3),NG (HCDR3)
3	1016P0011G10	PR001760	IGHV3-23	
4	1016P0016E9	PR001763	IGHV3-23	NxS/T (HCDR3),NG (HCDR3)
5	1016P0022E5	PR001764	IGHV3-23	
6	1016P0034F10	PR001766	IGHV3-23	
7	1016P0038G1	PR001767	IGHV3-53	DG (HCDR2)
8	1016P0039B9	PR001768	IGHV3-23	
9	1016P0042C5	PR001771	IGHV3-23	
10	1016P0045F7	PR001774	IGHV3-23	
11	1016P0046A9	PR001775	IGHV3-23	NxS/T (HFR3)
12	1016P0049C7	PR001776	IGHV3-23	DG (HCDR3)
13	1016P0058D11	PR001780	IGHV3-23	
14	1016P007F3	PR001781	IGHV3-23	
15	1016P0014G8	PR001830	IGHV3-23	
16	1016P0015C8	PR001831	IGHV3-23	NxS/T (HCDR3),NG (HCDR3)
17	1016P0016F8	PR001833	IGHV3-23	
18	1016P0019C9	PR001834	IGHV3-23	NxS/T (HCDR2)
19	1016P0020G4	PR001836	IGHV3-23	NxS/T (HCDR2),NG (HCDR2)
20	1016P0024B10	PR001837	IGHV3-23	
21	1016P0030B2	PR001838	IGHV3-23	DG (HCDR2)
22	1016P0037D2	PR001840	IGHV3-74	NS (HCDR2),DG (HCDR2)
23	1016P0045A3	PR001842	IGHV3-23	
24	R1016P142D03	PR007286	IGHV3-11	
25	R1016P142F06	PR007287	IGHV3-21	
26	R1016P144G12	PR007288	IGHV3-21	
27	R1016P145B11	PR007289	IGHV3-21	
28	R1016P145C05	PR007290	IGHV3-48	
29	R1016P145C07	PR007291	IGHV3-11	

[0207]

30	R1016P145D10	PR007292	IGHV3-11	
31	R1016P145E06	PR007293	IGHV3-21	
32	R1016P147A07	PR007294	IGHV3-21	
33	R1016P147A09	PR007295	IGHV3-11	
34	R1016P147B10	PR007296	IGHV3-21	
35	R1016P149F10	PR007297	IGHV3-11	
36	R1016P149G05	PR007298	IGHV3-21	
37	R1016P149H12	PR007299	IGHV3-21	
38	R1016P156E05	PR007300	IGHV3-21	

[0208] 对其中1个来自实施例2.1.2的具有潜在PTM位点的抗体，进行氨基酸突变得到的新的抗体分子(称为PTM变体)，突变位点见表15，得到的突变抗体信息见表16。

[0209] 表15 HCAb序列的突变位点设计

[0210]

初始抗体	变体	可变区突变	重组抗体亚型
PR001838	PR004469	G53A	人IgG1
PR001838	PR007381	F37V,P40A,E42G,T43K,K46E,G53A	人IgG1

[0211] 表16 HCAb抗体序列表

[0212]

抗体编号	重链	VH	HCDR1	HCDR2	HCDR3
PR001758	217	175	19	57	101
PR001759	218	176	15	58	102
PR001760	219	177	20	59	103
PR001763	220	178	20	60	104
PR001764	221	179	15	61	105
PR001766	222	180	15	60	106
PR001767	223	181	21	62	107
PR001768	224	182	20	63	108
PR001771	225	183	20	60	108
PR001774	226	184	22	64	109
PR001775	227	185	15	60	110
PR001776	228	186	15	65	111
PR001780	229	187	22	66	112
PR001781	230	188	15	49	113
PR001830	231	189	20	60	103
PR001831	232	190	15	63	104
PR001833	233	191	15	60	114
PR001834	234	192	23	67	105
PR001836	235	193	24	68	103
PR001837	236	194	15	60	105
PR001838	237	195	20	69	115
PR001840	238	196	15	70	116
PR001842	239	197	15	60	117
PR004469	240	198	20	71	115
PR007286	353	337	300	308	326
PR007287	354	338	300	309	327
PR007288	355	339	300	310	328
PR007289	356	340	300	308	329
PR007290	357	341	300	311	330
PR007291	358	342	300	312	331

[0213]

PR007292	359	343	300	308	332
PR007293	360	344	300	313	330
PR007294	361	345	300	314	329
PR007295	362	346	300	315	331
PR007296	363	347	300	314	327
PR007297	364	348	300	316	331
PR007298	365	349	300	308	333
PR007299	366	350	300	317	334
PR007300	367	351	300	315	331
PR007381	368	352	20	71	115

[0214] 实施例2.1.3.制备抗4-1BB全人源重组抗体

[0215] 将编码HCAb抗体的质粒转染哺乳动物宿主细胞(如人胚肾细胞HEK293),利用常规的重组蛋白表达和纯化技术,可以得到纯化的抗4-1BB重组重链抗体。具体说来,将HEK293细胞在FreeStyle™F17 Expression Medium培养基(Thermo,A1383504)扩培。瞬时转染开始之前,调节细胞浓度至6×10^5细胞/ml,于37℃8%CO_2摇床中培养24小时,细胞浓度在1.2×10^6细胞/ml。准备30ml培养的细胞,将上述编码HCAb重链的质粒30μg质粒溶解于1.5ml

Opti-MEM减血清培养基(Thermo,#31985088),再取1.5ml Opti-MEM溶入1mg/ml PEI(Polysciences,Inc,#23966-2)120μl,静置5分钟。把PEI缓慢加入质粒中,室温孵育10分钟,边摇晃培养瓶边缓慢滴入质粒PEI混合溶液,于37℃8%CO_2摇床中培养5天。5天后观测细胞活率。收集培养物,以3300G转速离心10分钟后取上清;然后将上清高速离心去除杂质。用PBS(pH7.4)平衡含有MabSelect™(GE Healthcare Life Science,#71-5020-91AE)的重力柱(Bio-Rad,#7311550),2-5倍柱体积冲洗。将上清样品过柱。用5-10倍柱体积的PBS冲洗柱子。再用pH3.5的0.1M甘氨酸洗脱目的蛋白,后用pH 8.0的Tris-HCl调节至中性,最后用超滤管(Millipore,UFC901024)浓缩换液至PBS缓冲液,得到纯化的抗4-1BB重链抗体溶液。抗体浓度用NanoDrop检测280nm吸光度测定,抗体的纯度用SEC-HPLC和SDS-PAGE测定。

[0216] 实施例2.1.4.利用HPLC-SEC分析蛋白纯度和多聚体

[0217] 使用分析型分子尺寸排阻层析色谱法(SEC)来分析蛋白样品的纯度和聚体形式。将分析型色谱柱TSKgel G3000SWxl(Tosoh Bioscience,08541,5μm,7.8mm x 30cm)连接到高压液相色谱仪(HPLC)(型号:Agilent Technologies,Agilent 1260Infinity II),用PBS缓冲液室温下平衡至少1小时。适量蛋白样品(至少10μg,样品浓度调整到1mg/ml)用0.22μm滤膜过滤后注射入系统,并设定HPLC程序:用PBS(pH 7.4)缓冲液将样品以1.0ml/min的流速流过色谱柱,最长时间为20分钟;检测波长280nm。采集后用ChemStation软件对色谱图进行积分并计算相关数据,生成分析报告,报告出样品内不同分子尺寸组份的滞留时间。

[0218] 实施例2.1.5.利用HPLC-HIC分析蛋白纯度和疏水性

[0219] 使用分析型疏水相互作用层析色谱法(HIC)来分析蛋白样品的纯度和疏水性。将分析型色谱柱TSKgel Buty1-NPR(Tosoh Bioscience,14947,4.6mm×3.5cm)连接到高压液相色谱仪(HPLC)(型号:Agilent Technologies,Agilent 1260Infinity II),用PBS缓冲液室温下平衡至少1小时。设定方法由16分钟内从100%流动相A(20mM组氨酸,1.8M硫酸铵,pH 6.0)至100%流动相B(20mM组氨酸,pH 6.0)的线性梯度,流速设定为0.7ml/min,蛋白样品浓度1mg/ml,进样体积20μl,检测波长280nm。采集后用ChemStation软件对色谱图进行积分并计算相关数据,生成分析报告,报告出样品内不同分子尺寸组份的滞留时间。

[0220] 实施例2.1.6.利用DSF测定抗体分子的热稳定性

[0221] 差示扫描荧光法(Differential Scanning Fluorimetry,DSF)是一种常用的高通量的用来测定蛋白质热稳定性的方法。它使用实时荧光定量PCR仪器通过监测与去折叠的蛋白分子结合的染料的荧光强度的变化,来反映蛋白质的变性的过程,从而反映出蛋白分子的热稳定性。本实施例利用DSF方法来测定蛋白分子热变性温度(Tm)。10μg蛋白加入96-孔PCR板(Thermo,AB-0700/W),接着加入2μl 100X稀释的染料SYPROTM(Invitrogen,2008138),然后加入缓冲液使得终体积为40μl每孔。将PCR板密封,放置于实时荧光定量PCR仪器(Bio-Rad CFX96 PCR System),先于25℃孵育5分钟,然后以0.2℃/0.2分钟的梯度逐渐从25℃升温至95℃,在测试结束时将温度降至25℃。使用FRET扫描模式并使用Bio-Rad CFX Maestro软件进行数据分析并计算出样品的Tm。

[0222] 表17抗4-1BB HCAB抗体的理化性质

[0223]

抗原结合蛋白	SEC-HPLC(%)纯度	Tm (℃) by DSF*	HIC-HPLC 滞留时间(分钟)	相应的硫酸氨浓度(M)	第一步纯化后产量 (mg/L)
PR001758	99.45	57	18.617	0.49	75.3
PR001759	84.47	61.2	17.846	0.58	58.3
PR001760	98.93	62.4	17.993	0.56	42
PR001763	85.12	62.6	17.035	0.67	69.5
PR001764	98.86	57.2	19.335	0.41	35.5
PR001766	97.69	60.6	18.7	0.48	27.5
PR001767	98.76	56	18.591	0.5	36.3
PR001768	99.01	63	20.555	0.28	25
PR001771	99.28	63.4	20.21	0.31	17.5
PR001774	99.79	56.2	20.378	0.29	11.4
PR001775	95.71	55.2	18.398	0.52	17
PR001776	99.1	56.6	20.352	0.3	10
PR001780	99.37	60.8	18.893	0.46	31
PR001781	99.59	61.4	20.564	0.27	11.7
PR001830	97.48	63.8	17.782	0.59	36.8

[0224]

PR001831	86.78	56.2	16.948	0.68	46.5
PR001833	99.29	58.2	17.6	0.61	42
PR001834	93.7	59	17.711	0.6	27.3
PR001836	99.48	57.4	17.684	0.6	38.3
PR001837	96.57	59.8	18.699	0.48	35.3
PR001838	98.55	63.8	16.785	0.7	42
PR001840	99.6	56.2	17.433	0.63	44.3
PR001842	98.47	55	18.224	0.54	16.5
PR004469	95.43	-	-	-	81.2
PR007286	-	56.2	20.4	0.31	10.68
PR007287	-	52.2	16.65	0.73	8.18
PR007288	-	-	-	-	2.46
PR007289	-	55.4	19.41	0.42	1.21
PR007290	-	51.2	20.03	0.35	6.81
PR007291	-	44.4	20.88	0.25	5.95
PR007292	-	50.6	16.04	0.79	8.90
PR007293	-	-	-	-	4.01
PR007294	-	-	-	-	1.81
PR007295	-	64	20.33	0.32	7.65
PR007296	-	58.2	18.89	0.48	1.12
PR007297	-	56.8	21.81	0.15	5.48
PR007298	-	50.4	16.22	0.77	10.68
PR007299	-	47.8	17.93	0.58	8.18
PR007300	-	50.4	20.75	0.27	2.46
PR007381	98.52%	-	-	-	152.5

[0225] 表17显示大部分4-1BB HCAB具有较好的理化性质。

[0226] 实施例2.2.4-1BB HCAb抗体与细胞表面4-1BB的结合

[0227] 本实施例是为了研究抗人4-1BB的HCAb单抗体外结合人和食蟹猴4-1BB的活性。采用过表达人4-1BB的CHO-K1细胞株(CHO-K1/hu 4-1BB,Genescript)、过表达食蟹猴4-1BB的CHO-K1细胞株(CHO-K1/cyno 4-1BB,Genescript)进行细胞水平上的抗体结合实验。简言之,消化细胞CHO-K1/hu 4-1BB和CHO-K1/cyno 4-1BB细胞,并用F12K完全培养基重悬,将细胞密度分别调整为1×10^6细胞/ml。以100μL细胞/孔接种于96孔V底板(Corning,#3894),随后加入100μl/孔,2倍于终浓度的3倍浓度梯度稀释的待测抗体。将细胞放置于4℃,避光孵育1小时。之后,加入100μl/孔预冷PBS漂洗细胞两次,于500g、4℃下离心5分钟,弃上清。再

加入100μl/孔荧光二抗(Alexa Fluor 488-conjugated AffiniPure Goat Anti-Human IgG,Fcγ Fragment Specific,Jackson,#109-545-06,1:500稀释),4℃,避光孵育30分钟。用100μl/孔预冷PBS洗涤细胞两次,于500g、4℃下离心5分钟,弃上清。最后,200μl/孔预冷PBS重悬细胞,使用BD FACS CANTOII读取荧光发光信号值。

[0228] 如图11A到图11M所示,本发明的抗4-1BB的HCAb抗体均能结合人4-1BB,且检测到的抗体结合能力与抗体浓度成正相关关系递增。与参照抗体(Urelumab和Utomilumab)相比,这些抗体能以较低的浓度更灵敏得结合人4-1BB,其中以PR001758-PR001760,PR001764,PR001830,PR001831,PR001833,PR001836,PR001838为最佳,其EC50均小于0.3nM,与参照抗体Utomilumab和Urelumab的EC50相当。PR007287,PR007292,PR007293,PR007294,PR007298结合CHO-K1/hu 4-1BB细胞的荧光最大值要高与参照抗体Utomilumab和Urelumab。

[0229] 如图12A到图12L所示,本发明的抗4-1BB的HCAb抗体均能结合猴4-1BB,且检测到的抗体结合能力与抗体浓度成正相关关系递增。与参照抗体Tab(Utomilumab)相比,这些抗体能以较低的浓度更灵敏得结合猴4-1BB,与参照抗体Utomilumab的EC50相当或更优。PR007287,PR007292,PR007293,PR007294,PR007298结合CHO-K1/hu 4-1BB细胞的荧光最大值要高与参照抗体Utomilumab和Urelumab。而参照抗体Urelumab不具有与猴4-1BB交叉结合的活性。

[0230] 实施例2.3.利用报告基因细胞系检测对4-1BB信号通路的刺激作用

[0231] 将表达CD32b的CHO-K1细胞(CHO-K1/CD32b)铺到96孔板(Perkin Elmer,#6005225)上,细胞量为1.5×10^4/孔,100μL/孔。37℃在5%CO_2环境下孵育过夜。去除上清液,加入40μL/孔的2倍的待测抗原结合蛋白稀释液,起始终浓度浓度为200nM,3倍浓度稀释或起始终浓度浓度为30nM,5倍浓度稀释,hlgG1为对照组。加入4.5×10^4/孔的可持续表达4-1BB和NF-Kb反应元件的荧光素酶报告基因的HEK293报告细胞(HEK293/4-1BB/NF-kb报告细胞,BPS Biosciences,#79289)40μL/孔。37℃在5%CO_2环境下培养6小时。加入ONE-Glo™荧光素酶试剂(Promega,#E6110),室温孵育5分钟,酶标仪检测发光值。

[0232] 结果如图13A到图13I所示,在CHO-K1/CD32b交联下,本申请所述大部分4-1BB抗原结合蛋白对4-1BB介导的NF-Kb信号通路的促进作用与其浓度成正相关关系递增。与参照抗体Tab(Utomilumab)相比,EC50比参照抗体相当或更低,且最大荧光值也与参照抗体相当或更高,说明这些抗体能以较低的浓度促进NF-Kb的激活,其中以PR001758,PR001759和PR001760,PR007286,PR007291,PR007295,PR007296,PR007297,PR007299,PR007300为最佳,其EC50均小于0.8nM,与参照抗体的EC50相当。

[0233] 结果如图13J所示,在没有CHO-K1/CD32b交联下,本申请所述所有4-1BB抗原结合蛋白对4-1BB介导的NF-Kb信号通路没有激活。而参照抗体Tab(Urelumab)仍然具有很强的激活作用。

[0234] 实施例2.4.抗原结合蛋白阻断4-1BB配体与4-1BB结合

[0235] 为了研究人4-1BB结合蛋白体外阻断人4-1BB与人4-1BBL结合的活性。采用过表达人4-1BB的CHO-K1细胞株(CHO-K1/hu4-1BB)进行细胞水平的人4-1BB/人4-1BBL结合阻断实验。简言之,消化CHO-K1/hu4-1BB细胞,并用F-12K完全培养基重悬,将细胞密度调整为1×10^6细胞/mL。以100μL细胞/孔接种于96孔V底板(Corning,#3894),随后加入100μL/孔,2倍

于终浓度的3倍浓度梯度稀释的待测抗原结合蛋白，混合均匀，其中抗原结合蛋白最高终浓度为100nM，共8个浓度，hIgG1作为对照。将细胞放置于4℃，避光孵育1小时。之后，4℃下离心5分钟，弃上清，随后加入50μL/孔，1μg/mL浓度的生物素标记的人4-1BBL蛋白(ACRO,41L-H82F9)，4℃，避光孵育30分钟。加入100μL/孔预冷PBS漂洗细胞两次，于500g，4℃下离心5分钟，弃上清。加入100μL/孔荧光二抗(PE Streptavidin,BD,#554061,1:200)，4℃，避光孵育30分钟。用200μL/孔预冷PBS洗涤细胞两次，于500g，4℃下离心5分钟，弃上清。最后，200μL/孔预冷PBS重悬细胞，使用BD FACS CANTOII读取荧光发光信号值，计算IC50，抑制率%＝1-$MFI_{(4\text{-}1BB\ Ab)}/MFI_{(iso)}$。

[0236] 结果如图14A到图14K所示。本申请所述4-1BB抗原结合蛋白分成了两类。一类能阻断人4-1BBL与细胞表面的人4-1BB结合，显示出与参照抗体Tab(Utomilumab)相当的阻断效果(PR001758,PR001759,PR001760,PR001764,PR001766,PR001776,PR001830,PR001831,PR001833,PR001834,PR001836,PR001837,PR001838,PR007287,PR007288,PR007289,PR007290,PR007291,PR007292,PR007293,PR007294,PR007295,PR007296,PR007298,PR007299,PR007300)；另外一类显示与参照抗体(Urelumab)相似，弱阻断或者无阻断效果(PR001763,PR001767,PR001768,PR001771,PR001774,PR001780,PR001781,PR001840,PR001842,PR007286,PR007297)。

[0237] 实施例2.5.抗原结合蛋白能在体外激活4-1BB通路

[0238] 使用10μg/ml的丝裂霉素(北京中生瑞泰科技,#10107409001)处理CHO-K1(ATCC,#CCL-61)或者是CHO-K1/CD32b(过表达人CD32b的CHO-K1细胞)的细胞，30分钟37℃。然后用10％FBS的F-12K培养液，洗涤4次。把处理过的细胞放入96孔板里，每孔1.5×10^4个，37℃保温箱培养过夜。第二天，使用MACS试剂盒(Miltenyi Biotec,#130-096-535)从人PBMC里分离人CD3阳性T细胞。首先确定细胞数量，然后根据细胞数量加入相应量的MACS缓冲液和Pan-T细胞生物素抗体，混匀，4℃静置5分钟。然后加入相应量微磁珠，4℃静置10分钟。通过LS柱的是CD3阳性的T细胞。将前一天96孔板的培养液洗掉，加入纯化的T细胞，每孔1×10^5个。然后加入相应浓度的4-1BB抗体或者是对照抗体，加入OKT3(eBiosciences,#16-0037-85)并且使其最终浓度达到0.3μg/ml。37℃保温箱培养72小时。72小时后，收取上清液，使用ELISA试剂盒(Invitrogen,#88-7316-88)来检测IFN-γ的含量。在96平底板里加入包被抗体，4℃过夜。第二天加入ELISA缓冲液，室温1小时。加入收取的上清液，室温培养2小时。洗板2次，加入检测抗体，室温1小时。洗板两次，加入HRP-链霉亲和素，室温孵育1小时。然后加入TMB底物，稍后加入ELISA终止液(BBI,E661006-0200)。酶标仪(PerkinElemer Enspire)读取450nm吸光度(OD450)值，计算IFN-γ浓度。

[0239] 结果如图15A到图15D所示，本实例中的绝大多数的4-1BB HCAB的激活作用都比Utomilumab更强，比如PR001758,PR001759,PR001760,PR001764,PR001830,PR001833,PR001834,PR001836,PR001837,PR001838在较低浓度1nM时对T细胞激活能力比参照抗体Utomilumab强。

[0240] 结果如图16A到图16B所示，PR0001758、PR001759和PR001760抗体均是CD32b交联依赖型激活4-1BB通路，并诱导激活T细胞的功能。在CHO-K1/CD32b细胞交联，其激活作用都比Utomilumab更强，而稍微比Urelumab弱。没有CHO-K1/CD32b细胞交联时，本实施例中的HCAb抗体则不能激活T细胞的功能，而Urelumab仍然能激活T细胞，这也被认为是Urelumab

毒性的原因。激活作用与抗体浓度成正相关关系递增,EC50均小于参照抗体Utomilumab,说明其能以较低浓度激活4-1BB通路,而且细胞因子干扰素gamma释放最大值也高于Utomilumab。

[0241] 实施例2.6.4-1BB抗体对重组4-1BB蛋白的结合亲和力测定

[0242] 按照制造商提供的详细操作和方法,使用Octet RED96仪器(Fortiebio)和抗人IgG Fc亲和素传感器(AHC传感器,Pall ForteBio,#18-5060)测定亲和力。具体地,用含有0.1%(w/w)BSA和0.02%(v/v)吐温20的PBS缓冲液(pH7.4)将人的4-1BB蛋白,His标签(Acrobiosystem,#41B-H5227)或食蟹猴的4-1BB蛋白,his标签(Acrobiosystem,#41B-C52H4),稀释至400nM,与AHC传感器孵育。将40nM的4-1BB抗体与负载人4-1BB蛋白或猴4-1BB蛋白的AHC传感器在30℃孵育3分钟。该反应混合物在含有0.1%(v/w)BSA和0.02%(v/v)吐温20的PBS缓冲液(pH7.4)中于30℃继续孵育5分钟。Octet Red 96实时记录4-1BB抗体与4-1BB蛋白的结合和分离信号。亲和力、关联和解离常数由Octet使用软件确定,结果如表18和表19所示。

[0243] 结果表明,PR001836和PR001838抗体的KD值在检测的抗体中不管结合人4-1BB或食蟹猴4-1BB都略低,表明其更强的4-1BB结合亲和力。

[0244] 表18抗体与人的4-1BB蛋白的结合亲和力

[0245]

抗体	抗原蛋白	抗体浓度 (nM)	KD (M)	kon(1/Ms)	kdis(1/s)	Response
PR001758	人 4-1BB	400	2.56E-08	2.26E+05	5.78E-03	0.3263
PR001759		400	1.23E-08	3.17E+05	3.89E-03	0.2843
PR001760		400	2.26E-08	2.68E+05	6.07E-03	0.2674

[0246]

PR001833		400	2.34E-08	2.16E+05	5.06E-03	0.3112
PR001830		400	2.49E-08	2.66E+05	6.64E-03	0.3073
PR001836		400	1.35E-08	2.39E+05	3.22E-03	0.2937
PR001838		400	1.12E-08	2.33E+05	2.61E-03	0.3093
PR001840		400	3.27E-08	1.07E+05	3.50E-03	0.2236

[0247] 表19抗体与食蟹猴的4-1BB蛋白的结合亲和力

[0248]

抗体	抗原蛋白	抗体浓度 (nM)	KD (M)	kon(1/Ms)	kdis(1/s)	Response
PR001758	食蟹猴 4-1BB	400	7.41E-09	1.51E+05	1.12E-03	0.274
PR001759		400	1.10E-08	2.15E+05	2.37E-03	0.2832
PR001760		400	2.06E-08	1.56E+05	3.21E-03	0.1779
PR001833		400	2.23E-08	1.39E+05	3.09E-03	0.2733
PR001830		400	1.81E-08	1.92E+05	3.47E-03	0.2222
PR001836		400	8.89E-09	1.65E+05	1.47E-03	0.2504
PR001838		400	1.03E-08	1.43E+05	1.46E-03	0.2242
PR001840		400	1.63E-08	6.20E+04	1.01E-03	0.2028

[0249] 实施例2.7.抗原结合蛋白的表位鉴定(Epitope binning)

[0250] 使用ForteBio Octet平台对实施例1得到的抗原结合蛋白和utomiluab、urelumab进行表位鉴定。简言之,将第一抗体负载至多个AHC尖端上,随后在测定缓冲液pH 7.5中获得60秒基线。然后将尖端暴露于组氨酸标记的4-1BB持续180秒,以允许抗原结合。将尖端转移至含有测定缓冲液中的第二抗体的孔持续90秒。如果第二抗体表现出明显结合,那么就

将它视为非竞争剂(即,在与第一抗体不同的表位区间中)。如果第二抗体不表现明显结合,那么就将它视为竞争剂(即,在与第一抗体相同的表位区间中)。通过比较第二抗体在第一抗体存在下与4-1BB的结合与第一抗体阻断本身来进行结合测定。抑制率通过公式计算,抑制率(%)=(A-B)/A*100(注:A:某抗体的100%信号,B:该抗体作为第二抗体的信号)。

[0251] 若抑制率大于80%,则意味着两种抗体具有非常相近的表位;若抑制率介于40-80%之间,则意味着两种抗体具有比较接近但是不完全重叠的表位;若抑制率小于40%,则意味着两种抗体具有不重叠的表位。

[0252] 结果如下表20所示,PR001760,PR001779,PR001838和PR001840与Utomiluab在4-1BB的结合位点重叠性高,但是与Urelumab的结合位点重叠性低;而PR001767的结合位点具有特异性,与Utomiluab和Urelumab都不同。

[0253] 表20本申请抗原结合蛋白与临床抗体的表位鉴定

[0254]

抑制率(%)		第二抗体						
		Utomilumab	Urelumab	PR001760	PR001767	PR001779	PR001838	PR001840
第一抗体	Utomilumab	93.31	-3.7	101.04	6.51	96.77	98.5	94.94
	Urelumab	-1.65	96.35	2.35	26.35	8.94	2.11	-7.98
	PR001760	78.72	-0.09	91.61	15.34	91.78	89.07	84.56
	PR001767	-9.54	2.12	-4.97	88.06	-9.85	1.14	49.51
	PR001779	42.12	0.52	65.34	9.28	89.03	63.36	69.98
	PR001838	83.94	-2.67	92.53	13.43	84.72	92.26	84.31
	PR001840	53.97	1.04	79.78	65.13	90.58	78.42	94.97

[0255]

[0256] 实施例2.8.抗原结合蛋白的特异性结合4-1BB

[0257] 4-1BB属于TNF肿瘤坏死因子受体超家族,该家族是由一大类多功能的受体组成,这些受体具有介导免疫和非免疫细胞功能。已鉴定出6种受体是发挥重要作用的免疫共同刺激者,包括CD40,OX40,4-1BB,CD27,GITR和CD30。同样,诱导型T细胞共刺激因子(ICOS)是另一类对激活的T细胞或记忆型T细胞的功能及存活有重要作用的受体。

[0258] 本实施例是通过流式检测TNF肿瘤坏死因子受体超家族的3个受体和ICOS来研究抗人4-1BB的HCAb单抗体外结合的特异性。采用过表达人4-1BB的CHO-K1细胞株(CHO-K1/hu 4-1BB,Genescript)、过表达人CD40的CHO-K1细胞株(CHO-K1/hu CD40,北京康源博创,#KC-1286)、过表达人OX40的CHO-K1细胞株(CHO-K1/hu OX40,Genescript,#M00561)和过表达人ICOS的HEK293细胞株(HEK293T/ICOS,Genescript,#KC-0210)进行细胞水平上的抗体结合实验。简言之,消化这些细胞,并用F12K或DMEM完全培养基重悬,将细胞密度分别调整为1×10^6细胞/ml。以100μL细胞/孔接种于96孔V底板(Corning,#3894),随后加入100μl/孔,2倍于终浓度的3倍浓度梯度稀释的待测抗体。将细胞放置于4℃,避光孵育1小时。之后,加入100μl/孔预冷PBS漂洗细胞两次,于500g、4℃下离心5分钟,弃上清。再加入100μl/孔荧光二抗(Alexa Fluor 488-conjugated AffiniPure Goat Anti-Human IgG,Fcγ Fragment Specific,Jackson,#109-545-06,1:1000稀释),4℃,避光孵育30分钟。用100μl/孔预冷PBS洗涤细胞两次,于500g、4℃下离心5分钟,弃上清。最后,200μl/孔预冷PBS重悬细胞,使用BD FACS CANTOII读取荧光发光信号值。

[0259] 结果如图17A到图17D所示,本申请所述的PR001758,PR001760,PR001836和PR001838特异性地结合CHO-K1/hu 4-1BB细胞,而不结合TNF肿瘤坏死因子受体超家族的其

他成员。

[0260] 小结

[0261] 本发明的积极进步效果在于：

[0262] 本发明的4-1BB抗体是一种全新的仅含“重链”的全人抗体，具有与人4-1BB和食蟹猴4-1BB特异性结合的活性。该4-1BB重链抗体的大小只有传统IgG抗体的一半，由于不含轻链的这一特点，使得该抗体可以用于双特异性抗体，并解决了轻链错配和异源二聚化的问题。

[0263] 实施例3.HER2×4-1BB双特异性抗体

[0264] 人表皮生长因子受体2(HER2)也称为ERBB2，HER-2，HER-2/neu，NEU，NGL，TKR1和c-erb B2，在大鼠中也称为ErbB2或neu，它是ErbB蛋白家族的一员，通常被称为表皮生长因子受体家族。是一种在乳腺癌中具有较高侵袭性的蛋白质。HER2是细胞膜表面结合的酪氨酸激酶，通常参与导致细胞生长和分化的信号转导途径。HER2被认为是一种孤儿受体，没有任何EGF配体家族能够激活它。大约30％的乳腺癌具有HER2基因扩增或其蛋白产物过表达，该受体在乳腺癌中的过表达与疾病复发和预后不良有关。HER2在发育，癌症，神经肌肉连接处的通讯以及细胞生长和分化的调节中发挥作用。

[0265] HER2×4-1BB双抗，旨在通过将T细胞与HER2阳性肿瘤细胞桥接起来促进4-1BB聚集，为肿瘤抗原特异性T细胞提供有效的共刺激信号，进一步增强T细胞受体(TCR)介导的活性并导致肿瘤解体。因此HER2×4-1BB介导的4-1BB的激活偏向于体内T细胞和肿瘤细胞的共定位，例如在原发性肿瘤与肿瘤浸润淋巴细胞(TIL)或含有肿瘤转移的淋巴结。

[0266] 在本实施例中，构建了同时靶向HER2和4-1BB的双特异性抗体，旨在通过一个或者多个作用机制来提高抗肿瘤效果和安全性。第一，HER2×4-1BB双抗富集于HER2高表达的肿瘤组织，T细胞与HER2阳性肿瘤细胞桥接起来促进4-1BB聚集，为肿瘤抗原特异性T细胞提供有效的共刺激信号，进一步增强T细胞受体(TCR)介导的T细胞的活性，提高抗肿瘤活性。因此HER2×4-1BB介导的4-1BB的激活偏向于体内T细胞和肿瘤细胞的共定位，例如在原发性肿瘤与肿瘤浸润淋巴细胞(TIL)或含有肿瘤转移的淋巴结。第二，本实施例所使用的抗4-1BB的激动型抗体的功能是依赖于分子交联的，它只能在肿瘤微环境中利用靶细胞来介导T细胞的激活，以避免类似Urelumab的单抗在正常组织中过度激活T细胞所带来的毒副作用。

[0267] 实施例3.1.HER2×4-1BB双特异性抗体的结构和设计

[0268] 本实施例使用抗HER2的IgG抗体trastuzumab，其相应的氨基酸序列来源于IMGT数据库。生产的抗体编号为PR000210，序列信息见表21。

[0269] 表21抗HER2的trastuzumab抗体序列表

[0270]

抗体编号	轻链	重链	VL	VH	LCDR1	LCDR2	LCDR3	HCDR1	HCDR2	HCDR3
PR000210	244	210	202	169	134	143	159	17	51	97

[0271] 本实施例使用的抗4-1BB的全人源H2L2抗体PR000448以及衍生的scFv来源于Harbour H2L2小鼠，其发现过程如实施例1所述。

[0272] 本实施例使用的抗4-1BB的全人源HCAb抗体来源于Harbour HCAb小鼠，其发现过程如实施例2所述。

[0273] 在本实施例及后续实施例中，阳性对照分子为抗HER2的IgG单抗PR000210

(trastuzumab类似物),亦为HER2×4-1BB双抗分子的HER2端的亲本单抗。

[0274] 在本实施例及后续实施例中,阳性对照分子为抗4-1BB的IgG单抗Uremulab和Utomilumab

[0275] 实施例3.1.1.利用抗HER2的IgG抗体和抗4-1BB的HCAb抗体构建IgG-VH四价对称结构的双特异性抗体

[0276] IgG-VH四价对称结构(如图18A所示)的结合蛋白包含两条多肽链:多肽链1,也称短链,从氨基末端到羧基末端,其包含VL_A-CL;多肽链2,也称长链,从氨基末端到羧基末端,其包含VH_A-CH1-h-CH2-CH3-L-VH_B。

[0277] 在一个实施方案中,多肽链2的CH3与VH_B直接融合联结,即L的长度为0。在另一个实施方案中,多肽链2的CH3经由连接肽L联结到VH_B;L可以是表22中所列序列。

[0278] 表22连接肽

[0279]

连接肽名字	连接肽长度	连接肽序列	序列编号
GS_4	4	GSGS	273
GS_5	5	GGGGS	274
GS_6	6	GGSGGS	275
GS_7	7	GGGGSGS	276
GS_15	15	GGGGSGGGGSGGGGS	277
GS_20	20	GGGGSGGGGSGGGGSGGGGS	278
GS_25	25	GGGGSGGGGSGGGGSGGGGSGGGGS	279
人 IgG1 铰链	15	EPKSCDKTHTCPPCP	280
人 IgG1 铰链 (C220S)	15	EPKSSDKTHTCPPCP	281
H1_15	15	EPKSSDKTHTPPPPP	282
G5-LH	15	GGGGGDKTHTCPPCP	283
H1_15-RT	17	EPKSSDKTHTPPPPPRT	284
L-GS_15-RT	18	LGGGGSGGGGSGGGGSRT	285
L-H1_15-RT	18	LEPKSSDKTHTPPPPPRT	286
KL-H1_15-RT	19	KLEPKSSDKTHTPPPPPRT	287
KL-H1_15-AS	19	KLEPKSSDKTHTPPPPPAS	288
RT-GS_5-KL	9	RTGGGGSKL	289

[0280]

RT-GS_15-KL	19	RTGGGGSGGGGSGGGGSKL	290
RT-GS_25-KL	29	RTGGGGSGGGGSGGGGSGGGGSGGGGSKL	291
EPKSSD	6	EPKSSD	292
AS-GS_15	17	ASGGGGSGGGGSGGGGS	293
GS_2	2	GS	

[0281] 利用抗HER2的IgG抗体和抗4-1BB的HCAb的重链抗体设计IgG-VH四价对称结构的HER2×4-1BB双抗分子,总结于表23;制备的双抗抗体分子样品并理化性质分析,总结于表24。

[0282] 表23 IgG-VH四价对称结构的HER2×4-1BB双抗分子

[0283]

双抗分子	HER2 抗体 (IgG)	4-1BB 抗体 (VH_B)	VH_B 相对 IgG 位置	连接肽（VH_B 和 IgG 之间）	Fc 类型（突变）
PR002812	trastuzumab	PR001758	重链 C 端	H1_15-RT	人 IgG1(L234A,L235A,P329G)
PR002813	trastuzumab	PR001760	重链 C 端	H1_15-RT	人 IgG1(L234A,L235A,P329G)
PR002815	trastuzumab	PR001764	重链 C 端	H1_15-RT	人 IgG1(L234A,L235A,P329G)
PR002820	trastuzumab	PR001774	重链 C 端	H1_15-RT	人 IgG1(L234A,L235A,P329G)
PR002821	trastuzumab	PR001775	重链 C 端	H1_15-RT	人 IgG1(L234A,L235A,P329G)
PR002822	trastuzumab	PR001780	重链 C 端	H1_15-RT	人 IgG1(L234A,L235A,P329G)
PR002823	trastuzumab	PR001781	重链 C 端	H1_15-RT	人 IgG1(L234A,L235A,P329G)
PR002824	trastuzumab	PR001830	重链 C 端	H1_15-RT	人 IgG1(L234A,L235A,P329G)
PR002825	trastuzumab	PR001831	重链 C 端	H1_15-RT	人 IgG1(L234A,L235A,P329G)
PR002826	trastuzumab	PR001833	重链 C 端	H1_15-RT	人 IgG1(L234A,L235A,P329G)
PR002827	trastuzumab	PR001836	重链 C 端	H1_15-RT	人 IgG1(L234A,L235A,P329G)
PR002828	trastuzumab	PR001838	重链 C 端	H1_15-RT	人 IgG1(L234A,L235A,P329G)
PR002829	trastuzumab	PR001840	重链 C 端	H1_15-RT	人 IgG1(L234A,L235A,P329G)

[0284] 表24 HER2×4-1BB双抗分子的理化性质

[0285]

双抗分子	表达体系和体积	质粒转染比例（短链：长链）	第一步纯化后产量(mg/L)	HPLC-SEC 纯度 (%)	HPLC-HIC 滞留时间(min)	DSF Tm1 (°C)
PR002812	Expi293F (10ml)	3 : 2	52.7	71.15	18.081	65.8
PR002813	Expi293F (10ml)	3 : 2	37.2	80.50	18.402	66.2
PR002815	Expi293F (10ml)	3 : 2	44.6	68.08	19.077	67.2
PR002820	Expi293F (10ml)	3 : 2	92.5	70.72	18.082	67.0
PR002821	Expi293F (10ml)	3 : 2	55.9	74.62	18.742	62.4
PR002822	Expi293F (10ml)	3 : 2	29.7	84.14	19.143	63.2
PR002823	Expi293F (10ml)	3 : 2	49.5	85.87	18.153	66.2
PR002824	Expi293F (10ml)	3 : 2	48.0	79.89	17.734	67.0
PR002825	Expi293F (10ml)	3 : 2	82.4	63.99	17.937	67.2
PR002826	Expi293F (10ml)	3 : 2	61.1	87.09	17.585	67.4
PR002827	Expi293F (10ml)	3 : 2	29.5	73.75	17.366	66.4
PR002828	Expi293F (10ml)	3 : 2	77.7	86.83	18.932	67.4
PR002829	Expi293F (10ml)	3 : 2	83.3	32.37	18.439	67.4

[0286] 实施例3.1.2.利用抗HER2的IgG抗体和抗4-1BB的H2L2抗体构建IgG-scFv四价对称结构的双特异性抗体

[0287] IgG-scFv四价对称结构(如图18B所示)的结合蛋白包含两条多肽链:多肽链1,也称短链,从氨基末端到羧基末端,其包含VL_A-CL;多肽链2,也称长链,从氨基末端到羧基末端,其包含VH_A-CH1-h-CH2-CH3-L1-VH_B L2-VL_B。

[0288] 或者

[0289] IgG-scFv四价对称结构(如图18C所示)的结合蛋白包含两条多肽链:多肽链1,也称短链,从氨基末端到羧基末端,其包含VL_A-CL;多肽链2,也称长链,从氨基末端到羧基末端,其包含VH_A-CH1-h-CH2-CH3-L1-VL_B L2-VH_B。

[0290] 多肽链2的连接肽L1和连接肽L2可以是表22中所列序列。

[0291] 利用抗HER2的IgG抗体和抗4-1BB的H2L2抗体设计IgG-scFv四价对称结构的HER2×4-1BB双抗分子,总结于表25;制备的双抗抗体分子样品并理化性质分析,总结于表26。双抗分子的序列见表27。

[0292] 表25 IgG-scFv四价对称结构的HER2×4-1BB双抗分子

[0293]

双抗分子	HER2 抗体 (IgG)	4-1BB 抗体 (scFv)	scFv 端结构	第一连接肽（Fc 和 scFv 之间）	第二连接肽（VH_B 和 VL_B 之间）	Fc 类型（突变）
PR001212	trastuzumab	PR000448	VH-连接肽-VL	KL-H1_15-RT	GS_15	人 IgG1
PR002811	trastuzumab	PR000448	VH-连接肽-VL	H1_15-RT	GS_15	人 IgG1 (L234A, L235A, P329G)

[0294] 表26 HER2×4-1BB双抗分子的理化性质

[0295]

双抗分子	表达体系和体积	质粒转染比例（短链：长链）	第一步纯化后产量 (mg/L)	HPLC-SEC 纯度 (%)	HPLC-HIC 滞留时间 (min)	DSF Tm1 (°C)
PR001212	HEK293F (30ml)	3 : 2	22.3	85.05	17.563	51.4
PR002811	Expi293F (10ml)	3 : 2	2.0			

[0296] 表27 HER2×4-1BB双抗分子的序列表

[0297]

抗体编号	多肽链 1	多肽链 2
PR001212	244	251
PR002811	244	252
PR002812	244	253
PR002813	244	254
PR002815	244	255
PR002820	244	256
PR002821	244	257
PR002822	244	258
PR002823	244	259
PR002824	244	260
PR002825	244	261

[0298]

PR002826	244	262
PR002827	244	263
PR002828	244	264
PR002829	244	265

[0299] 实施例3.2.FACS检测HER2×4-1BB双抗与SK-BR-3细胞的结合能力

[0300] 本实施例是为了研究4-1BB的双特异性抗体体外结合SK-BR-3的活性。SK-BR-3是高表达Her2的乳腺癌细胞，采用SK-BR-3进行细胞水平上的抗体结合实验。简言之，消化SK-BR-3细胞，并用完全培养基重悬，将细胞密度分别调整为1×10^6细胞/ml。以100μL细胞/孔接种于96孔V底板(Corning,#3894)，随后加入100μl/孔，2倍于终浓度的3倍浓度梯度稀释的待测抗体。将细胞放置于4℃，避光孵育1小时。之后，加入100μl/孔预冷PBS漂洗细胞两次，于500g、4℃下离心5分钟，弃上清。再加入100μl/孔荧光二抗(Alexa Fluor® 647AffiniPure Goat Anti-Human IgG,F(ab')2fragment specific,Jackson Immunoreserach,#109-605-006,1:1000稀释)，4℃，避光孵育30分钟。用100μl/孔预冷PBS

洗涤细胞两次，于500g、4℃下离心5分钟，弃上清。最后，200μl/孔预冷PBS重悬细胞，使用BD FACS CANTOII读取荧光发光信号值。

[0301] 如图19A到图19C所示，本发明的Her2×4-1BB的双特异性抗体均能结合人SK-BR-3，且检测到的抗体结合能力与抗体浓度成正相关关系递增。与参照抗体(Trastuzumab)相比，在相同浓度下，PR002813比参照抗体表现出更低的EC50，其他抗体则与参照抗体相当。

[0302] 实施例3.3.FACS检测HER2×4-1BB双抗与CHO-K1/hu 4-1BB细胞的结合能力

[0303] 本实施例是为了研究4-1BB的双特异性抗体体外结合4-1BB的活性。采用过表达人4-1BB的CHO-K1细胞株(CHO-K1/hu 4-1BB,Genescript)进行细胞水平上的抗体结合实验。简言之，消化细胞CHO-K1/hu 4-1BB细胞，并用F12K完全培养基重悬，将细胞密度分别调整为1×10^6细胞/ml。以100μL细胞/孔接种于96孔V底板(Corning,#3894)，随后加入100μl/孔，2倍于终浓度的3倍浓度梯度稀释的待测抗体。将细胞放置于4℃，避光孵育1小时。之后，加入100μl/孔预冷PBS漂洗细胞两次，于500g、4℃下离心5分钟，弃上清。再加入100μl/孔荧光二抗(AlexaFluor®647AffiniPure Goat Anti-Human IgG,F(ab')2fragment specific,Jackson Immunoreserach,#109-605-006,1:1000稀释)，4℃，避光孵育30分钟。用100μl/孔预冷PBS洗涤细胞两次，于500g、4℃下离心5分钟，弃上清。最后，200μl/孔预冷PBS重悬细胞，使用NovoCyte流式细胞仪(ACEA Biosciences)读取荧光发光信号值。

[0304] 如图20A到图20E所示，本发明的Her2×4-1BB的双特异性抗体均均能较好地结合人4-1BB，且检测到的抗体结合能力与抗体浓度成正相关关系递增。这些抗体能以较低的浓度更灵敏得结合人4-1BB，其中以PR002811，PR001212，PR002813和PR002824为最佳，EC50优于参照抗体Utomilumab。其它双抗与Utomilumab相当或者稍弱。但是最大MFI都高于参照抗体Utomilumab

[0305] 实施例3.4.FACS检测HER2×4-1BB双抗与CHO-K1/cyno 4-1BB细胞的结合能力

[0306] 本实施例是为了研究4-1BB的双特异性抗体体外结合4-1BB的活性。采用过表达食蟹猴4-1BB的CHO-K1细胞株(CHO-K1/cyno 4-1BB,Genescript)进行细胞水平上的抗体结合实验。简言之，消化细胞CHO-K1/cyno 4-1BB细胞，并用F12K完全培养基重悬，将细胞密度分别调整为1×10^6细胞/ml。以100μL细胞/孔接种于96孔V底板(Corning,#3894)，随后加入100μl/孔，2倍于终浓度的3倍浓度梯度稀释的待测抗体。将细胞放置于4℃，避光孵育1小时。之后，加入100μl/孔预冷PBS漂洗细胞两次，于500g、4℃下离心5分钟，弃上清。再加入100μl/孔荧光二抗(AlexaFluor®647AffiniPure Goat Anti-Human IgG,F(ab')2fragment specific,Jackson Immunoreserach,#109-605-006,1:1000稀释)，4℃，避光孵育30分钟。用100μl/孔预冷PBS洗涤细胞两次，于500g、4℃下离心5分钟，弃上清。最后，200μl/孔预冷PBS重悬细胞，使用NovoCyte流式细胞仪(ACEA Biosciences)读取荧光发光信号值。

[0307] 如图21A到图21B所示，本发明的HER2×4-1BB双抗均能较好地结合食蟹猴4-1BB，且检测到的抗体结合能力与抗体浓度成正相关关系递增。与参照抗体(Utomilumab)相比，PR001212,PR002824,PR002826-PR002829与食蟹猴4-1BB结合相当。

[0308] 实施例3.5.HER2/4-1BB双抗能在体外激活T细胞通路

[0309] 用PBS稀释1mg/ml的OKT3(eBiosciences,#16-0037-85)，每孔取100μL 0.08μg/ml OKT3包被96孔板(Corning,#3599)，使其最终浓度达到10μg/ml。4度包被过夜。第二天，消化SK-BR-3细胞，并用完全培养基重悬，将细胞密度分别调整为4×10^5细胞/ml备用。使用MACS

试剂盒(Miltenyi Biotec,#130-096-535)从人PBMC里分离人CD3阳性T细胞。首先确定细胞数量,然后根据细胞数量加入相应量的MACS缓冲液和Pan-T细胞生物素抗体,混匀,4℃静置5分钟。然后加入相应量微磁珠,4℃静置10分钟。通过LS柱的是CD3阳性的T细胞。将前一天96孔板包被的OKT3洗掉,加入50μL纯化的T细胞,每孔1×10^5个。再取50μL SK-BR-3细胞放入96孔板里,每孔2×10^4个。然后加入相应浓度的HER2/4-1BB的双特异性抗体或者是对照单抗,37℃5%CO_2培养箱箱培养。培养72小时后取上清液,使用ELISA试剂盒(Invitrogen,#88-7316)来检测IFN-γ的含量。按照供应商的说明书进行ELISA检测,简言之,在96平底板里加入包被抗体,4℃过夜。第二天加入ELISA缓冲液,室温1小时。加入收取的上清液,室温培养2小时。洗板2次,加入检测抗体,室温1小时。洗板两次,加入HRP-链霉亲和素,室温孵育1小时。然后加入TMB底物,10-30分钟加入ELISA终止液(BBI life sciences,#E661006-0200)。使用读板机(Molecular Devices,#SpectraMax Plus)读取OD450-570值。用Graphad 8.0分析该值并做图。

[0310] 如图22A到图22D所示,本发明的HER2×4-1BB双抗在肿瘤细胞SK-BR-3交联下均具有激活4-1BB介导的T细胞通路。其中PR002813和PR002827显示出较低的EC50和较高的IFN gamma释放值。

[0311] 小结

[0312] 本实施例利用抗Her2的IgG抗体的抗原结合结构域Fab和抗4-1BB的HCAb抗体的抗原结合结构域VH,构建了IgG-VH四价对称结构的HER2×4-1BB双抗分子。同时,利用抗Her2的IgG抗体的抗原结合结构域Fab和抗4-1BB的H2L2抗体,构建IgG-scFv四价对称结构的双特异性抗体。

[0313] 两种结构的抗HER2×4-1BB的双特异性抗体分子,通过不同的结构类型、相对位置、结合价数等参数来调节激活T细胞的功能活性。同时展现出了基于HCAb构建双特异性抗体分子结构的灵活性。

[0314] Urelumab对T细胞的激活是没有靶点特异性,这是其临床毒副作用的原因之一。但是,HER2×4-1BB双抗对T细胞激活作用是特异性依赖HER2的表达。在高表达HER2的细胞存在时,HER2×4-1BB双抗可以特异地激活T细胞。

[0315] 综上所述,本实施例构建出了功能活性突出、分子稳定性好的HER2×4-1BB双特异性抗体分子。

[0316] 实施例4.PD-L1×4-1BB双特异性抗体

[0317] 程序性死亡受体1(programmed death 1,PD-1)主要表达于T细胞等免疫细胞,它有两个配体,即程序性死亡配体-1(programmed death ligand 1,PD-L1)和PD-L2。PD-L1主要表达在抗原呈递细胞以及多种肿瘤细胞。PD-L1与PD-1相互作用会下调T细胞的活性,减弱细胞因子的分泌,起到免疫抑制作用。在许多人类肿瘤组织中均可检测到PD-L1蛋白的表达,肿瘤部位的微环境可诱导肿瘤细胞上的PD-L1的表达,表达的PD-L1有利于肿瘤的发生和生长,诱导抗肿瘤T细胞的凋亡,并进一步保护肿瘤细胞逃避免疫攻击。

[0318] 4-1BB(TNFRSF9,CD137)是一种隶属于TNF受体超家族的跨膜蛋白。4-1BB是在多种免疫细胞上表达的共刺激分子,为免疫活性的多功能调节剂。其诱导表达于活化的T细胞、NK细胞等免疫细胞。4-1BB通过其配体4-1BBL介导的三聚化来激活T细胞,促进细胞增殖和细胞因子释放。抗4-1BB的激动型抗体具有抑制肿瘤的功能,百时美施贵宝(BMS)公司的

Urelumab(BMS-663513)是最早进入临床试验的抗4-1BB的全人源单抗。Urelumab最初的临床结果发表于2008年,尽管在部分患者上观察到令人鼓舞的疗效,但数据显示Urelumab导致肝脏毒性,且与靶标和剂量有关。并且,因为在临床试验中有两位患者因肝毒性死亡,导致相关的临床试验被终止。

[0319] 在本实施例中,构建了同时靶向PD-L1和4-1BB的双特异性抗体,通过一个或者多个作用机制来提高抗肿瘤效果和安全性。第一,PD-L1×4-1BB双抗可以通过阻断PD-1/PD-L1信号通路来激活T细胞。第二,高表达于肿瘤细胞表面的PD-L1分子可以利用双抗分子促进T细胞表面的4-1BB分子的交联和三聚化并激活下游信号传导通路,进而促进T细胞的活化和增殖。第三,双抗分子介导的T细胞激活仅限于在肿瘤微环境内,这样可以避免类似Urelumab的单抗在正常组织中过度激活T细胞所带来的毒副作用。

[0320] 实施例4.1.PD-L1×4-1BB双特异性抗体的结构和设计

[0321] 本实施例使用抗PD-L1的IgG抗体PR000151(Atezolizumab类似物),其相应的氨基酸序列来源于IMGT数据库。

[0322] 本实施例使用的抗PD-L1的全人源IgG抗体PR000265来源于Harbour H2L2小鼠,其发现过程如下所述。

[0323] Harbour H2L2小鼠(Harbour Antibodies BV)是一种携带人免疫球蛋白免疫库的转基因小鼠,其产生的抗体具有完整的人的抗体可变结构域和大鼠恒定结构域。用可溶的重组人PD-L1蛋白(NovoProtein,#C764)对Harbour H2L2小鼠进行多轮免疫。当检测小鼠血清中PD-L1特异的抗体滴度达到一定的水平后,将小鼠的脾细胞取出并与骨髓瘤细胞系融合得到杂交瘤细胞;对杂交瘤细胞经过多轮筛选和克隆之后,鉴定出若干个特异识别PD-L1的单克隆抗体分子。对这些单克隆抗体进行进一步的鉴定,根据其对人PD-L1的结合能力、食蟹猴PD-L1的结合能力、抑制PD-L1与PD-1结合能力等参数,优选出数个候选抗体分子。然后对候选抗体分子进行序列分析和优化,得到数个变体序列。将抗体的VL和VH序列与相应的人的κ轻链恒定区和IgG1重链恒定区序列进行融合表达,得到重组全人源抗体分子。抗PD-L1的重组全人源IgG抗体列于表28。

[0324] 表28抗PD-L1的重组全人源IgG抗体列于表

[0325]

抗体编号	轻链	重链	VL	VH	LCDR1	LCDR2	LCDR3	HCDR1	HCDR2	HCDR3
PR000265	245	211	203	170	135	146	160	15	52	98
PR000151	241	207	199	166	131	143	156	14	48	94

[0326] 本实施例使用的抗4-1BB的全人源IgG抗体PR000197和PR000448来源于Harbour H2L2小鼠,其发现过程如实施例1所述。

[0327] 本实施例使用的抗4-1BB的全人源HCAb抗体PR001758、PR001760和PR001836来源于Harbour HCAB小鼠,其发现过程如实施例2所述。

[0328] 在本实施例及后续实施例中,阳性对照分子为抗PD-L1的IgG单抗PR000265。

[0329] 在本实施例及后续实施例中,阳性对照分子为抗4-1BB的IgG单抗Uremulab和Utomilumab。

[0330] 实施例4.1.1.利用抗PD-L1的IgG抗体和抗4-1BB的IgG抗体构建具有FIT-Ig结构的双特异性抗体分子

[0331] 本实施例利用抗PD-L1的IgG抗体PR000265或PR000151(atezolizumab类似物)的抗原结合结构域Fab,和抗4-1BB的IgG抗体PR000197或PR000448的抗原结合结构域Fab,来构建具有FIT-Ig结构的抗PD-L1×4-1BB的双特异性抗体分子。FIT-Ig结构的设计可以参考专利WO2015/103072A1,结构见图23A所示。

[0332] 所构建的分子总结于表29;并按照实施例1和2所述方法制备抗体分子样品并进行分析,总结于表30。表31列出了所述FIT-Ig结构的双抗分子的多肽链序列对应的序列编号。

[0333] 表29具有FIT-Ig结构的PD-L1×4-1BB双抗分子

[0334]

双抗分子	PDL1 抗体 (Fab A)	4-1BB 抗体 (Fab B)	4-1BB Fab 位置	连接肽（CL 和 VH_B 之间）	Fc 类型（突变）
PR000701	PR000265	PR000197	靠近 Fc	无	人 IgG4
PR003052	atezolizumab	PR000448	靠近 Fc	无	人 IgG4

[0335] 表30 FIT-Ig结构的PD-L1×4-1BB双抗分子蛋白的表达

[0336]

双抗分子	表达体系和体积	第一步纯化后产量 (mg/L)	SEC-HPLC 纯度 (%)
PR000701	HEK293-F (30ml)	198	79.88
PR003052	HEK293-6E (40ml)	47.5	87.76

[0337] 表31 FIT-Ig结构的PD-L1×4-1BB双抗分子的序列编号表

[0338]

抗体编号	多肽链1	多肽链2	多肽链3
PR000701	250	249	246
PR003052	267	266	246

[0339] 实施例4.1.2.利用抗PD-L1的IgG抗体和抗4-1BB的HCAb抗体构建Fab-HCAb结构的双特异性抗体分子

[0340] 本实施例利用抗PD-L1的IgG抗体PR000265的抗原结合结构域Fab,和抗4-1BB的HCAb抗体PR001758、PR001760或PR001836的抗原结合结构域VH,来构建多种结构的抗PD-L1×4-1BB的双特异性抗体分子。

[0341] 在本实施例及后续实施例中,阳性对照分子为抗PD-L1的IgG单抗PR000265,亦为PD-L1×4-1BB双抗分子的PD-L1端的亲本单抗。

[0342] 在本实施例及后续实施例中,阳性对照分子为抗4-1BB的IgG单抗urelumab(IgG4)或utomilumab(IgG2)。

[0343] 如图23B和图23C所示,Fab端来源于本实施例利用抗PD-L1的IgG抗体。VH端来源于抗4-1BB的HCAb抗体PR001758、PR001760或PR001836的抗原结合结构域VH。CL是轻链恒定区结构域。CH1、CH2和CH3分别是重链恒定区的第一、第二和第三结构域。L1和L2分别是第一和第二连接肽。

[0344] Fab(CL)-VH-Fc

[0345] 图23B结构的结合蛋白包含两条多肽链:多肽链1,也称短链,从氨基末端到羧基末端,其包含VH_A-CH1;多肽链2,也称长链,从氨基末端到羧基末端,其包含VL_A-CL-L1-VH_B-L2-CH2-CH3。在结构Fab(CL)-VH-Fc中,抗体A的VL_A和重链抗体B的VH_B融合在同一条多肽链上,这样可以避免VL_A和VH_B的缔合产生的错配副产物。

[0346] 多肽链2的VH_B经由连接肽L2联结到CH2;L2可以是IgG的铰链区或者铰链区衍生的连接肽序列;L2可以是表22中所列序列,优选为人IgG1铰链或者人IgG1铰链(C220S)或者G5-LH的序列。

[0347] 在一个实施方案中,多肽链2的CL与VH_B直接融合联结,即L1的长度为0。在另一个实施方案中,多肽链2的CL经由连接肽L1联结到VH_B;L1可以是表22中所列序列。

[0348] Fab(CH1)-VH-Fc

[0349] 图23C结构的结合蛋白包含两条多肽链:多肽链1,也称短链,从氨基末端到羧基末端,其包含VL_A-CL;多肽链2,也称长链,从氨基末端到羧基末端,其包含VH_A-CH1-L1-VH_B-L2-CH2-CH3。

[0350] 多肽链2的VH_B经由连接肽L2联结到CH2;L2可以是IgG的铰链区或者铰链区衍生的连接肽序列;L2可以是表22中所列序列,优选为人IgG1铰链或者人IgG1铰链(C220S)或者G5-LH的序列。

[0351] 在一个实施方案中,多肽链2的CH1与VH_B直接融合联结,即L1的长度为0。在另一个实施方案中,多肽链2的CH1经由连接肽L1联结到VH_B;L1可以是表22中所列序列。

[0352] 利用抗PD-L1的IgG抗体和抗4-1BB的重链抗体,设计Fab-HCAb对称结构的PD-L1×4-1BB双抗分子,总结于表32;制备的双抗分子理化性质分析,总结于表33。

[0353] 表32 Fab-HCAb对称结构的PD-L1×4-1BB双抗分子

[0354]

双抗分子	PD-L1 抗体 (Fab)	4-1BB 抗体 (VH_B)	第一连接肽 (Fab 和 VH_B 之间)	第二连接肽 (VH_B 和 CH2 之间)	Fc 类型 (突变)
PR004270	PR000265	PR001760	H1_15	人 IgG1 铰链 (C220S)	人 IgG1 (L234A, L235A)

[0355] 表33 Fab-HCAb对称结构的PD-L1×4-1BB双抗分子蛋白的表达

[0356]

双抗分子	表达体系和体积	质粒转染比例 (短链 : 长链)	第一步纯化后产量 (mg/L)	SEC-HPLC 纯度 (%)
PR004270	HEK293-6E (40ml)	3 : 2	77.50	92.33

[0357] 实施例4.1.3.构建IgG-VH四价对称结构分子

[0358] 利用抗PD-L1的IgG抗体和抗4-1BB的重链抗体,按照实施例3.1.1所述结构设计IgG-VH四价对称结构的PD-L1×4-1BB双抗分子(图23D),

[0359] 或者将抗4-1BB HCAb抗体的VH通过连接肽连接到PD-L1 IgG抗体的重链的N端(图23E所示)。图23E结构的结合蛋白包含两条不同的多肽链:多肽链1,也称短链,从氨基末端到羧基末端,其包含VL_A-CL;多肽链2,也称长链,从氨基末端到羧基末端,其包含VH_B-L-VH_A-CH1-h-CH2-CH3。在一个实施方案中,多肽链2的VH_B与VH_A直接融合联结,即L的长度为0。在另一个实施方案中,多肽链2的VH_B经由连接肽L联结到VH_A;L可以是表22中所列序列。

[0360] 利用抗PD-L1的IgG抗体和抗4-1BB的重链抗体,设计IgG-VH对称结构的PD-L1×4-1BB双抗分子,总结于表34;制备的双抗分子理化性质分析,总结于表35。

[0361] 表34 IgG-VH四价对称结构的PD-L1×4-1BB双抗分子

双抗分子	PD-L1 抗体(IgG)	4-1BB 抗体(VH_B)	VH_B 相对 IgG 位置	连接肽（VH_B 和 IgG 之间）	Fc 类型（突变）
PR003549	PR000265	PR001758	重链 C 端	H1_15-RT	人 IgG1(L234A,L235A,P329G)
PR003550	PR000265	PR001760	重链 C 端	H1_15-RT	人 IgG1(L234A,L235A,P329G)
PR003551	PR000265	PR001836	重链 C 端	H1_15-RT	人 IgG1(L234A,L235A,P329G)
PR004268	PR000265	PR001760	重链 N 端	GS_15	人 IgG1 (L234A, L235A)
PR007130	PR000265	PR004469	重链 C 端	GS_6	人 IgG1(L234A,L235A,G237A)
PR007132	PR000265	PR007286	重链 C 端	GS_6	人 IgG1(L234A,L235A,G237A)
PR007133	PR000265	PR007287	重链 C 端	GS_6	人 IgG1(L234A,L235A,G237A)
PR007135	PR000265	PR007288	重链 C 端	GS_6	人 IgG1(L234A,L235A,G237A)
PR007136	PR000265	PR007289	重链 C 端	GS_6	人 IgG1(L234A,L235A,G237A)
PR007137	PR000265	PR007290	重链 C 端	GS_6	人 IgG1(L234A,L235A,G237A)
PR007138	PR000265	PR007291	重链 C 端	GS_6	人 IgG1(L234A,L235A,G237A)
PR007139	PR000265	PR007292	重链 C 端	GS_6	人 IgG1(L234A,L235A,G237A)
PR007141	PR000265	PR007294	重链 C 端	GS_6	人 IgG1(L234A,L235A,G237A)
PR007142	PR000265	PR007295	重链 C 端	GS_6	人 IgG1(L234A,L235A,G237A)
PR007143	PR000265	PR007296	重链 C 端	GS_6	人 IgG1(L234A,L235A,G237A)
PR007145	PR000265	PR007297	重链 C 端	GS_6	人 IgG1(L234A,L235A,G237A)
PR007146	PR000265	PR007298	重链 C 端	GS_6	人 IgG1(L234A,L235A,G237A)
PR007149	PR000265	PR007300	重链 C 端	GS_6	人 IgG1(L234A,L235A,G237A)

[0362]

[0363] 表35 IgG-VH四价对称结构的PD-L1×4-1BB双抗分子蛋白的表达

双抗分子	表达体系和体积	第一步纯化后产量 (mg/L)	SEC-HPLC 纯度 (%)
PR003549	HEK293-F (30ml)	24.51	98.31
PR003550	HEK293-F (30ml)	42.16	95.41
PR003551	HEK293-F (30ml)	2.28	99.39
PR004268	HEK293-F (30ml)	31.4	97.94
PR007130	HEK293-F (40ml)	37	95.957
PR007132	HEK293-F (40ml)	36	94.96
PR007133	HEK293-F (40ml)	34	94.452
PR007135	HEK293-F (40ml)	43.8	94.557
PR007136	HEK293-F (40ml)	41.5	88.662
PR007137	HEK293-F (40ml)	23.6	93.763
PR007138	HEK293-F (40ml)	18.8	98.629
PR007139	HEK293-F (40ml)	31	96.865
PR007141	HEK293-F (40ml)	56.5	95.219

[0364]

PR007142	HEK293-F (40ml)	62	96.848
PR007143	HEK293-F (40ml)	56	95.094
PR007145	HEK293-F (40ml)	64	97.083
PR007146	HEK293-F (40ml)	60	97.014
PR007149	HEK293-F (40ml)	66.5	98.657

[0365]

[0366] 实施例4.1.4.PD-L1×4-1BB双抗分子及对照分子序列表

[0367] 表36列出了本实施例所构建的PD-L1×4-1BB双抗分子的序列所对应的序列号。

[0368] 表36本实施例的PD-L1×4-1BB双抗分子的序列编号表

[0369]

抗体编号	多肽链1	多肽链2	多肽链3
PR000701	250	249	246
PR003052	267	266	246
PR003549	245	268	
PR003550	245	269	
PR003551	245	270	
PR004270	249	272	
PR004268	245	271	
PR007130	245	369	
PR007132	245	370	
PR007133	245	371	
PR007135	245	372	
PR007136	245	373	
PR007137	245	374	
PR007138	245	375	
PR007139	245	376	
PR007141	245	377	
PR007142	245	378	
PR007143	245	379	
PR007145	245	380	
PR007146	245	381	
PR007149	245	382	

[0370] 实施例4.2.结合高表达人PD-L1的细胞

[0371] 本实施例是为了研究PD-L1×4-1BB双抗分子结合PD-L1的活性。

[0372] 利用流式细胞术FACS测试抗体分子与高表达人PD-L1的CHO-K1细胞株CHO-K1/hPDL1(南京金斯瑞,M00543)或者高表达人PD-L1的MDA-MB-231(ATCC,HTB-26)的结合能力。具体地,消化CHO-K1/hPDL1细胞或者MDA-MB-231并用完全培养基重悬;将细胞密度调整为1x10^{6}细胞/mL。接着将细胞以100μL/孔接种于96孔V底板(Corning,#3894),4℃下离心5分钟,弃上清。随后将梯度稀释的抗体分子以100μL/孔加入96孔板并混合均匀,抗体分子可以从最高终浓度为200nM按照3倍浓度梯度稀释的共12个浓度;hIgG1 iso(CrownBio,#C0001)作为同型对照。将细胞放置于4℃,避光孵育1小时。然后,加入100μL/孔预冷的FACS缓冲液(含有0.5%BSA的PBS缓冲液)漂洗细胞两次,4℃下500g离心5分钟,弃上清。接着,再加入100μL/孔荧光二抗(Goat human lgG(H+L)Alexa Fluor 488conjunction,Thermo,#A11013,1:1000稀释),放置于4℃,避光孵育1小时。随后以200μL/孔加入预冷的FACS缓冲液漂洗细胞两次,然后于4℃下500g离心5分钟,弃上清。最后,以200μL/孔加入预冷的FACS缓冲液重悬细胞。使用BD FACS CANTOII流式细胞仪读取荧光发光信号值。

[0373] 应用软件GraphPad Prism 8进行数据处理和作图分析,通过四参数非线性拟合,得到抗体对靶细胞的结合曲线及EC50值等参数。

[0374] 本实施例中,阳性对照分子为抗PD-L1的单抗PR000265,亦为PD-L1 x 4-1BB双抗分子的PD-L1端的亲本单抗。

[0375] 图24A所示,IgG-VH(C端)四价对称结构的双抗分子(PR003549,PR003550,PR003551)结合PD-L1的能力与亲本单抗PR000265的相似,而且其结合PD-L1的EC50值和MFI最大值略优于FIT-Ig结构的双抗分子(PR000701,PR003052)。

[0376] 图24B中所示,Fab-HCAb对称结构的双抗分子PR004270和IgG-VH(N端)四价对称结构的双抗分子PR004268结合PD-L1的能力与亲本单抗相似,其结合PD-L1的EC50值虽略弱于亲本单抗,但是结合的MFI最大值比亲本单抗更高。

[0377] 图24C-图24E所示,IgG-VH(C端)四价对称结构的双抗分子(PR007130,PR007132,PR007133,PR007135,PR007136,PR007137,PR007138,PR007139,PR007141,PR007142,PR007143,PR007145,PR007146,PR007149)结合PD-L1的能力与亲本单抗PR000265的相似。

[0378] 实施例4.3.结合过表达4-1BB的CHO-K1细胞

[0379] 本实施例是为了研究PD-L1×4-1BB双抗分子结合4-1BB的活性。

[0380] 利用流式细胞术FACS测试抗体分子与高表达人4-1BB的CHO-K1细胞株CHO-K1/hu4-1BB(南京金斯瑞,M00538)和高表达食蟹猴4-1BB的CHO-K1细胞株CHO-K1/cyno4-1BB(南京金斯瑞,M00569)等细胞的结合能力。具体地,消化细胞并用完全培养基重悬;将细胞密度调整为2×10^6细胞/mL。接着将细胞以100μL/孔(2×10^5细胞/孔)接种于96孔V底板(Corning,#3894),4℃下离心5分钟,弃上清。随后将梯度稀释的抗体分子以100μL/孔加入96孔板并混合均匀,抗体分子可以从最高终浓度为200nM按照3倍浓度梯度稀释的共12个浓度;hIgG1 iso(CrownBio,#C0001)作为同型对照。将细胞放置于4℃,避光孵育1小时。然后,加入100μL/孔预冷的FACS缓冲液(含有0.5%BSA的PBS缓冲液)漂洗细胞两次,4℃下500g离心5分钟,弃上清。接着,再加入100μL/孔荧光二抗(Goat human lgG(H+L)Alexa Fluor 488conjunction,Thermo,#A11013,1:1000稀释),放置于4℃,避光孵育1小时。随后以200μL/孔加入预冷的FACS缓冲液漂洗细胞两次,然后于4℃下500g离心5分钟,弃上清。最后,以200μL/孔加入预冷的FACS缓冲液重悬细胞。使用BD FACS CANTOII流式细胞仪读取荧光发光信号值。

[0381] 应用软件GraphPad Prism 8进行数据处理和作图分析,通过四参数非线性拟合,得到抗体对靶细胞的结合曲线及EC50值等参数。

[0382] 本实施例中,阳性对照分子为抗4-1BB的单抗Urelumab或tomilumab。

[0383] 实施例4.3.1.结合高表达人4-1BB的CHO-K1细胞CHO-K1/hu4-1BB

[0384] 图25A中所示,IgG-VH(C端)四价对称结构的双抗分子(PR003549,PR003550,PR003551)结合人4-1BB的能力优于FIT-Ig结构的双抗分子(PR000701,PR003052),而且在MFI最大值上优于阳性对照Urelumab。

[0385] 图25B中所示,Fab-HCAb对称结构的双抗分子PR004270和IgG-VH(N端)四价对称结构的双抗分子PR004268结合人4-1BB的能力在MFI最大值上优于阳性对照Urelumab和Utomilumab。

[0386] 图25C到图25E中所示,IgG-VH(C端)四价对称结构的双抗分子(PR007130,PR007132,PR007133,PR007135,PR007136,PR007137,PR007138,PR007139,PR007141,PR007142,PR007143,PR007145,PR007146,PR007149)结合人4-1BB在MFI最大值上优于阳性

对照Urelumab。

[0387] 实施例4.3.2.结合高表达食蟹猴4-1BB的CHO-K1细胞CHO-K1/cyno 4-1BB

[0388] 图26A和图26B中所示，本实施例的双抗分子可以结合食蟹猴4-1BB，而Urelumab不能。PR004270结合食蟹猴4-1BB的能力在MFI最大值上略优于Utomilumab。

[0389] 实施例4.4.高表达PD-L1的靶细胞介导的T细胞的特异性激活

[0390] 本实施例是为了研究PD-L1×4-1BB双抗分子在靶细胞的存在是通过结合4-1BB来激活T细胞的活性。靶细胞可以是不同程度表达PD-L1的细胞，例如高表达人PD-L1的CHO-K1/hPDL1(南京金斯瑞,M00543)，或者高表达人PD-L1的MDA-MB-231(ATCC,HTB-26)。效应细胞可以是分离的人PBMC或者T细胞。

[0391] 具体的，首先以100μL/孔将0.3μg/mL抗CD3抗体OKT3(Thermo,#16-0037-81)包板于96孔板(Corning,#3599)。接着，将人T细胞(从人PBMC中用T细胞分选试剂盒(Miltenyi,#130-096-535)分离得到)的密度调整为2×10^6细胞/mL，将靶细胞的密度调整为3×10^5细胞/mL，随后把两种细胞悬液各以50μL/孔接种于96孔板，最终效靶比为20:3。然后，以100μL/孔加入不同浓度的抗体分子，抗体终浓度可以是(10nM,1nM)，或者是20nM，或者是从最高终浓度为20nM按照5倍浓度梯度稀释的共8个浓度，两个复孔加样；hIgG1 iso(CrownBio,#C0001)和hIgG4 iso(CrownBio,#C0045)作为对照。将96孔板置于37℃，5％CO_2培养箱中孵育3天。分别收集培养48小时后和72小时后的上清液，用IL-2ELISA试剂盒(Thermo,#88-7025-88)检测48小时后的上清中IL-2浓度，用IFN-γELISA试剂盒(Thermo,#88-7316-77)检测72小时后的上清中IFN-γ浓度。ELISA检测方法参照相关试剂盒操作说明。

[0392] 应用软件GraphPad Prism 8进行数据处理和作图分析。

[0393] 本实施例中，阳性对照分子为抗4-1BB的单抗Urelumab。

[0394] 实施例4.4.1.CHO-K1/hPDL1介导的T细胞特异性激活

[0395] 图27A-图27D中所示，在靶细胞CHO-K1/hPDL1和T细胞混合的系统中，不依赖于交联的抗4-1BB单抗Urelumab可以激活T细胞释放IFN-γ，而依赖于交联的抗4-1BB单抗(PR000448,PR001758,PR001760,PR001836)则几乎不能激活T细胞。FIT-Ig结构的双抗分子(PR003502,PR000701)和IgG-VH四价对称结构的双抗分子(PR003549,PR003550,PR003551,PR004268,PR007130,PR007132,PR007133,PR007135,PR007136,PR007137,PR007138,PR007139,PR007141,PR007142,PR007143,PR007145,PR007146,PR007149)和Fab-HCAb结构的双抗分子(PR004270)都能够激活T细胞并释放细胞因子。这说明双抗分子对T细胞的激活是依赖于靶细胞的特异性的激活。而且IgG-VH四价对称结构的双抗分子(PR003549,PR003550,PR007130,PR007132,PR007133,PR007135,PR007136,PR007137,PR007138,PR007139,PR007141,PR007142,PR007143,PR007145,PR007146,PR007149)和Fab-HCAb结构的双抗分子(PR004270)比FIT-Ig结构的双抗分子(PR003502,PR000701)能够引起更高的细胞因子释放水平，显示出更强的T细胞激活能力，且优于Urelumab。

[0396] 实施例4.4.2.MDA-MB-231介导的T细胞特异性激活

[0397] 图27E中所示，在靶细胞MDA-MB-231和T细胞混合的系统中，IgG-VH四价对称结构的双抗分子(PR003549)和Fab-HCAb结构的双抗分子(PR004270)有相似的T细胞激活能力；优于FIT-Ig结构的双抗分子(PR003502,PR000701)。

[0398] 图27F和图27G中所示，在靶细胞MDA-MB-231和T细胞混合的系统中，IgG-VH四价对

称结构的双抗分子(PR003549)比Urelumab有更强T细胞激活能力,能更好地促进IFN-γ和IL-2的产生。

[0399] 图27H和图27I中所示,在靶细胞MDA-MB-231和T细胞混合的系统中,IgG-VH四价对称结构的双抗分子(PR007130,PR007132,PR007133,PR007138,PR007139,PR007141,PR007142,PR007143,PR007145,PR007146,PR007149)比Urelumab有相当的T细胞激活能力。

[0400] 实施例4.5.混合淋巴细胞反应(MLR)

[0401] 本实施例是利用混合淋巴细胞反应(MLR)来研究PD-L1×4-1BB双抗分子对T细胞的激活作用。

[0402] 第一步,利用CD14磁珠(Meltenyi,#130-050-201)从第一供体PBMC细胞(妙通生物)中分离单核细胞(monocytes);具体操作参照相关试剂盒说明书。然后加入50ng/mL重组人源IL-4(PeproTech,#200-02-A)和100ng/mL重组人源GM-CSF(PeproTech,#300-03-A),于37℃诱导7天后,获得未成熟的树突状细胞(iDC细胞)。继续加入1μg/ml的脂多糖Lipopolysaccharide(LPS,Sigma,#L6529),诱导24小时后,获得成熟的树突状细胞(mDC细胞)。第二步,利用T细胞分离试剂盒(Meltenyi,#130-096-535)从第二供体PBMC细胞(妙通生物)中分离得到T淋巴细胞。第三步,将获得的T细胞和mDC细胞按5:1比例接种至96孔板(1×10^5/孔的T细胞和2×10^4/孔的mDC细胞)。随后以50μL/孔加入不同浓度的抗体分子,抗体终浓度可以是(10nM,1nM),或者是从最高终浓度为50nM按照3倍浓度梯度稀释的共8个浓度,两个复孔加样;hIgG1 iso(CrownBio,#C0001)或者空白孔作为对照。于37℃,5%CO_2培养箱孵育5天。第四步,分别收集第3天和第5天的上清液,用IL-2ELISA试剂盒(Thermo,#88-7025-88)检测第4天的上清中IL-2浓度,用IFN-γELISA试剂盒(Thermo,#88-7316-77)检测第5天的上清中IFN-γ浓度。ELISA检测方法参照相关试剂盒操作说明。

[0403] 图28中所示,在多次独立的MLR实验中(不同的供体配对),抗4-1BB单抗对T细胞的激活作用有限,产生细胞因子的能力很弱;抗PD-L1单抗有较明显的激活作用。双抗分子可以进一步提高T细胞的功能。

[0404] 图28A到图28F中所示,IgG-VH四价对称结构的双抗分子(PR003549,PR003550,PR003551,PR007130,PR007132,PR007133,PR007138,PR007139,PR007141,PR007142,PR007143,PR007145,PR007146,PR007149)比母本PD-L1抗体PR000265能够引起更高的细胞因子释放水平,显示出更强的T细胞激活能力,说明双抗分子优于抗PD-L1单抗;

[0405] 图28A和图28D中所示,IgG-VH四价对称结构的双抗分子(PR003549,PR003550,PR003551)比FIT-Ig结构的双抗分子(PR003502,PR000701)能够引起更高的细胞因子释放水平,显示出更强的T细胞激活能力;而且双抗分子优于抗PD-L1单抗。

[0406] 图28G和图28H中所示,IgG-VH四价对称结构的双抗分子(PR003549,PR003550)和Fab-HCAb结构的双抗分子(PR004270)比FIT-Ig结构的双抗分子(PR003502,PR000701)能够引起更高的细胞因子释放水平,显示出更强的T细胞激活能力。

[0407] 图28I到图28K中所示,IgG-VH四价对称结构的双抗分子(PR003549,PR003550,PR003551)和Fab-HCAb结构的双抗分子(PR004270)显示出很强的T细胞激活能力。

[0408] 实施例4.6.药代动力学研究

[0409] 本实施例研究了具有Fab-HCAb对称结构的PD-L1×4-1BB双抗分子PR004270在小鼠体内的药代动力学性能。

[0410] 实施方法如下:对于每一个测试抗体分子,选取体重18-22克的雌性BALB/c小鼠6只,按5mg/kg的剂量通过静脉注射给与双特异性抗体。一组3只于给药前以及给药后15分钟、24小时(1天)、第4天、和第10天采集全血,另一组3只于只于给药前以及给药后5小时、第2天、第7天、和第14天采集全血。将全血静置30分钟使其凝固,随后离心并将分离的血清样品在-80℃下冻存直至分析。本实施例采用两种ELISA方法来定量测定小鼠血清中的药物浓度。ELISA方法一,即Fc端检测(总体检测)方法,通过包被于96孔板的山羊抗人Fc多克隆抗体来捕获小鼠血清中的含有人Fc的抗体,然后加入HRP标记的山羊抗人Fc第二抗体来检测;ELISA方法二,即PD-L1端检测(功能结构域检测)方法,通过包被于96孔板的人PD-L1蛋白来捕获小鼠血清中的特异识别PD-L1的抗体,然后加入HRP标记的山羊抗人Fc第二抗体来检测。使用Phoenix WinNonlin软件8.2版,选用非房室模型(NCA)分析药代动力学参数。

[0411] 如图29和表37中所示,Fab-HCAb结构的双抗分子PR004270有与常规IgG抗体相似的血清半衰期$t_{1/2}$值,功能结构域检测方法显示其$t_{1/2}$值超过10天。

[0412] 表37 PR004270在BALB/c小鼠体内的药代动力学

[0413]

双抗分子	PR004270
动物 (数量)	BALB/c 小鼠 (n=6)
抗体剂量	5 mg/kg, I.V.

[0414]

PK 参数	Fc 端检测	PD-L1 端检测
$T_{1/2}$ (hour)	465.6	256.5
V_d (mL/kg)	75.7	83.9
AUC (μg*hour/mL)	17,536	13,126
Cl (mL/hour/kg)	0.11	0.23
C_0 (μg/mL)	119.7	81.7

[0415] 小结

[0416] 本实施例利用抗PD-L1的IgG抗体的抗原结合结构域Fab和抗4-1BB的HCAb抗体的抗原结合结构域VH,构建了多种结构的抗PD-L1×4-1BB的双特异性抗体分子。展现出了基于HCAb构建双特异性抗体分子结构的灵活性,通过不同的结构类型、相对位置、结合价数等参数来调节激活T细胞的功能活性。

[0417] Urelumab对T细胞的激活是没有靶点特异性,这是其临床毒副作用的原因之一。PD-L1×4-1BB双抗对T细胞激活作用是特异性依赖PD-L1的表达。依赖于交联的抗4-1BB的HCAb单抗不能直接激活T细胞,但是,利用这些HCAb单抗构建的PD-L1×4-1BB双抗在高表达PD-L1的细胞存在时则可以特异地激活T细胞。

[0418] 基于HCAb的双抗结构,尤其是IgG-VH四价对称结构的双抗分子和Fab-HCAb结构的双抗分子,一方面保留了PD-L1端的活性,在MLR实验中体现出比对应的抗PD-L1亲本单抗更强的T细胞激活能力;另一方面靶细胞上高表达的PD-L1分子可以介导4-1BB的交联和三聚化以传递T细胞活化信号,其激活T细胞的能力甚至优于Urelumab。而且IgG-VH四价对称结构和Fab-HCAb对称结构的双抗分子显示出比FIT-Ig结构的双抗分子拥有更强的T细胞激活能力。

[0419] 综上所述,本实施例构建出了安全性好、功能活性突出、分子稳定性好的PD-L1 x

4-1BB双特异性抗体分子。

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[0278] Ser Ala Ile

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[0289] Gly Glu Ile

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[0319] Gly Lys Ile

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[0329] Gly Glu Ile

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[0718] Thr Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
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[0720] Asp Thr Ala Val Tyr Tyr Cys Ala Arg
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[0745] Thr Ser Lys Asn Gln Phe Ser Leu Lys Leu Asn Ser Val Thr Ala Ala

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[0784] Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser

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[0823] Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu

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[0836] Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Thr Arg Leu Thr Ala Glu

[0837] 20 25 30

[0838] Asp Thr Ala Val Tyr Phe Cys Ala Lys

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[0863] Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asp Ser Leu Lys Ala Glu

[0864] 20 25 30

[0865] Asp Thr Ala Val Tyr Tyr Cys Ala Lys

[0866] 35 40

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[0876] Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu

[0877] 20 25 30

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[0890] 20 25 30

[0891] Asp Ser Ala Val Tyr Phe Cys Ala Lys

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[0902] Asn Ser Thr Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu

[0903] 20 25 30

[0904] Asp Thr Ala Val Tyr Tyr Cys Ala Lys

[0905] 35 40

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[0915] Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu

[0916] 20 25 30

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[0927] 1 5 10 15

[0928] Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu

[0929] 20 25 30

[0930] Asp Thr Ala Val Tyr Phe Cys Ala Lys

[0931] 35 40

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[0940] 1 5 10 15

[0941] Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu

[0942] 20 25 30

[0943] Asp Thr Ala Gly Tyr His Cys Ala Lys

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[0953] 1 5 10 15

[0954] Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu

[0955] 20 25 30

[0956] Asp Thr Ala Val Tyr Tyr Cys Ala Lys

[0957] 35 40

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[0966] 1 5 10 15

[0967] Asn Ser Arg Asn Thr Leu Tyr Leu Gln Met Asn Arg Leu Thr Ala Glu

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[0969] Asp Thr Ala Val Tyr Phe Cys Ala Lys

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[0977] <400> 92

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[0979] 1 5 10 15

[0980] Asn Ala Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu

[0981] 20 25 30

[0982] Asp Thr Ala Val Tyr Tyr Cys Val Arg

[0983] 35 40

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[0994] 20 25 30

[0995] Asp Thr Ala Val Tyr Tyr Cys Ala Lys

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[1013] Glu Ala Tyr His Tyr Gly Ser Gly Ser Tyr Tyr Asp Asp Tyr Tyr Tyr

[1014] 1 5 10 15

[1015] Gly Met Asp Val

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[1025] Leu Thr Gly Pro Phe Asp Tyr

[1026] 1 5

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[1043] Asp Arg Ala Val Ala Gly Ala Phe Asp Ile

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[1071] 1 5 10 15

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[1109] 1 5 10 15
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[1118] 1 5 10 15
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[1127] 1 5 10 15
[1128] Asp Val
[1129] <210> 108
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[1135] <400> 108
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[1137] 1 5 10 15
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[1146] 1 5 10 15
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[1156] <210> 111
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[1161] <223> PR001776 HCDR3 Chothia
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[1164] 1 5 10 15
[1165] <210> 112
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[1170] <223> PR001780 HCDR3 Chothia

[1171] <400> 112

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[1188] <223> PR001833 HCDR3 Chothia

[1189] <400> 114

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[1191] 1 5 10 15

[1192] <210> 115

[1193] <211> 15

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[1198] Chothia

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[1219] 1 5 10 15
[1220] <210> 118
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[1236] Chothia
[1237] <400> 119
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[1239] 1 5 10
[1240] <210> 120
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[1257] 1 5 10

[1258] <210> 122

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[1263] <223> PR001767 HFWR4 Chothia

[1264] <400> 122

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[1266] 1 5 10

[1267] <210> 123

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[1274] Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser

[1275] 1 5 10

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[1282] <400> 124

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[1284] 1 5 10 15

[1285] Asp Arg Val Thr Ile Thr Cys

[1286] 20

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[1302] <220>
[1303] <223> PR000197 LFWR1 Chothia
[1304] <400> 126
[1305] Glu Phe Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
[1306] 1 5 10 15
[1307] Glu Arg Ala Thr Leu Ser Cys
[1308] 20
[1309] <210> 127
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[1311] <212> PRT
[1312] <213> Artificial Sequence
[1313] <220>
[1314] <223> PR000265 LFWR1 Chothia
[1315] <400> 127
[1316] Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
[1317] 1 5 10 15
[1318] Asp Arg Val Thr Val Thr Cys
[1319] 20
[1320] <210> 128
[1321] <211> 23
[1322] <212> PRT
[1323] <213> Artificial Sequence
[1324] <220>
[1325] <223> PR000447 LFWR1 Chothia, PR000448 LFWR1 Chothia, PR000980 LFWR1

[1326] Chothia
[1327] <400> 128
[1328] Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
[1329] 1 5 10 15
[1330] Glu Arg Ala Thr Leu Ser Cys
[1331] 20
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[1334] <212> PRT
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[1337] <223> PR000483 LFWR1 Chothia
[1338] <400> 129
[1339] Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
[1340] 1 5 10 15
[1341] Thr Ala Ser Ile Thr Cys
[1342] 20
[1343] <210> 130
[1344] <211> 23
[1345] <212> PRT
[1346] <213> Artificial Sequence
[1347] <220>
[1348] <223> PR000628 LFWR1 Chothia
[1349] <400> 130
[1350] Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
[1351] 1 5 10 15
[1352] Glu Arg Ala Thr Leu Ser Cys
[1353] 20
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[1355] <211> 11
[1356] <212> PRT
[1357] <213> Artificial Sequence
[1358] <220>
[1359] <223> PR000151 LCDR1 Chothia
[1360] <400> 131
[1361] Arg Ala Ser Gln Asp Val Ser Thr Ala Val Ala
[1362] 1 5 10
[1363] <210> 132
[1364] <211> 16

[1365] <212> PRT
[1366] <213> Artificial Sequence
[1367] <220>
[1368] <223> PR000196 LCDR1 Chothia
[1369] <400> 132
[1370] Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr Leu Asp
[1371] 1 5 10 15
[1372] <210> 133
[1373] <211> 11
[1374] <212> PRT
[1375] <213> Artificial Sequence
[1376] <220>
[1377] <223> PR000197 LCDR1 Chothia, PR000447 LCDR1 Chothia, PR000448 LCDR1
[1378] Chothia
[1379] <400> 133
[1380] Arg Ala Ser Gln Ser Ile Ser Ser Ile Leu Ala
[1381] 1 5 10
[1382] <210> 134
[1383] <211> 11
[1384] <212> PRT
[1385] <213> Artificial Sequence
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[1387] <223> PR000210 LCDR1 Chothia
[1388] <400> 134
[1389] Arg Ala Ser Gln Asp Val Asn Thr Ala Val Ala
[1390] 1 5 10
[1391] <210> 135
[1392] <211> 11
[1393] <212> PRT
[1394] <213> Artificial Sequence
[1395] <220>
[1396] <223> PR000265 LCDR1 Chothia
[1397] <400> 135
[1398] Arg Ala Ser Gln Ser Ile Tyr Ile Trp Leu Ala
[1399] 1 5 10
[1400] <210> 136
[1401] <211> 11
[1402] <212> PRT
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[1404] <220>

[1405] <223> PR000483 LCDR1 Chothia

[1406] <400> 136

[1407] Ser Gly Asp Asn Ile Gly Asp Gln Tyr Ala His

[1408] 1 5 10

[1409] <210> 137

[1410] <211> 11

[1411] <212> PRT

[1412] <213> Artificial Sequence

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[1414] <223> PR000628 LCDR1 Chothia

[1415] <400> 137

[1416] Arg Ala Ser Gln Ser Val Ser Ser Tyr Leu Ala

[1417] 1 5 10

[1418] <210> 138

[1419] <211> 15

[1420] <212> PRT

[1421] <213> Artificial Sequence

[1422] <220>

[1423] <223> PR000151 LFWR2 Chothia, PR000210 LFWR2 Chothia

[1424] <400> 138

[1425] Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr

[1426] 1 5 10 15

[1427] <210> 139

[1428] <211> 15

[1429] <212> PRT

[1430] <213> Artificial Sequence

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[1432] <223> PR000196 LFWR2 Chothia

[1433] <400> 139

[1434] Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Phe

[1435] 1 5 10 15

[1436] <210> 140

[1437] <211> 15

[1438] <212> PRT

[1439] <213> Artificial Sequence

[1440] <220>

[1441] <223> PR000197 LFWR2 Chothia, PR000447 LFWR2 Chothia, PR000448 LFWR2

[1442] Chothia

[1443] <400> 140

[1444] Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr

[1445] 1 5 10 15

[1446] <210> 141

[1447] <211> 15

[1448] <212> PRT

[1449] <213> Artificial Sequence

[1450] <220>

[1451] <223> PR000265 LFWR2 Chothia

[1452] <400> 141

[1453] Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile Tyr

[1454] 1 5 10 15

[1455] <210> 142

[1456] <211> 15

[1457] <212> PRT

[1458] <213> Artificial Sequence

[1459] <220>

[1460] <223> PR000483 LFWR2 Chothia

[1461] <400> 142

[1462] Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr

[1463] 1 5 10 15

[1464] <210> 143

[1465] <211> 7

[1466] <212> PRT

[1467] <213> Artificial Sequence

[1468] <220>

[1469] <223> PR000151 LCDR2 Chothia, PR000210 LCDR2 Chothia

[1470] <400> 143

[1471] Ser Ala Ser Phe Leu Tyr Ser

[1472] 1 5

[1473] <210> 144

[1474] <211> 7

[1475] <212> PRT

[1476] <213> Artificial Sequence

[1477] <220>

[1478] <223> PR000196 LCDR2 Chothia

[1479] <400> 144

[1480] Leu Gly Ser Asn Arg Ala Ser

[1481] 1 5

[1482] <210> 145
[1483] <211> 7
[1484] <212> PRT
[1485] <213> Artificial Sequence
[1486] <220>
[1487] <223> PR000197 LCDR2 Chothia, PR000447 LCDR2 Chothia, PR000448 LCDR2
[1488] Chothia
[1489] <400> 145
[1490] Gly Ala Ser Thr Arg Ala Thr
[1491] 1 5
[1492] <210> 146
[1493] <211> 7
[1494] <212> PRT
[1495] <213> Artificial Sequence
[1496] <220>
[1497] <223> PR000265 LCDR2 Chothia
[1498] <400> 146
[1499] Lys Ala Ser Ser Leu Glu Thr
[1500] 1 5
[1501] <210> 147
[1502] <211> 7
[1503] <212> PRT
[1504] <213> Artificial Sequence
[1505] <220>
[1506] <223> PR000483 LCDR2 Chothia
[1507] <400> 147
[1508] Gln Asp Lys Asn Arg Pro Ser
[1509] 1 5
[1510] <210> 148
[1511] <211> 7
[1512] <212> PRT
[1513] <213> Artificial Sequence
[1514] <220>
[1515] <223> PR000628 LCDR2 Chothia
[1516] <400> 148
[1517] Asp Ala Ser Asn Arg Ala Thr
[1518] 1 5
[1519] <210> 149
[1520] <211> 32

[1521] <212> PRT
[1522] <213> Artificial Sequence
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[1524] <223> PR000151 LFWR3 Chothia
[1525] <400> 149
[1526] Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
[1527] 1 5 10 15
[1528] Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
[1529] 20 25 30
[1530] <210> 150
[1531] <211> 32
[1532] <212> PRT
[1533] <213> Artificial Sequence
[1534] <220>
[1535] <223> PR000196 LFWR3 Chothia
[1536] <400> 150
[1537] Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
[1538] 1 5 10 15
[1539] Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys
[1540] 20 25 30
[1541] <210> 151
[1542] <211> 32
[1543] <212> PRT
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[1545] <220>
[1546] <223> PR000197 LFWR3 Chothia, PR000447 LFWR3 Chothia, PR000448 LFWR3
[1547] Chothia
[1548] <400> 151
[1549] Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr
[1550] 1 5 10 15
[1551] Leu Thr Ile Ser Ser Leu Gln Ser Glu Asp Phe Ala Val Tyr Tyr Cys
[1552] 20 25 30
[1553] <210> 152
[1554] <211> 32
[1555] <212> PRT
[1556] <213> Artificial Sequence
[1557] <220>
[1558] <223> PR000210 LFWR3 Chothia
[1559] <400> 152

[1560] Gly Val Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Thr Asp Phe Thr
[1561] 1 5 10 15
[1562] Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
[1563] 20 25 30
[1564] <210> 153
[1565] <211> 32
[1566] <212> PRT
[1567] <213> Artificial Sequence
[1568] <220>
[1569] <223> PR000265 LFWR3 Chothia
[1570] <400> 153
[1571] Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr
[1572] 1 5 10 15
[1573] Leu Thr Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys
[1574] 20 25 30
[1575] <210> 154
[1576] <211> 32
[1577] <212> PRT
[1578] <213> Artificial Sequence
[1579] <220>
[1580] <223> PR000483 LFWR3 Chothia
[1581] <400> 154
[1582] Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr
[1583] 1 5 10 15
[1584] Leu Thr Ile Ser Gly Thr Gln Ala Met Asp Glu Ala Asp Tyr Tyr Cys
[1585] 20 25 30
[1586] <210> 155
[1587] <211> 32
[1588] <212> PRT
[1589] <213> Artificial Sequence
[1590] <220>
[1591] <223> PR000628 LFWR3 Chothia
[1592] <400> 155
[1593] Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
[1594] 1 5 10 15
[1595] Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
[1596] 20 25 30
[1597] <210> 156
[1598] <211> 9

[1599] <212> PRT
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[1602] <223> PR000151 LCDR3 Chothia
[1603] <400> 156
[1604] Gln Gln Tyr Leu Tyr His Pro Ala Thr
[1605] 1 5
[1606] <210> 157
[1607] <211> 9
[1608] <212> PRT
[1609] <213> Artificial Sequence
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[1611] <223> PR000196 LCDR3 Chothia
[1612] <400> 157
[1613] Met Gln Ala Leu Gln Thr Pro Leu Thr
[1614] 1 5
[1615] <210> 158
[1616] <211> 9
[1617] <212> PRT
[1618] <213> Artificial Sequence
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[1620] <223> PR000197 LCDR3 Chothia, PR000447 LCDR3 Chothia, PR000448 LCDR3
[1621] Chothia
[1622] <400> 158
[1623] Gln Gln Tyr Tyr Asn Trp Pro Leu Thr
[1624] 1 5
[1625] <210> 159
[1626] <211> 9
[1627] <212> PRT
[1628] <213> Artificial Sequence
[1629] <220>
[1630] <223> PR000210 LCDR3 Chothia
[1631] <400> 159
[1632] Gln Gln His Tyr Thr Thr Pro Pro Thr
[1633] 1 5
[1634] <210> 160
[1635] <211> 9
[1636] <212> PRT
[1637] <213> Artificial Sequence

[1638] <220>
[1639] <223> PR000265 LCDR3 Chothia
[1640] <400> 160
[1641] Gln Gln Tyr Tyr Gly Ser Ser Arg Thr
[1642] 1 5
[1643] <210> 161
[1644] <211> 11
[1645] <212> PRT
[1646] <213> Artificial Sequence
[1647] <220>
[1648] <223> PR000483 LCDR3 Chothia
[1649] <400> 161
[1650] Ala Thr Tyr Thr Gly Phe Gly Ser Leu Ala Val
[1651] 1 5 10
[1652] <210> 162
[1653] <211> 11
[1654] <212> PRT
[1655] <213> Artificial Sequence
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[1657] <223> PR000628 LCDR3 Chothia
[1658] <400> 162
[1659] Gln Gln Arg Ser Asn Trp Pro Pro Ala Leu Thr
[1660] 1 5 10
[1661] <210> 163
[1662] <211> 10
[1663] <212> PRT
[1664] <213> Artificial Sequence
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[1666] <223> PR000151 LFWR4 Chothia, PR000210 LFWR4 Chothia, PR000265 LFWR4
[1667] Chothia
[1668] <400> 163
[1669] Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
[1670] 1 5 10
[1671] <210> 164
[1672] <211> 10
[1673] <212> PRT
[1674] <213> Artificial Sequence
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[1676] <223> PR000196 LFWR4 Chothia, PR000197 LFWR4 Chothia, PR000447 LFWR4

[1677] Chothia

[1678] <400> 164

[1679] Phe Gly Gly Gly Thr Lys Val Glu Ile Lys

[1680] 1 5 10

[1681] <210> 165

[1682] <211> 10

[1683] <212> PRT

[1684] <213> Artificial Sequence

[1685] <220>

[1686] <223> PR000483 LFWR4 Chothia

[1687] <400> 165

[1688] Phe Gly Gly Gly Thr Lys Leu Thr Val Leu

[1689] 1 5 10

[1690] <210> 166

[1691] <211> 118

[1692] <212> PRT

[1693] <213> Artificial Sequence

[1694] <220>

[1695] <223> PR000151 VH

[1696] <400> 166

[1697] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

[1698] 1 5 10 15

[1699] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ser

[1700] 20 25 30

[1701] Trp Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

[1702] 35 40 45

[1703] Ala Trp Ile Ser Pro Tyr Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val

[1704] 50 55 60

[1705] Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr

[1706] 65 70 75 80

[1707] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

[1708] 85 90 95

[1709] Ala Arg Arg His Trp Pro Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr

[1710] 100 105 110

[1711] Leu Val Thr Val Ser Ser

[1712] 115

[1713] <210> 167

[1714] <211> 129

[1715] <212> PRT

[1716] <213> Artificial Sequence
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[1718] <223> PR000196 VH
[1719] <400> 167
[1720] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Arg Gly Gly
[1721] 1 5 10 15
[1722] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
[1723] 20 25 30
[1724] Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[1725] 35 40 45
[1726] Ser Ala Ile Ser Gly Ser Gly Gly Asn Thr Tyr Tyr Ala Asp Ser Val
[1727] 50 55 60
[1728] Arg Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[1729] 65 70 75 80
[1730] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
[1731] 85 90 95
[1732] Ala Lys Glu Ala Tyr His Tyr Gly Ser Gly Ser Tyr Tyr Asp Asp Tyr
[1733] 100 105 110
[1734] Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
[1735] 115 120 125
[1736] Ser
[1737] <210> 168
[1738] <211> 115
[1739] <212> PRT
[1740] <213> Artificial Sequence
[1741] <220>
[1742] <223> PR000197 VH
[1743] <400> 168
[1744] Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
[1745] 1 5 10 15
[1746] Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr
[1747] 20 25 30
[1748] Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
[1749] 35 40 45
[1750] Gly Glu Ile Asn His Ser Gly Ser Thr Asp Ser Asn Pro Ser Leu Lys
[1751] 50 55 60
[1752] Gly Arg Val Thr Phe Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
[1753] 65 70 75 80
[1754] Lys Leu Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala

[1755] 85 90 95
[1756] Arg Leu Thr Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
[1757] 100 105 110
[1758] Val Ser Ser
[1759] 115
[1760] <210> 169
[1761] <211> 120
[1762] <212> PRT
[1763] <213> Artificial Sequence
[1764] <220>
[1765] <223> PR000210 VH
[1766] <400> 169
[1767] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[1768] 1 5 10 15
[1769] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
[1770] 20 25 30
[1771] Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[1772] 35 40 45
[1773] Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
[1774] 50 55 60
[1775] Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
[1776] 65 70 75 80
[1777] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[1778] 85 90 95
[1779] Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
[1780] 100 105 110
[1781] Gly Thr Leu Val Thr Val Ser Ser
[1782] 115 120
[1783] <210> 170
[1784] <211> 119
[1785] <212> PRT
[1786] <213> Artificial Sequence
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[1788] <223> PR000265 VH
[1789] <400> 170
[1790] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[1791] 1 5 10 15
[1792] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
[1793] 20 25 30

[1794] Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[1795] 35 40 45
[1796] Ala Asn Ile Lys Gln Glu Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
[1797] 50 55 60
[1798] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[1799] 65 70 75 80
[1800] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[1801] 85 90 95
[1802] Ala Arg Asp Arg Ala Val Ala Gly Ala Phe Asp Ile Trp Gly Gln Gly
[1803] 100 105 110
[1804] Thr Met Val Thr Val Ser Ser
[1805] 115
[1806] <210> 171
[1807] <211> 115
[1808] <212> PRT
[1809] <213> Artificial Sequence
[1810] <220>
[1811] <223> PR000447 VH
[1812] <400> 171
[1813] Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
[1814] 1 5 10 15
[1815] Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr
[1816] 20 25 30
[1817] Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
[1818] 35 40 45
[1819] Gly Glu Ile Ile His Ser Gly Ser Thr Asp Ser Asn Pro Ser Leu Lys
[1820] 50 55 60
[1821] Gly Arg Val Thr Phe Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
[1822] 65 70 75 80
[1823] Lys Leu Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
[1824] 85 90 95
[1825] Arg Leu Thr Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
[1826] 100 105 110
[1827] Val Ser Ser
[1828] 115
[1829] <210> 172
[1830] <211> 115
[1831] <212> PRT
[1832] <213> Artificial Sequence

[1833] <220>

[1834] <223> PR000448 VH, PR000980 VH

[1835] <400> 172

[1836] Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu

[1837] 1 5 10 15

[1838] Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr

[1839] 20 25 30

[1840] Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile

[1841] 35 40 45

[1842] Gly Glu Ile Gln His Ser Gly Ser Thr Asp Ser Asn Pro Ser Leu Lys

[1843] 50 55 60

[1844] Gly Arg Val Thr Phe Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu

[1845] 65 70 75 80

[1846] Lys Leu Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala

[1847] 85 90 95

[1848] Arg Leu Thr Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr

[1849] 100 105 110

[1850] Val Ser Ser

[1851] 115

[1852] <210> 173

[1853] <211> 116

[1854] <212> PRT

[1855] <213> Artificial Sequence

[1856] <220>

[1857] <223> PR000483 VH

[1858] <400> 173

[1859] Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu

[1860] 1 5 10 15

[1861] Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Ser Thr Tyr

[1862] 20 25 30

[1863] Trp Ile Ser Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met

[1864] 35 40 45

[1865] Gly Lys Ile Tyr Pro Gly Asp Ser Tyr Thr Asn Tyr Ser Pro Ser Phe

[1866] 50 55 60

[1867] Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr

[1868] 65 70 75 80

[1869] Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys

[1870] 85 90 95

[1871] Ala Arg Gly Tyr Gly Ile Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val

[1872] 100 105 110
[1873] Thr Val Ser Ser
[1874] 115
[1875] <210> 174
[1876] <211> 121
[1877] <212> PRT
[1878] <213> Artificial Sequence
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[1880] <223> PR000628 VH
[1881] <400> 174
[1882] Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
[1883] 1 5 10 15
[1884] Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr
[1885] 20 25 30
[1886] Tyr Trp Ser Trp Ile Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Ile
[1887] 35 40 45
[1888] Gly Glu Ile Asn His Gly Gly Tyr Val Thr Tyr Asn Pro Ser Leu Glu
[1889] 50 55 60
[1890] Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
[1891] 65 70 75 80
[1892] Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
[1893] 85 90 95
[1894] Arg Asp Tyr Gly Pro Gly Asn Tyr Asp Trp Tyr Phe Asp Leu Trp Gly
[1895] 100 105 110
[1896] Arg Gly Thr Leu Val Thr Val Ser Ser
[1897] 115 120
[1898] <210> 175
[1899] <211> 124
[1900] <212> PRT
[1901] <213> Artificial Sequence
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[1903] <223> PR001758 VH
[1904] <400> 175
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[1906] 1 5 10 15
[1907] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
[1908] 20 25 30
[1909] Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
[1910] 35 40 45

[1911] Ser Ser Ile Ser Gly Ser Gly Asp Asp Thr Tyr Tyr Gly Asp Ser Val
[1912] 50 55 60
[1913] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Gln Asn Thr Val Tyr
[1914] 65 70 75 80
[1915] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
[1916] 85 90 95
[1917] Ala Lys Glu Lys Ala Gly Thr Thr Gly Asp Tyr Tyr Tyr Asn Val Asp
[1918] 100 105 110
[1919] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
[1920] 115 120
[1921] <210> 176
[1922] <211> 124
[1923] <212> PRT
[1924] <213> Artificial Sequence
[1925] <220>
[1926] <223> PR001759 VH
[1927] <400> 176
[1928] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[1929] 1 5 10 15
[1930] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
[1931] 20 25 30
[1932] Ala Met Ser Trp Phe Arg Gln Pro Pro Glu Thr Gly Leu Gln Trp Val
[1933] 35 40 45
[1934] Ser Ser Ile Gly Gly Ser Gly Gly Asp Thr Tyr Tyr Ala Asp Ser Val
[1935] 50 55 60
[1936] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[1937] 65 70 75 80
[1938] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[1939] 85 90 95
[1940] Ala Lys Glu Gly Ser Asn Gly Thr Asp Asp Asn Tyr Tyr Asp Val Asp
[1941] 100 105 110
[1942] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
[1943] 115 120
[1944] <210> 177
[1945] <211> 124
[1946] <212> PRT
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[1948] <220>
[1949] <223> PR001760 VH

[1950] <400> 177

[1951] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly

[1952] 1 5 10 15

[1953] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr

[1954] 20 25 30

[1955] Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val

[1956] 35 40 45

[1957] Ser Ser Ile Ser Gly Ser Gly Val Ser Thr Tyr Tyr Ala Asp Ser Val

[1958] 50 55 60

[1959] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

[1960] 65 70 75 80

[1961] Leu Gln Met Thr Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr Phe Cys

[1962] 85 90 95

[1963] Ala Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val Asp

[1964] 100 105 110

[1965] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

[1966] 115 120

[1967] <210> 178

[1968] <211> 124

[1969] <212> PRT

[1970] <213> Artificial Sequence

[1971] <220>

[1972] <223> PR001763 VH

[1973] <400> 178

[1974] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

[1975] 1 5 10 15

[1976] Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Ser Asn Tyr

[1977] 20 25 30

[1978] Ala Met Ser Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val

[1979] 35 40 45

[1980] Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Phe Tyr Ala Asp Ser Val

[1981] 50 55 60

[1982] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

[1983] 65 70 75 80

[1984] Leu Gln Met Asn Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr Tyr Cys

[1985] 85 90 95

[1986] Ala Lys Glu Gly Ser Asn Gly Thr Asp Asp Tyr His Tyr Asp Ile Asp

[1987] 100 105 110

[1988] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

[1989] 115 120

[1990] <210> 179

[1991] <211> 124

[1992] <212> PRT

[1993] <213> Artificial Sequence

[1994] <220>

[1995] <223> PR001764 VH

[1996] <400> 179

[1997] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

[1998] 1 5 10 15

[1999] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr

[2000] 20 25 30

[2001] Ala Met Ser Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val

[2002] 35 40 45

[2003] Ser Ala Ile Ser Gly Gly Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val

[2004] 50 55 60

[2005] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

[2006] 65 70 75 80

[2007] Leu Gln Met Asp Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys

[2008] 85 90 95

[2009] Ala Lys Glu Gly Thr Thr Glu Thr Asp Asp Tyr His Tyr Asn Met Asp

[2010] 100 105 110

[2011] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

[2012] 115 120

[2013] <210> 180

[2014] <211> 124

[2015] <212> PRT

[2016] <213> Artificial Sequence

[2017] <220>

[2018] <223> PR001766 VH

[2019] <400> 180

[2020] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

[2021] 1 5 10 15

[2022] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr

[2023] 20 25 30

[2024] Ala Met Ser Trp Gly Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

[2025] 35 40 45

[2026] Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val

[2027] 50 55 60

[2028] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[2029] 65 70 75 80
[2030] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[2031] 85 90 95
[2032] Ala Lys Glu Lys Thr Gly Thr Thr Gly Asp Tyr Tyr Tyr Asp Met Asp
[2033] 100 105 110
[2034] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
[2035] 115 120
[2036] <210> 181
[2037] <211> 126
[2038] <212> PRT
[2039] <213> Artificial Sequence
[2040] <220>
[2041] <223> PR001767 VH
[2042] <400> 181
[2043] Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Ile Gln Pro Gly Gly
[2044] 1 5 10 15
[2045] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Asn
[2046] 20 25 30
[2047] Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[2048] 35 40 45
[2049] Ser Val Ile Tyr Ser Asp Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
[2050] 50 55 60
[2051] Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
[2052] 65 70 75 80
[2053] Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
[2054] 85 90 95
[2055] Arg Asp Arg Tyr Tyr Gly Ser Gly Asn Tyr Pro Thr Ala Tyr Tyr Gly
[2056] 100 105 110
[2057] Met Asp Val Arg Gly Gln Gly Thr Thr Val Thr Val Ser Ser
[2058] 115 120 125
[2059] <210> 182
[2060] <211> 124
[2061] <212> PRT
[2062] <213> Artificial Sequence
[2063] <220>
[2064] <223> PR001768 VH
[2065] <400> 182
[2066] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

[2067] 1 5 10 15
[2068] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
[2069] 20 25 30
[2070] Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[2071] 35 40 45
[2072] Ser Ser Ile Ser Gly Ser Gly Asp Ser Thr Tyr Tyr Ala Asp Ser Val
[2073] 50 55 60
[2074] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[2075] 65 70 75 80
[2076] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[2077] 85 90 95
[2078] Ala Lys Glu Gly Thr Gly Thr Thr Ser Asp Tyr Tyr Tyr Asn Val Asp
[2079] 100 105 110
[2080] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
[2081] 115 120
[2082] <210> 183
[2083] <211> 124
[2084] <212> PRT
[2085] <213> Artificial Sequence
[2086] <220>
[2087] <223> PR001771 VH
[2088] <400> 183
[2089] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[2090] 1 5 10 15
[2091] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
[2092] 20 25 30
[2093] Ala Met Thr Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Val
[2094] 35 40 45
[2095] Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
[2096] 50 55 60
[2097] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[2098] 65 70 75 80
[2099] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[2100] 85 90 95
[2101] Ala Lys Glu Gly Thr Gly Thr Thr Ser Asp Tyr Tyr Tyr Asn Val Asp
[2102] 100 105 110
[2103] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
[2104] 115 120
[2105] <210> 184

[2106] <211> 124
[2107] <212> PRT
[2108] <213> Artificial Sequence
[2109] <220>
[2110] <223> PR001774 VH
[2111] <400> 184
[2112] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[2113] 1 5 10 15
[2114] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
[2115] 20 25 30
[2116] Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
[2117] 35 40 45
[2118] Ser Thr Ile Ser Gly Ser Gly Asp Thr Thr Tyr Tyr Ala Asp Ser Val
[2119] 50 55 60
[2120] Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ser Lys Asn Thr Leu Tyr
[2121] 65 70 75 80
[2122] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Ser Ala Val Tyr Phe Cys
[2123] 85 90 95
[2124] Ala Lys Glu Ala Thr Ala Met Ala Ser Asp Tyr Tyr Tyr Gly Val Asp
[2125] 100 105 110
[2126] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
[2127] 115 120
[2128] <210> 185
[2129] <211> 123
[2130] <212> PRT
[2131] <213> Artificial Sequence
[2132] <220>
[2133] <223> PR001775 VH
[2134] <400> 185
[2135] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Ser Gly Gly
[2136] 1 5 10 15
[2137] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
[2138] 20 25 30
[2139] Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[2140] 35 40 45
[2141] Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Asp Tyr Ala Asp Ser Val
[2142] 50 55 60
[2143] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Thr Asn Thr Leu Tyr
[2144] 65 70 75 80

[2145] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[2146] 85 90 95
[2147] Ala Lys Glu Arg Ala Tyr Asp Tyr Ser Asn Tyr Val Asp Phe Asp Tyr
[2148] 100 105 110
[2149] Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
[2150] 115 120
[2151] <210> 186
[2152] <211> 125
[2153] <212> PRT
[2154] <213> Artificial Sequence
[2155] <220>
[2156] <223> PR001776 VH
[2157] <400> 186
[2158] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[2159] 1 5 10 15
[2160] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
[2161] 20 25 30
[2162] Ala Met Ser Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
[2163] 35 40 45
[2164] Ser Ala Ile Ser Ser Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
[2165] 50 55 60
[2166] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[2167] 65 70 75 80
[2168] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[2169] 85 90 95
[2170] Ala Lys Asp Gly Val Thr Thr Pro Ser Tyr Tyr Tyr Tyr Tyr Asp Met
[2171] 100 105 110
[2172] Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
[2173] 115 120 125
[2174] <210> 187
[2175] <211> 124
[2176] <212> PRT
[2177] <213> Artificial Sequence
[2178] <220>
[2179] <223> PR001780 VH
[2180] <400> 187
[2181] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
[2182] 1 5 10 15
[2183] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe

[2184] 20 25 30
[2185] Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[2186] 35 40 45
[2187] Ser Thr Ile Ser Gly Ser Gly Asp Asn Thr Tyr Tyr Ala Asp Ser Val
[2188] 50 55 60
[2189] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[2190] 65 70 75 80
[2191] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
[2192] 85 90 95
[2193] Ala Lys Glu Asp Thr Ala Val Ala Ser Asp Tyr Tyr Tyr Asn Ile Asp
[2194] 100 105 110
[2195] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
[2196] 115 120
[2197] <210> 188
[2198] <211> 124
[2199] <212> PRT
[2200] <213> Artificial Sequence
[2201] <220>
[2202] <223> PR001781 VH
[2203] <400> 188
[2204] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Leu Gly Gly
[2205] 1 5 10 15
[2206] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
[2207] 20 25 30
[2208] Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
[2209] 35 40 45
[2210] Ser Ser Ile Ser Gly Ser Gly Gly Asn Thr Tyr Tyr Ala Asp Ser Val
[2211] 50 55 60
[2212] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[2213] 65 70 75 80
[2214] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[2215] 85 90 95
[2216] Ala Lys Glu Arg Thr Gly Thr Thr Gly Asp Tyr Tyr Tyr Asn Val Asp
[2217] 100 105 110
[2218] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
[2219] 115 120
[2220] <210> 189
[2221] <211> 124
[2222] <212> PRT

[2223] <213> Artificial Sequence
[2224] <220>
[2225] <223> PR001830 VH
[2226] <400> 189
[2227] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[2228] 1 5 10 15
[2229] Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Ser Asn Tyr
[2230] 20 25 30
[2231] Ala Met Ser Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
[2232] 35 40 45
[2233] Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Phe Tyr Ala Asp Ser Val
[2234] 50 55 60
[2235] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[2236] 65 70 75 80
[2237] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
[2238] 85 90 95
[2239] Ala Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val Asp
[2240] 100 105 110
[2241] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
[2242] 115 120
[2243] <210> 190
[2244] <211> 124
[2245] <212> PRT
[2246] <213> Artificial Sequence
[2247] <220>
[2248] <223> PR001831 VH
[2249] <400> 190
[2250] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Ile Gln Pro Gly Gly
[2251] 1 5 10 15
[2252] Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Thr Phe Ser Ser Tyr
[2253] 20 25 30
[2254] Ala Met Ser Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
[2255] 35 40 45
[2256] Ser Ser Ile Ser Gly Ser Gly Asp Ser Thr Tyr Tyr Ala Asp Ser Val
[2257] 50 55 60
[2258] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[2259] 65 70 75 80
[2260] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Gly Tyr His Cys
[2261] 85 90 95

[2262] Ala Lys Glu Gly Ser Asn Gly Thr Asp Asp Tyr His Tyr Asp Ile Asp
[2263] 100 105 110
[2264] Val Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
[2265] 115 120
[2266] <210> 191
[2267] <211> 124
[2268] <212> PRT
[2269] <213> Artificial Sequence
[2270] <220>
[2271] <223> PR001833 VH
[2272] <400> 191
[2273] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[2274] 1 5 10 15
[2275] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
[2276] 20 25 30
[2277] Ala Met Ser Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
[2278] 35 40 45
[2279] Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Phe Tyr Ala Asp Ser Val
[2280] 50 55 60
[2281] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[2282] 65 70 75 80
[2283] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
[2284] 85 90 95
[2285] Ala Lys Glu Gly Ala Thr Glu Thr Asp Asp Tyr His Phe Asn Thr Asp
[2286] 100 105 110
[2287] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
[2288] 115 120
[2289] <210> 192
[2290] <211> 124
[2291] <212> PRT
[2292] <213> Artificial Sequence
[2293] <220>
[2294] <223> PR001834 VH
[2295] <400> 192
[2296] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[2297] 1 5 10 15
[2298] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Gly Tyr
[2299] 20 25 30
[2300] Ala Met Thr Trp Val Arg Gln Pro Pro Glu Lys Gly Leu Glu Trp Val

[2301] 35 40 45
[2302] Ser Ser Ile Ser Gly Ser Gly Asn Asn Thr Phe Tyr Ala Asp Ser Val
[2303] 50 55 60
[2304] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[2305] 65 70 75 80
[2306] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[2307] 85 90 95
[2308] Ala Lys Glu Gly Thr Thr Glu Thr Asp Asp Tyr His Tyr Asn Met Asp
[2309] 100 105 110
[2310] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
[2311] 115 120
[2312] <210> 193
[2313] <211> 124
[2314] <212> PRT
[2315] <213> Artificial Sequence
[2316] <220>
[2317] <223> PR001836 VH
[2318] <400> 193
[2319] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[2320] 1 5 10 15
[2321] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Ser Asn Phe
[2322] 20 25 30
[2323] Ala Met Thr Trp Val Arg Gln Pro Pro Glu Lys Gly Leu Lys Trp Val
[2324] 35 40 45
[2325] Ser Ser Ile Asn Gly Ser Gly Phe Asn Thr Tyr Tyr Thr Asp Ser Val
[2326] 50 55 60
[2327] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr
[2328] 65 70 75 80
[2329] Leu Gln Met Asn Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr Phe Cys
[2330] 85 90 95
[2331] Ala Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val Asp
[2332] 100 105 110
[2333] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
[2334] 115 120
[2335] <210> 194
[2336] <211> 124
[2337] <212> PRT
[2338] <213> Artificial Sequence
[2339] <220>

[2340] <223> PR001837 VH

[2341] <400> 194

[2342] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

[2343] 1 5 10 15

[2344] Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Thr Phe Ser Ser Tyr

[2345] 20 25 30

[2346] Ala Met Ser Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val

[2347] 35 40 45

[2348] Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Phe Tyr Ala Asp Ser Val

[2349] 50 55 60

[2350] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

[2351] 65 70 75 80

[2352] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

[2353] 85 90 95

[2354] Ala Lys Glu Gly Thr Thr Glu Thr Asp Asp Tyr His Tyr Asn Met Asp

[2355] 100 105 110

[2356] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser

[2357] 115 120

[2358] <210> 195

[2359] <211> 124

[2360] <212> PRT

[2361] <213> Artificial Sequence

[2362] <220>

[2363] <223> PR001838 VH

[2364] <400> 195

[2365] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

[2366] 1 5 10 15

[2367] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr

[2368] 20 25 30

[2369] Ala Met Ser Trp Phe Arg Gln Pro Pro Glu Thr Gly Leu Lys Trp Val

[2370] 35 40 45

[2371] Ser Ser Ile Asp Gly Ser Gly Gly Asp Thr Tyr Tyr Ala Asp Ser Val

[2372] 50 55 60

[2373] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

[2374] 65 70 75 80

[2375] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

[2376] 85 90 95

[2377] Ala Lys Glu Gly Ser His Gly Thr Asp Asp Ser His Tyr Asp Val Asp

[2378] 100 105 110

[2379] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
[2380] 115 120
[2381] <210> 196
[2382] <211> 123
[2383] <212> PRT
[2384] <213> Artificial Sequence
[2385] <220>
[2386] <223> PR001840 VH
[2387] <400> 196
[2388] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[2389] 1 5 10 15
[2390] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
[2391] 20 25 30
[2392] Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Val Trp Val
[2393] 35 40 45
[2394] Ser Arg Ile Asn Ser Asp Gly Ser Ser Thr Ser Tyr Ala Asp Ser Val
[2395] 50 55 60
[2396] Gln Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
[2397] 65 70 75 80
[2398] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[2399] 85 90 95
[2400] Val Arg Lys Gly Ser Ser Ser Tyr Tyr His Tyr Ser Ile Glu Asp Asp
[2401] 100 105 110
[2402] Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
[2403] 115 120
[2404] <210> 197
[2405] <211> 124
[2406] <212> PRT
[2407] <213> Artificial Sequence
[2408] <220>
[2409] <223> PR001842 VH
[2410] <400> 197
[2411] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[2412] 1 5 10 15
[2413] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
[2414] 20 25 30
[2415] Ala Met Ser Trp Gly Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[2416] 35 40 45
[2417] Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val

[2418] 50 55 60
[2419] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[2420] 65 70 75 80
[2421] Leu His Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[2422] 85 90 95
[2423] Ala Lys Glu Lys Val Ala Thr Thr Gly Asp Tyr Tyr Tyr Asp Met Asp
[2424] 100 105 110
[2425] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
[2426] 115 120
[2427] <210> 198
[2428] <211> 124
[2429] <212> PRT
[2430] <213> Artificial Sequence
[2431] <220>
[2432] <223> PR004469 VH
[2433] <400> 198
[2434] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[2435] 1 5 10 15
[2436] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
[2437] 20 25 30
[2438] Ala Met Ser Trp Phe Arg Gln Pro Pro Glu Thr Gly Leu Lys Trp Val
[2439] 35 40 45
[2440] Ser Ser Ile Asp Ala Ser Gly Gly Asp Thr Tyr Tyr Ala Asp Ser Val
[2441] 50 55 60
[2442] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[2443] 65 70 75 80
[2444] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[2445] 85 90 95
[2446] Ala Lys Glu Gly Ser His Gly Thr Asp Asp Ser His Tyr Asp Val Asp
[2447] 100 105 110
[2448] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
[2449] 115 120
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[2457] Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
[2458] 1 5 10 15
[2459] Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala
[2460] 20 25 30
[2461] Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
[2462] 35 40 45
[2463] Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
[2464] 50 55 60
[2465] Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
[2466] 65 70 75 80
[2467] Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Leu Tyr His Pro Ala
[2468] 85 90 95
[2469] Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
[2470] 100 105
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[2477] <400> 200
[2478] Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
[2479] 1 5 10 15
[2480] Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
[2481] 20 25 30
[2482] Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
[2483] 35 40 45
[2484] Pro Gln Leu Leu Ile Phe Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
[2485] 50 55 60
[2486] Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
[2487] 65 70 75 80
[2488] Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
[2489] 85 90 95
[2490] Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
[2491] 100 105 110
[2492] <210> 201
[2493] <211> 107
[2494] <212> PRT
[2495] <213> Artificial Sequence

[2496] <220>
[2497] <223> PR000197 VL
[2498] <400> 201
[2499] Glu Phe Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
[2500] 1 5 10 15
[2501] Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Ile
[2502] 20 25 30
[2503] Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
[2504] 35 40 45
[2505] Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
[2506] 50 55 60
[2507] Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
[2508] 65 70 75 80
[2509] Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Asn Trp Pro Leu
[2510] 85 90 95
[2511] Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
[2512] 100 105
[2513] <210> 202
[2514] <211> 107
[2515] <212> PRT
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[2519] <400> 202
[2520] Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
[2521] 1 5 10 15
[2522] Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
[2523] 20 25 30
[2524] Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
[2525] 35 40 45
[2526] Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
[2527] 50 55 60
[2528] Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
[2529] 65 70 75 80
[2530] Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
[2531] 85 90 95
[2532] Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
[2533] 100 105
[2534] <210> 203

[2535] <211> 107
[2536] <212> PRT
[2537] <213> Artificial Sequence
[2538] <220>
[2539] <223> PR000265 VL
[2540] <400> 203
[2541] Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
[2542] 1 5 10 15
[2543] Asp Arg Val Thr Val Thr Cys Arg Ala Ser Gln Ser Ile Tyr Ile Trp
[2544] 20 25 30
[2545] Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile
[2546] 35 40 45
[2547] Tyr Lys Ala Ser Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
[2548] 50 55 60
[2549] Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
[2550] 65 70 75 80
[2551] Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Gly Ser Ser Arg
[2552] 85 90 95
[2553] Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
[2554] 100 105
[2555] <210> 204
[2556] <211> 107
[2557] <212> PRT
[2558] <213> Artificial Sequence
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[2560] <223> PR000447 VL, PR000448 VL, PR000980 VL
[2561] <400> 204
[2562] Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
[2563] 1 5 10 15
[2564] Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Ile
[2565] 20 25 30
[2566] Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
[2567] 35 40 45
[2568] Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
[2569] 50 55 60
[2570] Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
[2571] 65 70 75 80
[2572] Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Asn Trp Pro Leu
[2573] 85 90 95

[2574] Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
[2575] 100 105
[2576] <210> 205
[2577] <211> 108
[2578] <212> PRT
[2579] <213> Artificial Sequence
[2580] <220>
[2581] <223> PR000483 VL
[2582] <400> 205
[2583] Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
[2584] 1 5 10 15
[2585] Thr Ala Ser Ile Thr Cys Ser Gly Asp Asn Ile Gly Asp Gln Tyr Ala
[2586] 20 25 30
[2587] His Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
[2588] 35 40 45
[2589] Gln Asp Lys Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
[2590] 50 55 60
[2591] Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
[2592] 65 70 75 80
[2593] Asp Glu Ala Asp Tyr Tyr Cys Ala Thr Tyr Thr Gly Phe Gly Ser Leu
[2594] 85 90 95
[2595] Ala Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
[2596] 100 105
[2597] <210> 206
[2598] <211> 109
[2599] <212> PRT
[2600] <213> Artificial Sequence
[2601] <220>
[2602] <223> PR000628 VL
[2603] <400> 206
[2604] Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
[2605] 1 5 10 15
[2606] Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
[2607] 20 25 30
[2608] Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
[2609] 35 40 45
[2610] Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
[2611] 50 55 60
[2612] Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro

[2613] 65 70 75 80
[2614] Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
[2615] 85 90 95
[2616] Ala Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
[2617] 100 105
[2618] <210> 207
[2619] <211> 448
[2620] <212> PRT
[2621] <213> Artificial Sequence
[2622] <220>
[2623] <223> PR000151 HC
[2624] <400> 207
[2625] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[2626] 1 5 10 15
[2627] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ser
[2628] 20 25 30
[2629] Trp Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[2630] 35 40 45
[2631] Ala Trp Ile Ser Pro Tyr Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
[2632] 50 55 60
[2633] Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
[2634] 65 70 75 80
[2635] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[2636] 85 90 95
[2637] Ala Arg Arg His Trp Pro Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr
[2638] 100 105 110
[2639] Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
[2640] 115 120 125
[2641] Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
[2642] 130 135 140
[2643] Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
[2644] 145 150 155 160
[2645] Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
[2646] 165 170 175
[2647] Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
[2648] 180 185 190
[2649] Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
[2650] 195 200 205
[2651] Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr

[2652] 210 215 220

[2653] His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser

[2654] 225 230 235 240

[2655] Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg

[2656] 245 250 255

[2657] Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro

[2658] 260 265 270

[2659] Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala

[2660] 275 280 285

[2661] Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val

[2662] 290 295 300

[2663] Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr

[2664] 305 310 315 320

[2665] Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr

[2666] 325 330 335

[2667] Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu

[2668] 340 345 350

[2669] Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys

[2670] 355 360 365

[2671] Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser

[2672] 370 375 380

[2673] Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp

[2674] 385 390 395 400

[2675] Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser

[2676] 405 410 415

[2677] Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala

[2678] 420 425 430

[2679] Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

[2680] 435 440 445

[2681] <210> 208

[2682] <211> 456

[2683] <212> PRT

[2684] <213> Artificial Sequence

[2685] <220>

[2686] <223> PR000196 HC

[2687] <400> 208

[2688] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Arg Gly Gly

[2689] 1 5 10 15

[2690] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr

[2691] 20 25 30
[2692] Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[2693] 35 40 45
[2694] Ser Ala Ile Ser Gly Ser Gly Gly Asn Thr Tyr Tyr Ala Asp Ser Val
[2695] 50 55 60
[2696] Arg Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[2697] 65 70 75 80
[2698] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
[2699] 85 90 95
[2700] Ala Lys Glu Ala Tyr His Tyr Gly Ser Gly Ser Tyr Tyr Asp Asp Tyr
[2701] 100 105 110
[2702] Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
[2703] 115 120 125
[2704] Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
[2705] 130 135 140
[2706] Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
[2707] 145 150 155 160
[2708] Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
[2709] 165 170 175
[2710] Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
[2711] 180 185 190
[2712] Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
[2713] 195 200 205
[2714] Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
[2715] 210 215 220
[2716] Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
[2717] 225 230 235 240
[2718] Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
[2719] 245 250 255
[2720] Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
[2721] 260 265 270
[2722] Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
[2723] 275 280 285
[2724] Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
[2725] 290 295 300
[2726] Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
[2727] 305 310 315 320
[2728] Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
[2729] 325 330 335

[2730] Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
[2731] 340 345 350
[2732] Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr
[2733] 355 360 365
[2734] Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
[2735] 370 375 380
[2736] Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
[2737] 385 390 395 400
[2738] Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
[2739] 405 410 415
[2740] Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
[2741] 420 425 430
[2742] Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
[2743] 435 440 445
[2744] Ser Leu Ser Leu Ser Leu Gly Lys
[2745] 450 455
[2746] <210> 209
[2747] <211> 442
[2748] <212> PRT
[2749] <213> Artificial Sequence
[2750] <220>
[2751] <223> PR000197 HC
[2752] <400> 209
[2753] Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
[2754] 1 5 10 15
[2755] Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr
[2756] 20 25 30
[2757] Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
[2758] 35 40 45
[2759] Gly Glu Ile Asn His Ser Gly Ser Thr Asp Ser Asn Pro Ser Leu Lys
[2760] 50 55 60
[2761] Gly Arg Val Thr Phe Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
[2762] 65 70 75 80
[2763] Lys Leu Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
[2764] 85 90 95
[2765] Arg Leu Thr Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
[2766] 100 105 110
[2767] Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
[2768] 115 120 125

[2769] Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val
[2770] 130 135 140
[2771] Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
[2772] 145 150 155 160
[2773] Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
[2774] 165 170 175
[2775] Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
[2776] 180 185 190
[2777] Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys
[2778] 195 200 205
[2779] Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
[2780] 210 215 220
[2781] Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
[2782] 225 230 235 240
[2783] Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
[2784] 245 250 255
[2785] Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
[2786] 260 265 270
[2787] Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
[2788] 275 280 285
[2789] Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
[2790] 290 295 300
[2791] His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
[2792] 305 310 315 320
[2793] Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
[2794] 325 330 335
[2795] Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu
[2796] 340 345 350
[2797] Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
[2798] 355 360 365
[2799] Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
[2800] 370 375 380
[2801] Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
[2802] 385 390 395 400
[2803] Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn
[2804] 405 410 415
[2805] Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
[2806] 420 425 430
[2807] Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys

[2808] 435 440

[2809] <210> 210

[2810] <211> 450

[2811] <212> PRT

[2812] <213> Artificial Sequence

[2813] <220>

[2814] <223> PR000210 HC

[2815] <400> 210

[2816] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

[2817] 1 5 10 15

[2818] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr

[2819] 20 25 30

[2820] Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

[2821] 35 40 45

[2822] Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val

[2823] 50 55 60

[2824] Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr

[2825] 65 70 75 80

[2826] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

[2827] 85 90 95

[2828] Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln

[2829] 100 105 110

[2830] Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val

[2831] 115 120 125

[2832] Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala

[2833] 130 135 140

[2834] Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser

[2835] 145 150 155 160

[2836] Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val

[2837] 165 170 175

[2838] Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro

[2839] 180 185 190

[2840] Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys

[2841] 195 200 205

[2842] Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp

[2843] 210 215 220

[2844] Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly

[2845] 225 230 235 240

[2846] Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile

[2847] 245 250 255

[2848] Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu

[2849] 260 265 270

[2850] Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His

[2851] 275 280 285

[2852] Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg

[2853] 290 295 300

[2854] Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys

[2855] 305 310 315 320

[2856] Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu

[2857] 325 330 335

[2858] Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr

[2859] 340 345 350

[2860] Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu

[2861] 355 360 365

[2862] Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp

[2863] 370 375 380

[2864] Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val

[2865] 385 390 395 400

[2866] Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp

[2867] 405 410 415

[2868] Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His

[2869] 420 425 430

[2870] Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro

[2871] 435 440 445

[2872] Gly Lys

[2873] 450

[2874] <210> 211

[2875] <211> 449

[2876] <212> PRT

[2877] <213> Artificial Sequence

[2878] <220>

[2879] <223> PR000265 HC

[2880] <400> 211

[2881] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

[2882] 1 5 10 15

[2883] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr

[2884] 20 25 30

[2885] Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

[2886] 35 40 45
[2887] Ala Asn Ile Lys Gln Glu Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
[2888] 50 55 60
[2889] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[2890] 65 70 75 80
[2891] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[2892] 85 90 95
[2893] Ala Arg Asp Arg Ala Val Ala Gly Ala Phe Asp Ile Trp Gly Gln Gly
[2894] 100 105 110
[2895] Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
[2896] 115 120 125
[2897] Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
[2898] 130 135 140
[2899] Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
[2900] 145 150 155 160
[2901] Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
[2902] 165 170 175
[2903] Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
[2904] 180 185 190
[2905] Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
[2906] 195 200 205
[2907] Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
[2908] 210 215 220
[2909] Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
[2910] 225 230 235 240
[2911] Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
[2912] 245 250 255
[2913] Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
[2914] 260 265 270
[2915] Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
[2916] 275 280 285
[2917] Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val
[2918] 290 295 300
[2919] Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
[2920] 305 310 315 320
[2921] Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
[2922] 325 330 335
[2923] Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
[2924] 340 345 350

[2925] Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
[2926] 355 360 365
[2927] Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
[2928] 370 375 380
[2929] Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
[2930] 385 390 395 400
[2931] Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
[2932] 405 410 415
[2933] Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
[2934] 420 425 430
[2935] Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[2936] 435 440 445
[2937] Lys
[2938] <210> 212
[2939] <211> 442
[2940] <212> PRT
[2941] <213> Artificial Sequence
[2942] <220>
[2943] <223> PR000447 HC
[2944] <400> 212
[2945] Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
[2946] 1 5 10 15
[2947] Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr
[2948] 20 25 30
[2949] Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
[2950] 35 40 45
[2951] Gly Glu Ile Ile His Ser Gly Ser Thr Asp Ser Asn Pro Ser Leu Lys
[2952] 50 55 60
[2953] Gly Arg Val Thr Phe Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
[2954] 65 70 75 80
[2955] Lys Leu Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
[2956] 85 90 95
[2957] Arg Leu Thr Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
[2958] 100 105 110
[2959] Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
[2960] 115 120 125
[2961] Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val
[2962] 130 135 140
[2963] Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala

[2964] 145 150 155 160
[2965] Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
[2966] 165 170 175
[2967] Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
[2968] 180 185 190
[2969] Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys
[2970] 195 200 205
[2971] Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
[2972] 210 215 220
[2973] Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
[2974] 225 230 235 240
[2975] Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
[2976] 245 250 255
[2977] Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
[2978] 260 265 270
[2979] Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
[2980] 275 280 285
[2981] Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
[2982] 290 295 300
[2983] His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
[2984] 305 310 315 320
[2985] Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
[2986] 325 330 335
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[2988] 340 345 350
[2989] Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
[2990] 355 360 365
[2991] Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
[2992] 370 375 380
[2993] Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
[2994] 385 390 395 400
[2995] Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn
[2996] 405 410 415
[2997] Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
[2998] 420 425 430
[2999] Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
[3000] 435 440
[3001] <210> 213
[3002] <211> 442

[3003] <212> PRT
[3004] <213> Artificial Sequence
[3005] <220>
[3006] <223> PR000448 HC
[3007] <400> 213
[3008] Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
[3009] 1 5 10 15
[3010] Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr
[3011] 20 25 30
[3012] Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
[3013] 35 40 45
[3014] Gly Glu Ile Gln His Ser Gly Ser Thr Asp Ser Asn Pro Ser Leu Lys
[3015] 50 55 60
[3016] Gly Arg Val Thr Phe Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
[3017] 65 70 75 80
[3018] Lys Leu Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
[3019] 85 90 95
[3020] Arg Leu Thr Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
[3021] 100 105 110
[3022] Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
[3023] 115 120 125
[3024] Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val
[3025] 130 135 140
[3026] Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
[3027] 145 150 155 160
[3028] Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
[3029] 165 170 175
[3030] Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
[3031] 180 185 190
[3032] Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys
[3033] 195 200 205
[3034] Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys
[3035] 210 215 220
[3036] Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
[3037] 225 230 235 240
[3038] Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
[3039] 245 250 255
[3040] Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp
[3041] 260 265 270

[3042] Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
[3043] 275 280 285
[3044] Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
[3045] 290 295 300
[3046] His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
[3047] 305 310 315 320
[3048] Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
[3049] 325 330 335
[3050] Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu
[3051] 340 345 350
[3052] Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
[3053] 355 360 365
[3054] Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
[3055] 370 375 380
[3056] Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
[3057] 385 390 395 400
[3058] Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn
[3059] 405 410 415
[3060] Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
[3061] 420 425 430
[3062] Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
[3063] 435 440
[3064] <210> 214
[3065] <211> 442
[3066] <212> PRT
[3067] <213> Artificial Sequence
[3068] <220>
[3069] <223> PR000483 HC
[3070] <400> 214
[3071] Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
[3072] 1 5 10 15
[3073] Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Ser Thr Tyr
[3074] 20 25 30
[3075] Trp Ile Ser Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
[3076] 35 40 45
[3077] Gly Lys Ile Tyr Pro Gly Asp Ser Tyr Thr Asn Tyr Ser Pro Ser Phe
[3078] 50 55 60
[3079] Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
[3080] 65 70 75 80

[3081] Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
[3082] 85 90 95
[3083] Ala Arg Gly Tyr Gly Ile Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
[3084] 100 105 110
[3085] Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
[3086] 115 120 125
[3087] Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu
[3088] 130 135 140
[3089] Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
[3090] 145 150 155 160
[3091] Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
[3092] 165 170 175
[3093] Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe
[3094] 180 185 190
[3095] Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr
[3096] 195 200 205
[3097] Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro
[3098] 210 215 220
[3099] Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro
[3100] 225 230 235 240
[3101] Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
[3102] 245 250 255
[3103] Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp
[3104] 260 265 270
[3105] Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
[3106] 275 280 285
[3107] Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val
[3108] 290 295 300
[3109] His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
[3110] 305 310 315 320
[3111] Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly
[3112] 325 330 335
[3113] Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
[3114] 340 345 350
[3115] Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
[3116] 355 360 365
[3117] Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
[3118] 370 375 380
[3119] Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe

[3120] 385 390 395 400
[3121] Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
[3122] 405 410 415
[3123] Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
[3124] 420 425 430
[3125] Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[3126] 435 440
[3127] <210> 215
[3128] <211> 448
[3129] <212> PRT
[3130] <213> Artificial Sequence
[3131] <220>
[3132] <223> PR000628 HC
[3133] <400> 215
[3134] Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
[3135] 1 5 10 15
[3136] Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr
[3137] 20 25 30
[3138] Tyr Trp Ser Trp Ile Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Ile
[3139] 35 40 45
[3140] Gly Glu Ile Asn His Gly Gly Tyr Val Thr Tyr Asn Pro Ser Leu Glu
[3141] 50 55 60
[3142] Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
[3143] 65 70 75 80
[3144] Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
[3145] 85 90 95
[3146] Arg Asp Tyr Gly Pro Gly Asn Tyr Asp Trp Tyr Phe Asp Leu Trp Gly
[3147] 100 105 110
[3148] Arg Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
[3149] 115 120 125
[3150] Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
[3151] 130 135 140
[3152] Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
[3153] 145 150 155 160
[3154] Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
[3155] 165 170 175
[3156] Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
[3157] 180 185 190
[3158] Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His

[3159] 195 200 205

[3160] Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly

[3161] 210 215 220

[3162] Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser

[3163] 225 230 235 240

[3164] Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg

[3165] 245 250 255

[3166] Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro

[3167] 260 265 270

[3168] Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala

[3169] 275 280 285

[3170] Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val

[3171] 290 295 300

[3172] Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr

[3173] 305 310 315 320

[3174] Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr

[3175] 325 330 335

[3176] Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu

[3177] 340 345 350

[3178] Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys

[3179] 355 360 365

[3180] Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser

[3181] 370 375 380

[3182] Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp

[3183] 385 390 395 400

[3184] Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser

[3185] 405 410 415

[3186] Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala

[3187] 420 425 430

[3188] Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys

[3189] 435 440 445

[3190] <210> 216

[3191] <211> 445

[3192] <212> PRT

[3193] <213> Artificial Sequence

[3194] <220>

[3195] <223> PR000980 HC

[3196] <400> 216

[3197] Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu

[3198] 1 5 10 15
[3199] Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr
[3200] 20 25 30
[3201] Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
[3202] 35 40 45
[3203] Gly Glu Ile Gln His Ser Gly Ser Thr Asp Ser Asn Pro Ser Leu Lys
[3204] 50 55 60
[3205] Gly Arg Val Thr Phe Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
[3206] 65 70 75 80
[3207] Lys Leu Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
[3208] 85 90 95
[3209] Arg Leu Thr Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
[3210] 100 105 110
[3211] Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
[3212] 115 120 125
[3213] Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
[3214] 130 135 140
[3215] Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
[3216] 145 150 155 160
[3217] Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
[3218] 165 170 175
[3219] Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
[3220] 180 185 190
[3221] Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
[3222] 195 200 205
[3223] Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys
[3224] 210 215 220
[3225] Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu
[3226] 225 230 235 240
[3227] Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
[3228] 245 250 255
[3229] Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
[3230] 260 265 270
[3231] Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
[3232] 275 280 285
[3233] Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
[3234] 290 295 300
[3235] Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
[3236] 305 310 315 320

[3237] Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
[3238] 325 330 335
[3239] Ala Lys Gly Gln Pro Arg Arg Pro Gln Val Tyr Thr Leu Pro Pro Ser
[3240] 340 345 350
[3241] Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
[3242] 355 360 365
[3243] Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
[3244] 370 375 380
[3245] Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
[3246] 385 390 395 400
[3247] Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
[3248] 405 410 415
[3249] Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
[3250] 420 425 430
[3251] His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[3252] 435 440 445
[3253] <210> 217
[3254] <211> 356
[3255] <212> PRT
[3256] <213> Artificial Sequence
[3257] <220>
[3258] <223> PR001758 HC
[3259] <400> 217
[3260] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Leu Gly Gly
[3261] 1 5 10 15
[3262] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
[3263] 20 25 30
[3264] Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
[3265] 35 40 45
[3266] Ser Ser Ile Ser Gly Ser Gly Asp Asp Thr Tyr Tyr Gly Asp Ser Val
[3267] 50 55 60
[3268] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Gln Asn Thr Val Tyr
[3269] 65 70 75 80
[3270] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
[3271] 85 90 95
[3272] Ala Lys Glu Lys Ala Gly Thr Thr Gly Asp Tyr Tyr Tyr Asn Val Asp
[3273] 100 105 110
[3274] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser
[3275] 115 120 125

[3276] Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
[3277] 130 135 140
[3278] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
[3279] 145 150 155 160
[3280] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
[3281] 165 170 175
[3282] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
[3283] 180 185 190
[3284] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
[3285] 195 200 205
[3286] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
[3287] 210 215 220
[3288] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
[3289] 225 230 235 240
[3290] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
[3291] 245 250 255
[3292] Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
[3293] 260 265 270
[3294] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[3295] 275 280 285
[3296] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
[3297] 290 295 300
[3298] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
[3299] 305 310 315 320
[3300] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
[3301] 325 330 335
[3302] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
[3303] 340 345 350
[3304] Ser Pro Gly Lys
[3305] 355
[3306] <210> 218
[3307] <211> 356
[3308] <212> PRT
[3309] <213> Artificial Sequence
[3310] <220>
[3311] <223> PR001759 HC
[3312] <400> 218
[3313] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[3314] 1 5 10 15

[3315] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
[3316] 20 25 30
[3317] Ala Met Ser Trp Phe Arg Gln Pro Pro Glu Thr Gly Leu Gln Trp Val
[3318] 35 40 45
[3319] Ser Ser Ile Gly Gly Ser Gly Gly Asp Thr Tyr Tyr Ala Asp Ser Val
[3320] 50 55 60
[3321] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[3322] 65 70 75 80
[3323] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[3324] 85 90 95
[3325] Ala Lys Glu Gly Ser Asn Gly Thr Asp Asp Asn Tyr Tyr Asp Val Asp
[3326] 100 105 110
[3327] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser
[3328] 115 120 125
[3329] Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
[3330] 130 135 140
[3331] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
[3332] 145 150 155 160
[3333] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
[3334] 165 170 175
[3335] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
[3336] 180 185 190
[3337] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
[3338] 195 200 205
[3339] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
[3340] 210 215 220
[3341] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
[3342] 225 230 235 240
[3343] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
[3344] 245 250 255
[3345] Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
[3346] 260 265 270
[3347] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[3348] 275 280 285
[3349] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
[3350] 290 295 300
[3351] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
[3352] 305 310 315 320
[3353] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val

[3354] 325 330 335
[3355] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
[3356] 340 345 350
[3357] Ser Pro Gly Lys
[3358] 355
[3359] <210> 219
[3360] <211> 356
[3361] <212> PRT
[3362] <213> Artificial Sequence
[3363] <220>
[3364] <223> PR001760 HC
[3365] <400> 219
[3366] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
[3367] 1 5 10 15
[3368] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
[3369] 20 25 30
[3370] Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
[3371] 35 40 45
[3372] Ser Ser Ile Ser Gly Ser Gly Val Ser Thr Tyr Tyr Ala Asp Ser Val
[3373] 50 55 60
[3374] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[3375] 65 70 75 80
[3376] Leu Gln Met Thr Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr Phe Cys
[3377] 85 90 95
[3378] Ala Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val Asp
[3379] 100 105 110
[3380] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser
[3381] 115 120 125
[3382] Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
[3383] 130 135 140
[3384] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
[3385] 145 150 155 160
[3386] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
[3387] 165 170 175
[3388] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
[3389] 180 185 190
[3390] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
[3391] 195 200 205
[3392] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn

[3393] 210 215 220
[3394] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
[3395] 225 230 235 240
[3396] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
[3397] 245 250 255
[3398] Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
[3399] 260 265 270
[3400] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[3401] 275 280 285
[3402] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
[3403] 290 295 300
[3404] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
[3405] 305 310 315 320
[3406] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
[3407] 325 330 335
[3408] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
[3409] 340 345 350
[3410] Ser Pro Gly Lys
[3411] 355
[3412] <210> 220
[3413] <211> 356
[3414] <212> PRT
[3415] <213> Artificial Sequence
[3416] <220>
[3417] <223> PR001763 HC
[3418] <400> 220
[3419] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[3420] 1 5 10 15
[3421] Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Ser Asn Tyr
[3422] 20 25 30
[3423] Ala Met Ser Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
[3424] 35 40 45
[3425] Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Phe Tyr Ala Asp Ser Val
[3426] 50 55 60
[3427] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[3428] 65 70 75 80
[3429] Leu Gln Met Asn Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[3430] 85 90 95
[3431] Ala Lys Glu Gly Ser Asn Gly Thr Asp Asp Tyr His Tyr Asp Ile Asp

[3432] 100 105 110
[3433] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser
[3434] 115 120 125
[3435] Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
[3436] 130 135 140
[3437] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
[3438] 145 150 155 160
[3439] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
[3440] 165 170 175
[3441] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
[3442] 180 185 190
[3443] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
[3444] 195 200 205
[3445] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
[3446] 210 215 220
[3447] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
[3448] 225 230 235 240
[3449] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
[3450] 245 250 255
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[3452] 260 265 270
[3453] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[3454] 275 280 285
[3455] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
[3456] 290 295 300
[3457] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
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[3459] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
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[3462] 340 345 350
[3463] Ser Pro Gly Lys
[3464] 355
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[3471] <400> 221

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[3474] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
[3475] 20 25 30
[3476] Ala Met Ser Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
[3477] 35 40 45
[3478] Ser Ala Ile Ser Gly Gly Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
[3479] 50 55 60
[3480] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[3481] 65 70 75 80
[3482] Leu Gln Met Asp Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[3483] 85 90 95
[3484] Ala Lys Glu Gly Thr Thr Glu Thr Asp Asp Tyr His Tyr Asn Met Asp
[3485] 100 105 110
[3486] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser
[3487] 115 120 125
[3488] Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
[3489] 130 135 140
[3490] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
[3491] 145 150 155 160
[3492] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
[3493] 165 170 175
[3494] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
[3495] 180 185 190
[3496] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
[3497] 195 200 205
[3498] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
[3499] 210 215 220
[3500] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
[3501] 225 230 235 240
[3502] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
[3503] 245 250 255
[3504] Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
[3505] 260 265 270
[3506] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[3507] 275 280 285
[3508] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
[3509] 290 295 300

[3510] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
[3511] 305 310 315 320
[3512] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
[3513] 325 330 335
[3514] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
[3515] 340 345 350
[3516] Ser Pro Gly Lys
[3517] 355
[3518] <210> 222
[3519] <211> 356
[3520] <212> PRT
[3521] <213> Artificial Sequence
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[3523] <223> PR001766 HC
[3524] <400> 222
[3525] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[3526] 1 5 10 15
[3527] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
[3528] 20 25 30
[3529] Ala Met Ser Trp Gly Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[3530] 35 40 45
[3531] Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
[3532] 50 55 60
[3533] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[3534] 65 70 75 80
[3535] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[3536] 85 90 95
[3537] Ala Lys Glu Lys Thr Gly Thr Thr Gly Asp Tyr Tyr Tyr Asp Met Asp
[3538] 100 105 110
[3539] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser
[3540] 115 120 125
[3541] Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
[3542] 130 135 140
[3543] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
[3544] 145 150 155 160
[3545] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
[3546] 165 170 175
[3547] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
[3548] 180 185 190

[3549] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
[3550] 195 200 205
[3551] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
[3552] 210 215 220
[3553] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
[3554] 225 230 235 240
[3555] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
[3556] 245 250 255
[3557] Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
[3558] 260 265 270
[3559] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[3560] 275 280 285
[3561] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
[3562] 290 295 300
[3563] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
[3564] 305 310 315 320
[3565] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
[3566] 325 330 335
[3567] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
[3568] 340 345 350
[3569] Ser Pro Gly Lys
[3570] 355
[3571] <210> 223
[3572] <211> 358
[3573] <212> PRT
[3574] <213> Artificial Sequence
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[3576] <223> PR001767 HC
[3577] <400> 223
[3578] Glu Val Gln Leu Val Glu Thr Gly Gly Gly Leu Ile Gln Pro Gly Gly
[3579] 1 5 10 15
[3580] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Val Ser Ser Asn
[3581] 20 25 30
[3582] Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[3583] 35 40 45
[3584] Ser Val Ile Tyr Ser Asp Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
[3585] 50 55 60
[3586] Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
[3587] 65 70 75 80

[3588] Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
[3589] 85 90 95
[3590] Arg Asp Arg Tyr Tyr Gly Ser Gly Asn Tyr Pro Thr Ala Tyr Tyr Gly
[3591] 100 105 110
[3592] Met Asp Val Arg Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro
[3593] 115 120 125
[3594] Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
[3595] 130 135 140
[3596] Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
[3597] 145 150 155 160
[3598] Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
[3599] 165 170 175
[3600] Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
[3601] 180 185 190
[3602] Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
[3603] 195 200 205
[3604] Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
[3605] 210 215 220
[3606] Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
[3607] 225 230 235 240
[3608] Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
[3609] 245 250 255
[3610] Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
[3611] 260 265 270
[3612] Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
[3613] 275 280 285
[3614] Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
[3615] 290 295 300
[3616] Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
[3617] 305 310 315 320
[3618] Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
[3619] 325 330 335
[3620] Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
[3621] 340 345 350
[3622] Ser Leu Ser Pro Gly Lys
[3623] 355
[3624] <210> 224
[3625] <211> 356
[3626] <212> PRT

[3627] <213> Artificial Sequence
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[3629] <223> PR001768 HC
[3630] <400> 224
[3631] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[3632] 1 5 10 15
[3633] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
[3634] 20 25 30
[3635] Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[3636] 35 40 45
[3637] Ser Ser Ile Ser Gly Ser Gly Asp Ser Thr Tyr Tyr Ala Asp Ser Val
[3638] 50 55 60
[3639] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[3640] 65 70 75 80
[3641] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[3642] 85 90 95
[3643] Ala Lys Glu Gly Thr Gly Thr Thr Ser Asp Tyr Tyr Tyr Asn Val Asp
[3644] 100 105 110
[3645] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser
[3646] 115 120 125
[3647] Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
[3648] 130 135 140
[3649] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
[3650] 145 150 155 160
[3651] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
[3652] 165 170 175
[3653] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
[3654] 180 185 190
[3655] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
[3656] 195 200 205
[3657] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
[3658] 210 215 220
[3659] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
[3660] 225 230 235 240
[3661] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
[3662] 245 250 255
[3663] Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
[3664] 260 265 270
[3665] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val

[3666] 275 280 285
[3667] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
[3668] 290 295 300
[3669] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
[3670] 305 310 315 320
[3671] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
[3672] 325 330 335
[3673] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
[3674] 340 345 350
[3675] Ser Pro Gly Lys
[3676] 355
[3677] <210> 225
[3678] <211> 356
[3679] <212> PRT
[3680] <213> Artificial Sequence
[3681] <220>
[3682] <223> PR001771 HC
[3683] <400> 225
[3684] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[3685] 1 5 10 15
[3686] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
[3687] 20 25 30
[3688] Ala Met Thr Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Val
[3689] 35 40 45
[3690] Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
[3691] 50 55 60
[3692] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[3693] 65 70 75 80
[3694] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[3695] 85 90 95
[3696] Ala Lys Glu Gly Thr Gly Thr Thr Ser Asp Tyr Tyr Tyr Asn Val Asp
[3697] 100 105 110
[3698] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser
[3699] 115 120 125
[3700] Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
[3701] 130 135 140
[3702] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
[3703] 145 150 155 160
[3704] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser

[3705] 165 170 175
[3706] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
[3707] 180 185 190
[3708] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
[3709] 195 200 205
[3710] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
[3711] 210 215 220
[3712] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
[3713] 225 230 235 240
[3714] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
[3715] 245 250 255
[3716] Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
[3717] 260 265 270
[3718] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[3719] 275 280 285
[3720] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
[3721] 290 295 300
[3722] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
[3723] 305 310 315 320
[3724] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
[3725] 325 330 335
[3726] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
[3727] 340 345 350
[3728] Ser Pro Gly Lys
[3729] 355
[3730] <210> 226
[3731] <211> 356
[3732] <212> PRT
[3733] <213> Artificial Sequence
[3734] <220>
[3735] <223> PR001774 HC
[3736] <400> 226
[3737] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[3738] 1 5 10 15
[3739] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
[3740] 20 25 30
[3741] Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
[3742] 35 40 45
[3743] Ser Thr Ile Ser Gly Ser Gly Asp Thr Thr Tyr Tyr Ala Asp Ser Val

[3744] 50 55 60

[3745] Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ser Lys Asn Thr Leu Tyr

[3746] 65 70 75 80

[3747] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Ser Ala Val Tyr Phe Cys

[3748] 85 90 95

[3749] Ala Lys Glu Ala Thr Ala Met Ala Ser Asp Tyr Tyr Tyr Gly Val Asp

[3750] 100 105 110

[3751] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser

[3752] 115 120 125

[3753] Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu

[3754] 130 135 140

[3755] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu

[3756] 145 150 155 160

[3757] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser

[3758] 165 170 175

[3759] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu

[3760] 180 185 190

[3761] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr

[3762] 195 200 205

[3763] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn

[3764] 210 215 220

[3765] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro

[3766] 225 230 235 240

[3767] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln

[3768] 245 250 255

[3769] Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val

[3770] 260 265 270

[3771] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val

[3772] 275 280 285

[3773] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro

[3774] 290 295 300

[3775] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr

[3776] 305 310 315 320

[3777] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val

[3778] 325 330 335

[3779] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu

[3780] 340 345 350

[3781] Ser Pro Gly Lys

[3782] 355

[3783] <210> 227
[3784] <211> 355
[3785] <212> PRT
[3786] <213> Artificial Sequence
[3787] <220>
[3788] <223> PR001775 HC
[3789] <400> 227
[3790] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Ser Gly Gly
[3791] 1 5 10 15
[3792] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
[3793] 20 25 30
[3794] Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[3795] 35 40 45
[3796] Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Asp Tyr Ala Asp Ser Val
[3797] 50 55 60
[3798] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Thr Asn Thr Leu Tyr
[3799] 65 70 75 80
[3800] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[3801] 85 90 95
[3802] Ala Lys Glu Arg Ala Tyr Asp Tyr Ser Asn Tyr Val Asp Phe Asp Tyr
[3803] 100 105 110
[3804] Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Glu Pro Lys Ser Cys
[3805] 115 120 125
[3806] Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
[3807] 130 135 140
[3808] Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
[3809] 145 150 155 160
[3810] Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
[3811] 165 170 175
[3812] Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
[3813] 180 185 190
[3814] His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
[3815] 195 200 205
[3816] Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
[3817] 210 215 220
[3818] Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
[3819] 225 230 235 240
[3820] Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
[3821] 245 250 255

[3822] Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
[3823] 260 265 270
[3824] Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
[3825] 275 280 285
[3826] Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
[3827] 290 295 300
[3828] Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
[3829] 305 310 315 320
[3830] Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
[3831] 325 330 335
[3832] His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
[3833] 340 345 350
[3834] Pro Gly Lys
[3835] 355
[3836] <210> 228
[3837] <211> 357
[3838] <212> PRT
[3839] <213> Artificial Sequence
[3840] <220>
[3841] <223> PR001776 HC
[3842] <400> 228
[3843] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[3844] 1 5 10 15
[3845] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
[3846] 20 25 30
[3847] Ala Met Ser Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
[3848] 35 40 45
[3849] Ser Ala Ile Ser Ser Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
[3850] 50 55 60
[3851] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[3852] 65 70 75 80
[3853] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[3854] 85 90 95
[3855] Ala Lys Asp Gly Val Thr Thr Pro Ser Tyr Tyr Tyr Tyr Tyr Asp Met
[3856] 100 105 110
[3857] Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys
[3858] 115 120 125
[3859] Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
[3860] 130 135 140

[3861] Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
[3862] 145 150 155 160
[3863] Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
[3864] 165 170 175
[3865] Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
[3866] 180 185 190
[3867] Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
[3868] 195 200 205
[3869] Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
[3870] 210 215 220
[3871] Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
[3872] 225 230 235 240
[3873] Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
[3874] 245 250 255
[3875] Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
[3876] 260 265 270
[3877] Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
[3878] 275 280 285
[3879] Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
[3880] 290 295 300
[3881] Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
[3882] 305 310 315 320
[3883] Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
[3884] 325 330 335
[3885] Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
[3886] 340 345 350
[3887] Leu Ser Pro Gly Lys
[3888] 355
[3889] <210> 229
[3890] <211> 356
[3891] <212> PRT
[3892] <213> Artificial Sequence
[3893] <220>
[3894] <223> PR001780 HC
[3895] <400> 229
[3896] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
[3897] 1 5 10 15
[3898] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
[3899] 20 25 30

[3900] Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[3901] 35 40 45
[3902] Ser Thr Ile Ser Gly Ser Gly Asp Asn Thr Tyr Tyr Ala Asp Ser Val
[3903] 50 55 60
[3904] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[3905] 65 70 75 80
[3906] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
[3907] 85 90 95
[3908] Ala Lys Glu Asp Thr Ala Val Ala Ser Asp Tyr Tyr Tyr Asn Ile Asp
[3909] 100 105 110
[3910] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser
[3911] 115 120 125
[3912] Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
[3913] 130 135 140
[3914] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
[3915] 145 150 155 160
[3916] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
[3917] 165 170 175
[3918] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
[3919] 180 185 190
[3920] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
[3921] 195 200 205
[3922] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
[3923] 210 215 220
[3924] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
[3925] 225 230 235 240
[3926] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
[3927] 245 250 255
[3928] Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
[3929] 260 265 270
[3930] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[3931] 275 280 285
[3932] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
[3933] 290 295 300
[3934] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
[3935] 305 310 315 320
[3936] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
[3937] 325 330 335
[3938] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu

[3939] 340 345 350

[3940] Ser Pro Gly Lys

[3941] 355

[3942] <210> 230

[3943] <211> 356

[3944] <212> PRT

[3945] <213> Artificial Sequence

[3946] <220>

[3947] <223> PR001781 HC

[3948] <400> 230

[3949] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Leu Gly Gly

[3950] 1 5 10 15

[3951] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr

[3952] 20 25 30

[3953] Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val

[3954] 35 40 45

[3955] Ser Ser Ile Ser Gly Ser Gly Gly Asn Thr Tyr Tyr Ala Asp Ser Val

[3956] 50 55 60

[3957] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

[3958] 65 70 75 80

[3959] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

[3960] 85 90 95

[3961] Ala Lys Glu Arg Thr Gly Thr Thr Gly Asp Tyr Tyr Tyr Asn Val Asp

[3962] 100 105 110

[3963] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser

[3964] 115 120 125

[3965] Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu

[3966] 130 135 140

[3967] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu

[3968] 145 150 155 160

[3969] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser

[3970] 165 170 175

[3971] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu

[3972] 180 185 190

[3973] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr

[3974] 195 200 205

[3975] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn

[3976] 210 215 220

[3977] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro

[3978] 225 230 235 240
[3979] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
[3980] 245 250 255
[3981] Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
[3982] 260 265 270
[3983] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[3984] 275 280 285
[3985] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
[3986] 290 295 300
[3987] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
[3988] 305 310 315 320
[3989] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
[3990] 325 330 335
[3991] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
[3992] 340 345 350
[3993] Ser Pro Gly Lys
[3994] 355
[3995] <210> 231
[3996] <211> 356
[3997] <212> PRT
[3998] <213> Artificial Sequence
[3999] <220>
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[4001] <400> 231
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[4003] 1 5 10 15
[4004] Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Ser Asn Tyr
[4005] 20 25 30
[4006] Ala Met Ser Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
[4007] 35 40 45
[4008] Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Phe Tyr Ala Asp Ser Val
[4009] 50 55 60
[4010] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[4011] 65 70 75 80
[4012] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
[4013] 85 90 95
[4014] Ala Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val Asp
[4015] 100 105 110
[4016] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser

[4017] 115 120 125
[4018] Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
[4019] 130 135 140
[4020] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
[4021] 145 150 155 160
[4022] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
[4023] 165 170 175
[4024] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
[4025] 180 185 190
[4026] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
[4027] 195 200 205
[4028] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
[4029] 210 215 220
[4030] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
[4031] 225 230 235 240
[4032] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
[4033] 245 250 255
[4034] Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
[4035] 260 265 270
[4036] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[4037] 275 280 285
[4038] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
[4039] 290 295 300
[4040] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
[4041] 305 310 315 320
[4042] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
[4043] 325 330 335
[4044] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
[4045] 340 345 350
[4046] Ser Pro Gly Lys
[4047] 355
[4048] <210> 232
[4049] <211> 356
[4050] <212> PRT
[4051] <213> Artificial Sequence
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[4053] <223> PR001831 HC
[4054] <400> 232
[4055] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Ile Gln Pro Gly Gly

[4056] 1 5 10 15
[4057] Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Thr Phe Ser Ser Tyr
[4058] 20 25 30
[4059] Ala Met Ser Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
[4060] 35 40 45
[4061] Ser Ser Ile Ser Gly Ser Gly Asp Ser Thr Tyr Tyr Ala Asp Ser Val
[4062] 50 55 60
[4063] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[4064] 65 70 75 80
[4065] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Gly Tyr His Cys
[4066] 85 90 95
[4067] Ala Lys Glu Gly Ser Asn Gly Thr Asp Asp Tyr His Tyr Asp Ile Asp
[4068] 100 105 110
[4069] Val Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Glu Pro Lys Ser
[4070] 115 120 125
[4071] Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
[4072] 130 135 140
[4073] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
[4074] 145 150 155 160
[4075] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
[4076] 165 170 175
[4077] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
[4078] 180 185 190
[4079] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
[4080] 195 200 205
[4081] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
[4082] 210 215 220
[4083] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
[4084] 225 230 235 240
[4085] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
[4086] 245 250 255
[4087] Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
[4088] 260 265 270
[4089] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[4090] 275 280 285
[4091] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
[4092] 290 295 300
[4093] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
[4094] 305 310 315 320

[4095] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
[4096] 325 330 335
[4097] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
[4098] 340 345 350
[4099] Ser Pro Gly Lys
[4100] 355
[4101] <210> 233
[4102] <211> 356
[4103] <212> PRT
[4104] <213> Artificial Sequence
[4105] <220>
[4106] <223> PR001833 HC
[4107] <400> 233
[4108] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[4109] 1 5 10 15
[4110] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
[4111] 20 25 30
[4112] Ala Met Ser Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
[4113] 35 40 45
[4114] Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Phe Tyr Ala Asp Ser Val
[4115] 50 55 60
[4116] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[4117] 65 70 75 80
[4118] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Phe Cys
[4119] 85 90 95
[4120] Ala Lys Glu Gly Ala Thr Glu Thr Asp Asp Tyr His Phe Asn Thr Asp
[4121] 100 105 110
[4122] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser
[4123] 115 120 125
[4124] Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
[4125] 130 135 140
[4126] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
[4127] 145 150 155 160
[4128] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
[4129] 165 170 175
[4130] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
[4131] 180 185 190
[4132] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
[4133] 195 200 205

[4134] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
[4135] 210 215 220
[4136] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
[4137] 225 230 235 240
[4138] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
[4139] 245 250 255
[4140] Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
[4141] 260 265 270
[4142] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[4143] 275 280 285
[4144] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
[4145] 290 295 300
[4146] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
[4147] 305 310 315 320
[4148] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
[4149] 325 330 335
[4150] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
[4151] 340 345 350
[4152] Ser Pro Gly Lys
[4153] 355
[4154] <210> 234
[4155] <211> 356
[4156] <212> PRT
[4157] <213> Artificial Sequence
[4158] <220>
[4159] <223> PR001834 HC
[4160] <400> 234
[4161] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[4162] 1 5 10 15
[4163] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Gly Tyr
[4164] 20 25 30
[4165] Ala Met Thr Trp Val Arg Gln Pro Pro Glu Lys Gly Leu Glu Trp Val
[4166] 35 40 45
[4167] Ser Ser Ile Ser Gly Ser Gly Asn Asn Thr Phe Tyr Ala Asp Ser Val
[4168] 50 55 60
[4169] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[4170] 65 70 75 80
[4171] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[4172] 85 90 95

[4173] Ala Lys Glu Gly Thr Thr Glu Thr Asp Asp Tyr His Tyr Asn Met Asp
[4174] 100 105 110
[4175] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser
[4176] 115 120 125
[4177] Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
[4178] 130 135 140
[4179] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
[4180] 145 150 155 160
[4181] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
[4182] 165 170 175
[4183] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
[4184] 180 185 190
[4185] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
[4186] 195 200 205
[4187] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
[4188] 210 215 220
[4189] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
[4190] 225 230 235 240
[4191] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
[4192] 245 250 255
[4193] Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
[4194] 260 265 270
[4195] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[4196] 275 280 285
[4197] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
[4198] 290 295 300
[4199] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
[4200] 305 310 315 320
[4201] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
[4202] 325 330 335
[4203] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
[4204] 340 345 350
[4205] Ser Pro Gly Lys
[4206] 355
[4207] <210> 235
[4208] <211> 356
[4209] <212> PRT
[4210] <213> Artificial Sequence
[4211] <220>

[4212] <223> PR001836 HC

[4213] <400> 235

[4214] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[4215] 1 5 10 15
[4216] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Ser Asn Phe
[4217] 20 25 30
[4218] Ala Met Thr Trp Val Arg Gln Pro Pro Glu Lys Gly Leu Lys Trp Val
[4219] 35 40 45
[4220] Ser Ser Ile Asn Gly Ser Gly Phe Asn Thr Tyr Tyr Thr Asp Ser Val
[4221] 50 55 60
[4222] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr
[4223] 65 70 75 80
[4224] Leu Gln Met Asn Arg Leu Thr Ala Glu Asp Thr Ala Val Tyr Phe Cys
[4225] 85 90 95
[4226] Ala Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val Asp
[4227] 100 105 110
[4228] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser
[4229] 115 120 125
[4230] Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
[4231] 130 135 140
[4232] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
[4233] 145 150 155 160
[4234] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
[4235] 165 170 175
[4236] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
[4237] 180 185 190
[4238] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
[4239] 195 200 205
[4240] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
[4241] 210 215 220
[4242] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
[4243] 225 230 235 240
[4244] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
[4245] 245 250 255
[4246] Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
[4247] 260 265 270
[4248] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[4249] 275 280 285
[4250] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro

[4251] 290 295 300
[4252] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
[4253] 305 310 315 320
[4254] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
[4255] 325 330 335
[4256] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
[4257] 340 345 350
[4258] Ser Pro Gly Lys
[4259] 355
[4260] <210> 236
[4261] <211> 356
[4262] <212> PRT
[4263] <213> Artificial Sequence
[4264] <220>
[4265] <223> PR001837 HC
[4266] <400> 236
[4267] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[4268] 1 5 10 15
[4269] Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Thr Phe Ser Ser Tyr
[4270] 20 25 30
[4271] Ala Met Ser Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
[4272] 35 40 45
[4273] Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Phe Tyr Ala Asp Ser Val
[4274] 50 55 60
[4275] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[4276] 65 70 75 80
[4277] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[4278] 85 90 95
[4279] Ala Lys Glu Gly Thr Thr Glu Thr Asp Asp Tyr His Tyr Asn Met Asp
[4280] 100 105 110
[4281] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser
[4282] 115 120 125
[4283] Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
[4284] 130 135 140
[4285] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
[4286] 145 150 155 160
[4287] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
[4288] 165 170 175
[4289] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu

[4290] 180 185 190
[4291] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
[4292] 195 200 205
[4293] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
[4294] 210 215 220
[4295] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
[4296] 225 230 235 240
[4297] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
[4298] 245 250 255
[4299] Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
[4300] 260 265 270
[4301] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[4302] 275 280 285
[4303] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
[4304] 290 295 300
[4305] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
[4306] 305 310 315 320
[4307] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
[4308] 325 330 335
[4309] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
[4310] 340 345 350
[4311] Ser Pro Gly Lys
[4312] 355
[4313] <210> 237
[4314] <211> 356
[4315] <212> PRT
[4316] <213> Artificial Sequence
[4317] <220>
[4318] <223> PR001838 HC
[4319] <400> 237
[4320] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[4321] 1 5 10 15
[4322] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
[4323] 20 25 30
[4324] Ala Met Ser Trp Phe Arg Gln Pro Pro Glu Thr Gly Leu Lys Trp Val
[4325] 35 40 45
[4326] Ser Ser Ile Asp Gly Ser Gly Gly Asp Thr Tyr Tyr Ala Asp Ser Val
[4327] 50 55 60
[4328] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

[4329] 65 70 75 80
[4330] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[4331] 85 90 95
[4332] Ala Lys Glu Gly Ser His Gly Thr Asp Asp Ser His Tyr Asp Val Asp
[4333] 100 105 110
[4334] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser
[4335] 115 120 125
[4336] Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
[4337] 130 135 140
[4338] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
[4339] 145 150 155 160
[4340] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
[4341] 165 170 175
[4342] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
[4343] 180 185 190
[4344] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
[4345] 195 200 205
[4346] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
[4347] 210 215 220
[4348] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
[4349] 225 230 235 240
[4350] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
[4351] 245 250 255
[4352] Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
[4353] 260 265 270
[4354] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[4355] 275 280 285
[4356] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
[4357] 290 295 300
[4358] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
[4359] 305 310 315 320
[4360] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
[4361] 325 330 335
[4362] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
[4363] 340 345 350
[4364] Ser Pro Gly Lys
[4365] 355
[4366] <210> 238
[4367] <211> 355

[4368] <212> PRT

[4369] <213> Artificial Sequence

[4370] <220>

[4371] <223> PR001840 HC

[4372] <400> 238

[4373] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

[4374] 1 5 10 15

[4375] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr

[4376] 20 25 30

[4377] Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Val Trp Val

[4378] 35 40 45

[4379] Ser Arg Ile Asn Ser Asp Gly Ser Ser Thr Ser Tyr Ala Asp Ser Val

[4380] 50 55 60

[4381] Gln Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr

[4382] 65 70 75 80

[4383] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

[4384] 85 90 95

[4385] Val Arg Lys Gly Ser Ser Ser Tyr Tyr His Tyr Ser Ile Glu Asp Asp

[4386] 100 105 110

[4387] Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Glu Pro Lys Ser Cys

[4388] 115 120 125

[4389] Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly

[4390] 130 135 140

[4391] Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met

[4392] 145 150 155 160

[4393] Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His

[4394] 165 170 175

[4395] Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val

[4396] 180 185 190

[4397] His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr

[4398] 195 200 205

[4399] Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly

[4400] 210 215 220

[4401] Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile

[4402] 225 230 235 240

[4403] Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val

[4404] 245 250 255

[4405] Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser

[4406] 260 265 270

[4407] Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
[4408] 275 280 285
[4409] Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
[4410] 290 295 300
[4411] Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
[4412] 305 310 315 320
[4413] Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
[4414] 325 330 335
[4415] His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
[4416] 340 345 350
[4417] Pro Gly Lys
[4418] 355
[4419] <210> 239
[4420] <211> 356
[4421] <212> PRT
[4422] <213> Artificial Sequence
[4423] <220>
[4424] <223> PR001842 HC
[4425] <400> 239
[4426] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[4427] 1 5 10 15
[4428] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
[4429] 20 25 30
[4430] Ala Met Ser Trp Gly Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[4431] 35 40 45
[4432] Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
[4433] 50 55 60
[4434] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[4435] 65 70 75 80
[4436] Leu His Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[4437] 85 90 95
[4438] Ala Lys Glu Lys Val Ala Thr Thr Gly Asp Tyr Tyr Tyr Asp Met Asp
[4439] 100 105 110
[4440] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser
[4441] 115 120 125
[4442] Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
[4443] 130 135 140
[4444] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
[4445] 145 150 155 160

[4446] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
[4447] 165 170 175
[4448] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
[4449] 180 185 190
[4450] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
[4451] 195 200 205
[4452] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
[4453] 210 215 220
[4454] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
[4455] 225 230 235 240
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[4457] 245 250 255
[4458] Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
[4459] 260 265 270
[4460] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[4461] 275 280 285
[4462] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
[4463] 290 295 300
[4464] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
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[4466] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
[4467] 325 330 335
[4468] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
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[4470] Ser Pro Gly Lys
[4471] 355
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[4481] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
[4482] 20 25 30
[4483] Ala Met Ser Trp Phe Arg Gln Pro Pro Glu Thr Gly Leu Lys Trp Val
[4484] 35 40 45

[4485] Ser Ser Ile Asp Ala Ser Gly Gly Asp Thr Tyr Tyr Ala Asp Ser Val
[4486] 50 55 60
[4487] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[4488] 65 70 75 80
[4489] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[4490] 85 90 95
[4491] Ala Lys Glu Gly Ser His Gly Thr Asp Asp Ser His Tyr Asp Val Asp
[4492] 100 105 110
[4493] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser
[4494] 115 120 125
[4495] Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
[4496] 130 135 140
[4497] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
[4498] 145 150 155 160
[4499] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
[4500] 165 170 175
[4501] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
[4502] 180 185 190
[4503] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
[4504] 195 200 205
[4505] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
[4506] 210 215 220
[4507] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
[4508] 225 230 235 240
[4509] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
[4510] 245 250 255
[4511] Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
[4512] 260 265 270
[4513] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[4514] 275 280 285
[4515] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
[4516] 290 295 300
[4517] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
[4518] 305 310 315 320
[4519] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
[4520] 325 330 335
[4521] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
[4522] 340 345 350
[4523] Ser Pro Gly Lys

[4524] 355

[4525] <210> 241

[4526] <211> 214

[4527] <212> PRT

[4528] <213> Artificial Sequence

[4529] <220>

[4530] <223> PR000151 LC

[4531] <400> 241

[4532] Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly

[4533] 1 5 10 15

[4534] Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala

[4535] 20 25 30

[4536] Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile

[4537] 35 40 45

[4538] Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly

[4539] 50 55 60

[4540] Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro

[4541] 65 70 75 80

[4542] Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Leu Tyr His Pro Ala

[4543] 85 90 95

[4544] Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala

[4545] 100 105 110

[4546] Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly

[4547] 115 120 125

[4548] Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala

[4549] 130 135 140

[4550] Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln

[4551] 145 150 155 160

[4552] Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser

[4553] 165 170 175

[4554] Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr

[4555] 180 185 190

[4556] Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser

[4557] 195 200 205

[4558] Phe Asn Arg Gly Glu Cys

[4559] 210

[4560] <210> 242

[4561] <211> 219

[4562] <212> PRT

[4563] <213> Artificial Sequence
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[4565] <223> PR000196 LC
[4566] <400> 242
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[4568] 1 5 10 15
[4569] Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
[4570] 20 25 30
[4571] Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
[4572] 35 40 45
[4573] Pro Gln Leu Leu Ile Phe Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
[4574] 50 55 60
[4575] Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
[4576] 65 70 75 80
[4577] Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
[4578] 85 90 95
[4579] Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
[4580] 100 105 110
[4581] Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
[4582] 115 120 125
[4583] Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
[4584] 130 135 140
[4585] Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
[4586] 145 150 155 160
[4587] Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
[4588] 165 170 175
[4589] Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
[4590] 180 185 190
[4591] Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
[4592] 195 200 205
[4593] Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
[4594] 210 215
[4595] <210> 243
[4596] <211> 214
[4597] <212> PRT
[4598] <213> Artificial Sequence
[4599] <220>
[4600] <223> PR000197 LC
[4601] <400> 243

[4602] Glu Phe Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
[4603] 1 5 10 15
[4604] Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Ile
[4605] 20 25 30
[4606] Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
[4607] 35 40 45
[4608] Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
[4609] 50 55 60
[4610] Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
[4611] 65 70 75 80
[4612] Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Asn Trp Pro Leu
[4613] 85 90 95
[4614] Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
[4615] 100 105 110
[4616] Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
[4617] 115 120 125
[4618] Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
[4619] 130 135 140
[4620] Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
[4621] 145 150 155 160
[4622] Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
[4623] 165 170 175
[4624] Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
[4625] 180 185 190
[4626] Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
[4627] 195 200 205
[4628] Phe Asn Arg Gly Glu Cys
[4629] 210
[4630] <210> 244
[4631] <211> 214
[4632] <212> PRT
[4633] <213> Artificial Sequence
[4634] <220>
[4635] <223> PR000210 LC, PR001212链, PR002811链, PR002812链, PR002813
[4636] <400> 244
[4637] Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
[4638] 1 5 10 15
[4639] Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
[4640] 20 25 30

[4641] Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
[4642] 35 40 45
[4643] Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
[4644] 50 55 60
[4645] Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
[4646] 65 70 75 80
[4647] Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
[4648] 85 90 95
[4649] Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
[4650] 100 105 110
[4651] Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
[4652] 115 120 125
[4653] Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
[4654] 130 135 140
[4655] Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
[4656] 145 150 155 160
[4657] Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
[4658] 165 170 175
[4659] Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
[4660] 180 185 190
[4661] Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
[4662] 195 200 205
[4663] Phe Asn Arg Gly Glu Cys
[4664] 210
[4665] <210> 245
[4666] <211> 214
[4667] <212> PRT
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[4669] <220>
[4670] <223> PR000265 LC, PR003549链, PR003550链, PR003551链, PR004268
[4671] <400> 245
[4672] Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
[4673] 1 5 10 15
[4674] Asp Arg Val Thr Val Thr Cys Arg Ala Ser Gln Ser Ile Tyr Ile Trp
[4675] 20 25 30
[4676] Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile
[4677] 35 40 45
[4678] Tyr Lys Ala Ser Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
[4679] 50 55 60

[4680] Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
[4681] 65 70 75 80
[4682] Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Gly Ser Ser Arg
[4683] 85 90 95
[4684] Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
[4685] 100 105 110
[4686] Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
[4687] 115 120 125
[4688] Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
[4689] 130 135 140
[4690] Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
[4691] 145 150 155 160
[4692] Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
[4693] 165 170 175
[4694] Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
[4695] 180 185 190
[4696] Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
[4697] 195 200 205
[4698] Phe Asn Arg Gly Glu Cys
[4699] 210
[4700] <210> 246
[4701] <211> 214
[4702] <212> PRT
[4703] <213> Artificial Sequence
[4704] <220>
[4705] <223> PR000447 LC, PR000448 LC, PR000701链, PR000980 LC, PR003052链
[4706] <400> 246
[4707] Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
[4708] 1 5 10 15
[4709] Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Ile
[4710] 20 25 30
[4711] Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
[4712] 35 40 45
[4713] Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
[4714] 50 55 60
[4715] Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
[4716] 65 70 75 80
[4717] Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Asn Trp Pro Leu
[4718] 85 90 95

[4719] Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
[4720] 100 105 110
[4721] Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
[4722] 115 120 125
[4723] Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
[4724] 130 135 140
[4725] Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
[4726] 145 150 155 160
[4727] Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
[4728] 165 170 175
[4729] Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
[4730] 180 185 190
[4731] Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
[4732] 195 200 205
[4733] Phe Asn Arg Gly Glu Cys
[4734] 210
[4735] <210> 247
[4736] <211> 214
[4737] <212> PRT
[4738] <213> Artificial Sequence
[4739] <220>
[4740] <223> PR000483 LC
[4741] <400> 247
[4742] Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly Gln
[4743] 1 5 10 15
[4744] Thr Ala Ser Ile Thr Cys Ser Gly Asp Asn Ile Gly Asp Gln Tyr Ala
[4745] 20 25 30
[4746] His Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
[4747] 35 40 45
[4748] Gln Asp Lys Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
[4749] 50 55 60
[4750] Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
[4751] 65 70 75 80
[4752] Asp Glu Ala Asp Tyr Tyr Cys Ala Thr Tyr Thr Gly Phe Gly Ser Leu
[4753] 85 90 95
[4754] Ala Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
[4755] 100 105 110
[4756] Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
[4757] 115 120 125

[4758] Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
[4759] 130 135 140
[4760] Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
[4761] 145 150 155 160
[4762] Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
[4763] 165 170 175
[4764] Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
[4765] 180 185 190
[4766] Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
[4767] 195 200 205
[4768] Ala Pro Thr Glu Cys Ser
[4769] 210
[4770] <210> 248
[4771] <211> 216
[4772] <212> PRT
[4773] <213> Artificial Sequence
[4774] <220>
[4775] <223> PR000628 LC
[4776] <400> 248
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[4778] 1 5 10 15
[4779] Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
[4780] 20 25 30
[4781] Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
[4782] 35 40 45
[4783] Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
[4784] 50 55 60
[4785] Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
[4786] 65 70 75 80
[4787] Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
[4788] 85 90 95
[4789] Ala Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val
[4790] 100 105 110
[4791] Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys
[4792] 115 120 125
[4793] Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
[4794] 130 135 140
[4795] Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
[4796] 145 150 155 160

[4797] Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser
[4798] 165 170 175
[4799] Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys
[4800] 180 185 190
[4801] Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
[4802] 195 200 205
[4803] Lys Ser Phe Asn Arg Gly Glu Cys
[4804] 210 215
[4805] <210> 249
[4806] <211> 222
[4807] <212> PRT
[4808] <213> Artificial Sequence
[4809] <220>
[4810] <223> PR000701链, PR004270链
[4811] <400> 249
[4812] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[4813] 1 5 10 15
[4814] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
[4815] 20 25 30
[4816] Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[4817] 35 40 45
[4818] Ala Asn Ile Lys Gln Glu Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
[4819] 50 55 60
[4820] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[4821] 65 70 75 80
[4822] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[4823] 85 90 95
[4824] Ala Arg Asp Arg Ala Val Ala Gly Ala Phe Asp Ile Trp Gly Gln Gly
[4825] 100 105 110
[4826] Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
[4827] 115 120 125
[4828] Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
[4829] 130 135 140
[4830] Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
[4831] 145 150 155 160
[4832] Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
[4833] 165 170 175
[4834] Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
[4835] 180 185 190

[4836] Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
[4837] 195 200 205
[4838] Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
[4839] 210 215 220
[4840] <210> 250
[4841] <211> 656
[4842] <212> PRT
[4843] <213> Artificial Sequence
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[4845] <223> PR000701链
[4846] <400> 250
[4847] Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
[4848] 1 5 10 15
[4849] Asp Arg Val Thr Val Thr Cys Arg Ala Ser Gln Ser Ile Tyr Ile Trp
[4850] 20 25 30
[4851] Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile
[4852] 35 40 45
[4853] Tyr Lys Ala Ser Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
[4854] 50 55 60
[4855] Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
[4856] 65 70 75 80
[4857] Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Gly Ser Ser Arg
[4858] 85 90 95
[4859] Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
[4860] 100 105 110
[4861] Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
[4862] 115 120 125
[4863] Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
[4864] 130 135 140
[4865] Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
[4866] 145 150 155 160
[4867] Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
[4868] 165 170 175
[4869] Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
[4870] 180 185 190
[4871] Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
[4872] 195 200 205
[4873] Phe Asn Arg Gly Glu Cys Gln Val Gln Leu Gln Gln Trp Gly Ala Gly
[4874] 210 215 220

[4875] Leu Leu Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly
[4876] 225 230 235 240
[4877] Gly Ser Phe Ser Gly Tyr Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly
[4878] 245 250 255
[4879] Lys Gly Leu Glu Trp Ile Gly Glu Ile Asn His Ser Gly Ser Thr Asp
[4880] 260 265 270
[4881] Ser Asn Pro Ser Leu Lys Gly Arg Val Thr Phe Ser Val Asp Thr Ser
[4882] 275 280 285
[4883] Lys Asn Gln Phe Ser Leu Lys Leu Asn Ser Val Thr Ala Ala Asp Thr
[4884] 290 295 300
[4885] Ala Val Tyr Tyr Cys Ala Arg Leu Thr Gly Pro Phe Asp Tyr Trp Gly
[4886] 305 310 315 320
[4887] Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
[4888] 325 330 335
[4889] Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
[4890] 340 345 350
[4891] Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
[4892] 355 360 365
[4893] Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
[4894] 370 375 380
[4895] Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
[4896] 385 390 395 400
[4897] Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His
[4898] 405 410 415
[4899] Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly
[4900] 420 425 430
[4901] Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser
[4902] 435 440 445
[4903] Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
[4904] 450 455 460
[4905] Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro
[4906] 465 470 475 480
[4907] Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
[4908] 485 490 495
[4909] Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val
[4910] 500 505 510
[4911] Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
[4912] 515 520 525
[4913] Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr

[4914] 530 535 540
[4915] Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
[4916] 545 550 555 560
[4917] Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
[4918] 565 570 575
[4919] Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
[4920] 580 585 590
[4921] Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
[4922] 595 600 605
[4923] Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser
[4924] 610 615 620
[4925] Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
[4926] 625 630 635 640
[4927] Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
[4928] 645 650 655
[4929] <210> 251
[4930] <211> 705
[4931] <212> PRT
[4932] <213> Artificial Sequence
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[4934] <223> PR001212链
[4935] <400> 251
[4936] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[4937] 1 5 10 15
[4938] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
[4939] 20 25 30
[4940] Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[4941] 35 40 45
[4942] Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
[4943] 50 55 60
[4944] Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
[4945] 65 70 75 80
[4946] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[4947] 85 90 95
[4948] Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
[4949] 100 105 110
[4950] Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
[4951] 115 120 125
[4952] Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala

[4953] 130 135 140
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[5020] Ile Ser Ser Leu Gln Ser Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln
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[5022] Tyr Tyr Asn Trp Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
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[5048] 115 120 125

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[5051] Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser

[5052] 145 150 155 160

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[5054] 165 170 175

[5055] Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro

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[5061] Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly

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[5065] Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu

[5066] 260 265 270

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[5068] 275 280 285

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[5084] 405 410 415
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[5095] Gly Tyr Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
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[5097] Trp Ile Gly Glu Ile Gln His Ser Gly Ser Thr Asp Ser Asn Pro Ser
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[5103] Cys Ala Arg Leu Thr Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu
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[5106] 580 585 590
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[5115] Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser
[5116] 660 665 670
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[5136] Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
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[5146] Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
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[5148] Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
[5149] 165 170 175
[5150] Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
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[5153] 195 200 205
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[5156] Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
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[5161] 260 265 270
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[5163] 275 280 285
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[5175] 370 375 380
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[5184] Gly Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro
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[5186] Arg Thr Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Leu

[5187] 465 470 475 480
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[5189] 485 490 495
[5190] Arg Tyr Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu
[5191] 500 505 510
[5192] Trp Val Ser Ser Ile Ser Gly Ser Gly Asp Asp Thr Tyr Tyr Gly Asp
[5193] 515 520 525
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[5196] Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
[5197] 545 550 555 560
[5198] Phe Cys Ala Lys Glu Lys Ala Gly Thr Thr Gly Asp Tyr Tyr Tyr Asn
[5199] 565 570 575
[5200] Val Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
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[5215] Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
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[5217] Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
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[5226] 130 135 140
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[5229] Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
[5230] 165 170 175
[5231] Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
[5232] 180 185 190
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[5234] 195 200 205
[5235] Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
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[5238] 225 230 235 240
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[5242] 260 265 270
[5243] Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
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[5247] Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
[5248] 305 310 315 320
[5249] Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu
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[5254] 355 360 365
[5255] Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
[5256] 370 375 380
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[5260] 405 410 415
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[5270] 485 490 495
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[5279] Phe Cys Ala Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn
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[5294] Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
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[5323] 260 265 270
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[5327] 290 295 300
[5328] Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
[5329] 305 310 315 320
[5330] Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu
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[5336] Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
[5337] 370 375 380
[5338] Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
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[5341] 405 410 415
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[5343] 420 425 430
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[5347] 450 455 460
[5348] Arg Thr Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro
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[5355] 515 520 525
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[5358] Leu Tyr Leu Gln Met Asp Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr
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[5360] Tyr Cys Ala Lys Glu Gly Thr Thr Glu Thr Asp Asp Tyr His Tyr Asn
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[5410] 305 310 315 320
[5411] Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu
[5412] 325 330 335
[5413] Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
[5414] 340 345 350
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[5417] Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
[5418] 370 375 380
[5419] Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
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[5421] Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
[5422] 405 410 415
[5423] Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
[5424] 420 425 430
[5425] Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
[5426] 435 440 445
[5427] Gly Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro
[5428] 450 455 460
[5429] Arg Thr Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro
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[5431] Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
[5432] 485 490 495
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[5437] Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ser Lys Asn Thr
[5438] 530 535 540
[5439] Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Ser Ala Val Tyr
[5440] 545 550 555 560
[5441] Phe Cys Ala Lys Glu Ala Thr Ala Met Ala Ser Asp Tyr Tyr Tyr Gly
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[5456] Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[5457] 35 40 45
[5458] Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
[5459] 50 55 60

[5460] Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
[5461] 65 70 75 80
[5462] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
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[5464] Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
[5465] 100 105 110
[5466] Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
[5467] 115 120 125
[5468] Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
[5469] 130 135 140
[5470] Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
[5471] 145 150 155 160
[5472] Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
[5473] 165 170 175
[5474] Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
[5475] 180 185 190
[5476] Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
[5477] 195 200 205
[5478] Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
[5479] 210 215 220
[5480] Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
[5481] 225 230 235 240
[5482] Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
[5483] 245 250 255
[5484] Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
[5485] 260 265 270
[5486] Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
[5487] 275 280 285
[5488] Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
[5489] 290 295 300
[5490] Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
[5491] 305 310 315 320
[5492] Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu
[5493] 325 330 335
[5494] Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
[5495] 340 345 350
[5496] Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
[5497] 355 360 365
[5498] Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp

[5499] 370 375 380

[5500] Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val

[5501] 385 390 395 400

[5502] Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp

[5503] 405 410 415

[5504] Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His

[5505] 420 425 430

[5506] Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro

[5507] 435 440 445

[5508] Gly Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro

[5509] 450 455 460

[5510] Arg Thr Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Ser

[5511] 465 470 475 480

[5512] Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser

[5513] 485 490 495

[5514] Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu

[5515] 500 505 510

[5516] Trp Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Asp Tyr Ala Asp

[5517] 515 520 525

[5518] Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Thr Asn Thr

[5519] 530 535 540

[5520] Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr

[5521] 545 550 555 560

[5522] Tyr Cys Ala Lys Glu Arg Ala Tyr Asp Tyr Ser Asn Tyr Val Asp Phe

[5523] 565 570 575

[5524] Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser

[5525] 580 585

[5526] <210> 258

[5527] <211> 590

[5528] <212> PRT

[5529] <213> Artificial Sequence

[5530] <220>

[5531] <223> PR002822链

[5532] <400> 258

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[5536] 20 25 30

[5537] Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

[5538] 35 40 45
[5539] Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
[5540] 50 55 60
[5541] Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
[5542] 65 70 75 80
[5543] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[5544] 85 90 95
[5545] Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
[5546] 100 105 110
[5547] Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
[5548] 115 120 125
[5549] Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
[5550] 130 135 140
[5551] Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
[5552] 145 150 155 160
[5553] Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
[5554] 165 170 175
[5555] Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
[5556] 180 185 190
[5557] Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
[5558] 195 200 205
[5559] Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
[5560] 210 215 220
[5561] Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
[5562] 225 230 235 240
[5563] Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
[5564] 245 250 255
[5565] Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
[5566] 260 265 270
[5567] Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
[5568] 275 280 285
[5569] Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
[5570] 290 295 300
[5571] Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
[5572] 305 310 315 320
[5573] Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu
[5574] 325 330 335
[5575] Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
[5576] 340 345 350

[5577] Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
[5578] 355 360 365
[5579] Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
[5580] 370 375 380
[5581] Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
[5582] 385 390 395 400
[5583] Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
[5584] 405 410 415
[5585] Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
[5586] 420 425 430
[5587] Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
[5588] 435 440 445
[5589] Gly Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro
[5590] 450 455 460
[5591] Arg Thr Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Ile Gln Pro
[5592] 465 470 475 480
[5593] Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
[5594] 485 490 495
[5595] Ser Phe Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
[5596] 500 505 510
[5597] Trp Val Ser Thr Ile Ser Gly Ser Gly Asp Asn Thr Tyr Tyr Ala Asp
[5598] 515 520 525
[5599] Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr
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[5601] Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
[5602] 545 550 555 560
[5603] Phe Cys Ala Lys Glu Asp Thr Ala Val Ala Ser Asp Tyr Tyr Tyr Asn
[5604] 565 570 575
[5605] Ile Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
[5606] 580 585 590
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[5608] <211> 590
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[5612] <223> PR002823链
[5613] <400> 259
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[5616] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
[5617] 20 25 30
[5618] Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[5619] 35 40 45
[5620] Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
[5621] 50 55 60
[5622] Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
[5623] 65 70 75 80
[5624] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[5625] 85 90 95
[5626] Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
[5627] 100 105 110
[5628] Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
[5629] 115 120 125
[5630] Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
[5631] 130 135 140
[5632] Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
[5633] 145 150 155 160
[5634] Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
[5635] 165 170 175
[5636] Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
[5637] 180 185 190
[5638] Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
[5639] 195 200 205
[5640] Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
[5641] 210 215 220
[5642] Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
[5643] 225 230 235 240
[5644] Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
[5645] 245 250 255
[5646] Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
[5647] 260 265 270
[5648] Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
[5649] 275 280 285
[5650] Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
[5651] 290 295 300
[5652] Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
[5653] 305 310 315 320
[5654] Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu

[5655] 325 330 335
[5656] Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
[5657] 340 345 350
[5658] Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
[5659] 355 360 365
[5660] Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
[5661] 370 375 380
[5662] Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
[5663] 385 390 395 400
[5664] Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
[5665] 405 410 415
[5666] Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
[5667] 420 425 430
[5668] Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
[5669] 435 440 445
[5670] Gly Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro
[5671] 450 455 460
[5672] Arg Thr Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Leu
[5673] 465 470 475 480
[5674] Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
[5675] 485 490 495
[5676] Ser Tyr Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu
[5677] 500 505 510
[5678] Trp Val Ser Ser Ile Ser Gly Ser Gly Gly Asn Thr Tyr Tyr Ala Asp
[5679] 515 520 525
[5680] Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr
[5681] 530 535 540
[5682] Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
[5683] 545 550 555 560
[5684] Tyr Cys Ala Lys Glu Arg Thr Gly Thr Thr Gly Asp Tyr Tyr Tyr Asn
[5685] 565 570 575
[5686] Val Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
[5687] 580 585 590
[5688] <210> 260
[5689] <211> 590
[5690] <212> PRT
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[5693] <223> PR002824链

[5694] <400> 260

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[5697] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
[5698] 20 25 30
[5699] Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[5700] 35 40 45
[5701] Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
[5702] 50 55 60
[5703] Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
[5704] 65 70 75 80
[5705] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[5706] 85 90 95
[5707] Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
[5708] 100 105 110
[5709] Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
[5710] 115 120 125
[5711] Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
[5712] 130 135 140
[5713] Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
[5714] 145 150 155 160
[5715] Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
[5716] 165 170 175
[5717] Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
[5718] 180 185 190
[5719] Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
[5720] 195 200 205
[5721] Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
[5722] 210 215 220
[5723] Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
[5724] 225 230 235 240
[5725] Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
[5726] 245 250 255
[5727] Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
[5728] 260 265 270
[5729] Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
[5730] 275 280 285
[5731] Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
[5732] 290 295 300

[5733] Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
[5734] 305 310 315 320
[5735] Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu
[5736] 325 330 335
[5737] Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
[5738] 340 345 350
[5739] Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
[5740] 355 360 365
[5741] Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
[5742] 370 375 380
[5743] Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
[5744] 385 390 395 400
[5745] Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
[5746] 405 410 415
[5747] Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
[5748] 420 425 430
[5749] Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
[5750] 435 440 445
[5751] Gly Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro
[5752] 450 455 460
[5753] Arg Thr Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro
[5754] 465 470 475 480
[5755] Gly Gly Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Ser
[5756] 485 490 495
[5757] Asn Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu
[5758] 500 505 510
[5759] Trp Val Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Phe Tyr Ala Asp
[5760] 515 520 525
[5761] Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr
[5762] 530 535 540
[5763] Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
[5764] 545 550 555 560
[5765] Phe Cys Ala Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn
[5766] 565 570 575
[5767] Val Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
[5768] 580 585 590
[5769] <210> 261
[5770] <211> 590
[5771] <212> PRT

[5772] <213> Artificial Sequence
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[5774] <223> PR002825链
[5775] <400> 261
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[5778] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
[5779] 20 25 30
[5780] Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[5781] 35 40 45
[5782] Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
[5783] 50 55 60
[5784] Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
[5785] 65 70 75 80
[5786] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[5787] 85 90 95
[5788] Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
[5789] 100 105 110
[5790] Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
[5791] 115 120 125
[5792] Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
[5793] 130 135 140
[5794] Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
[5795] 145 150 155 160
[5796] Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
[5797] 165 170 175
[5798] Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
[5799] 180 185 190
[5800] Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
[5801] 195 200 205
[5802] Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
[5803] 210 215 220
[5804] Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
[5805] 225 230 235 240
[5806] Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
[5807] 245 250 255
[5808] Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
[5809] 260 265 270
[5810] Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His

[5811] 275 280 285
[5812] Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
[5813] 290 295 300
[5814] Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
[5815] 305 310 315 320
[5816] Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu
[5817] 325 330 335
[5818] Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
[5819] 340 345 350
[5820] Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
[5821] 355 360 365
[5822] Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
[5823] 370 375 380
[5824] Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
[5825] 385 390 395 400
[5826] Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
[5827] 405 410 415
[5828] Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
[5829] 420 425 430
[5830] Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
[5831] 435 440 445
[5832] Gly Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro
[5833] 450 455 460
[5834] Arg Thr Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Ile Gln Pro
[5835] 465 470 475 480
[5836] Gly Gly Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Thr Phe Ser
[5837] 485 490 495
[5838] Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu
[5839] 500 505 510
[5840] Trp Val Ser Ser Ile Ser Gly Ser Gly Asp Ser Thr Tyr Tyr Ala Asp
[5841] 515 520 525
[5842] Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr
[5843] 530 535 540
[5844] Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Gly Tyr
[5845] 545 550 555 560
[5846] His Cys Ala Lys Glu Gly Ser Asn Gly Thr Asp Asp Tyr His Tyr Asp
[5847] 565 570 575
[5848] Ile Asp Val Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
[5849] 580 585 590

[5850] <210> 262
[5851] <211> 590
[5852] <212> PRT
[5853] <213> Artificial Sequence
[5854] <220>
[5855] <223> PR002826链
[5856] <400> 262
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[5859] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr
[5860] 20 25 30
[5861] Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[5862] 35 40 45
[5863] Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
[5864] 50 55 60
[5865] Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
[5866] 65 70 75 80
[5867] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[5868] 85 90 95
[5869] Ser Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
[5870] 100 105 110
[5871] Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
[5872] 115 120 125
[5873] Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
[5874] 130 135 140
[5875] Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
[5876] 145 150 155 160
[5877] Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
[5878] 165 170 175
[5879] Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
[5880] 180 185 190
[5881] Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
[5882] 195 200 205
[5883] Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
[5884] 210 215 220
[5885] Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
[5886] 225 230 235 240
[5887] Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
[5888] 245 250 255

[5889] Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
[5890] 260 265 270
[5891] Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
[5892] 275 280 285
[5893] Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
[5894] 290 295 300
[5895] Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
[5896] 305 310 315 320
[5897] Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu
[5898] 325 330 335
[5899] Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
[5900] 340 345 350
[5901] Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
[5902] 355 360 365
[5903] Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
[5904] 370 375 380
[5905] Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
[5906] 385 390 395 400
[5907] Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
[5908] 405 410 415
[5909] Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
[5910] 420 425 430
[5911] Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
[5912] 435 440 445
[5913] Gly Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro
[5914] 450 455 460
[5915] Arg Thr Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro
[5916] 465 470 475 480
[5917] Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
[5918] 485 490 495
[5919] Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu
[5920] 500 505 510
[5921] Trp Val Ser Ser Ile Ser Gly Ser Gly Gly Ser Thr Phe Tyr Ala Asp
[5922] 515 520 525
[5923] Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr
[5924] 530 535 540
[5925] Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
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[5927] Phe Cys Ala Lys Glu Gly Ala Thr Glu Thr Asp Asp Tyr His Phe Asn

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[5942] Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
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[5958] Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
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[5960] Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
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[5962] Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
[5963] 195 200 205
[5964] Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
[5965] 210 215 220
[5966] Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly

[5967] 225 230 235 240
[5968] Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
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[5970] Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
[5971] 260 265 270
[5972] Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
[5973] 275 280 285
[5974] Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
[5975] 290 295 300
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[5977] 305 310 315 320
[5978] Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu
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[5980] Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
[5981] 340 345 350
[5982] Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
[5983] 355 360 365
[5984] Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
[5985] 370 375 380
[5986] Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
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[5989] 405 410 415
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[5995] 450 455 460
[5996] Arg Thr Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro
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[5998] Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ile Phe Ser
[5999] 485 490 495
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[6002] Trp Val Ser Ser Ile Asn Gly Ser Gly Phe Asn Thr Tyr Tyr Thr Asp
[6003] 515 520 525
[6004] Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Arg Asn Thr
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[6008] Phe Cys Ala Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn
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[6011] 580 585 590
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[6024] 35 40 45
[6025] Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
[6026] 50 55 60
[6027] Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
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[6038] 145 150 155 160
[6039] Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
[6040] 165 170 175
[6041] Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
[6042] 180 185 190
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[6044] 195 200 205

[6045] Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
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[6047] Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
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[6051] Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
[6052] 260 265 270
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[6057] Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
[6058] 305 310 315 320
[6059] Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu
[6060] 325 330 335
[6061] Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
[6062] 340 345 350
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[6064] 355 360 365
[6065] Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
[6066] 370 375 380
[6067] Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
[6068] 385 390 395 400
[6069] Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
[6070] 405 410 415
[6071] Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
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[6075] Gly Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro
[6076] 450 455 460
[6077] Arg Thr Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro
[6078] 465 470 475 480
[6079] Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
[6080] 485 490 495
[6081] Asn Tyr Ala Met Ser Trp Phe Arg Gln Pro Pro Glu Thr Gly Leu Lys
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[6087] Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
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[6089] Tyr Cys Ala Lys Glu Gly Ser His Gly Thr Asp Asp Ser His Tyr Asp
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[6104] Tyr Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[6105] 35 40 45
[6106] Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val
[6107] 50 55 60
[6108] Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
[6109] 65 70 75 80
[6110] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
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[6120] Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
[6121] 165 170 175
[6122] Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro

[6123] 180 185 190
[6124] Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
[6125] 195 200 205
[6126] Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
[6127] 210 215 220
[6128] Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
[6129] 225 230 235 240
[6130] Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
[6131] 245 250 255
[6132] Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
[6133] 260 265 270
[6134] Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
[6135] 275 280 285
[6136] Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
[6137] 290 295 300
[6138] Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
[6139] 305 310 315 320
[6140] Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu
[6141] 325 330 335
[6142] Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
[6143] 340 345 350
[6144] Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
[6145] 355 360 365
[6146] Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
[6147] 370 375 380
[6148] Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
[6149] 385 390 395 400
[6150] Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
[6151] 405 410 415
[6152] Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
[6153] 420 425 430
[6154] Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
[6155] 435 440 445
[6156] Gly Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro
[6157] 450 455 460
[6158] Arg Thr Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro
[6159] 465 470 475 480
[6160] Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
[6161] 485 490 495

[6162] Ser Tyr Trp Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Val
[6163] 500 505 510
[6164] Trp Val Ser Arg Ile Asn Ser Asp Gly Ser Ser Thr Ser Tyr Ala Asp
[6165] 515 520 525
[6166] Ser Val Gln Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr
[6167] 530 535 540
[6168] Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
[6169] 545 550 555 560
[6170] Tyr Cys Val Arg Lys Gly Ser Ser Ser Tyr Tyr His Tyr Ser Ile Glu
[6171] 565 570 575
[6172] Asp Asp Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
[6173] 580 585
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[6175] <211> 221
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[6183] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ser
[6184] 20 25 30
[6185] Trp Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[6186] 35 40 45
[6187] Ala Trp Ile Ser Pro Tyr Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
[6188] 50 55 60
[6189] Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
[6190] 65 70 75 80
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[6193] Ala Arg Arg His Trp Pro Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr
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[6195] Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
[6196] 115 120 125
[6197] Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
[6198] 130 135 140
[6199] Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
[6200] 145 150 155 160

[6201] Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
[6202] 165 170 175
[6203] Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
[6204] 180 185 190
[6205] Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
[6206] 195 200 205
[6207] Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
[6208] 210 215 220
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[6217] 1 5 10 15
[6218] Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala
[6219] 20 25 30
[6220] Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
[6221] 35 40 45
[6222] Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
[6223] 50 55 60
[6224] Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
[6225] 65 70 75 80
[6226] Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Leu Tyr His Pro Ala
[6227] 85 90 95
[6228] Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
[6229] 100 105 110
[6230] Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
[6231] 115 120 125
[6232] Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
[6233] 130 135 140
[6234] Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
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[6236] Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
[6237] 165 170 175
[6238] Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
[6239] 180 185 190

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[6243] 210 215 220
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[6248] Lys Gly Leu Glu Trp Ile Gly Glu Ile Gln His Ser Gly Ser Thr Asp
[6249] 260 265 270
[6250] Ser Asn Pro Ser Leu Lys Gly Arg Val Thr Phe Ser Val Asp Thr Ser
[6251] 275 280 285
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[6253] 290 295 300
[6254] Ala Val Tyr Tyr Cys Ala Arg Leu Thr Gly Pro Phe Asp Tyr Trp Gly
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[6256] Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
[6257] 325 330 335
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[6259] 340 345 350
[6260] Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
[6261] 355 360 365
[6262] Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
[6263] 370 375 380
[6264] Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
[6265] 385 390 395 400
[6266] Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His
[6267] 405 410 415
[6268] Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly
[6269] 420 425 430
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[6281] 515 520 525
[6282] Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr
[6283] 530 535 540
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[6285] 545 550 555 560
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[6292] Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser
[6293] 610 615 620
[6294] Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
[6295] 625 630 635 640
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[6312] 50 55 60
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[6315] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
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[6317] Ala Arg Asp Arg Ala Val Ala Gly Ala Phe Asp Ile Trp Gly Gln Gly

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[6324] 145 150 155 160
[6325] Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
[6326] 165 170 175
[6327] Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
[6328] 180 185 190
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[6331] Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
[6332] 210 215 220
[6333] Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
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[6335] Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
[6336] 245 250 255
[6337] Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
[6338] 260 265 270
[6339] Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
[6340] 275 280 285
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[6344] 305 310 315 320
[6345] Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys
[6346] 325 330 335
[6347] Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
[6348] 340 345 350
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[6351] Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
[6352] 370 375 380
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[6357] Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
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[6362] 450 455 460
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[6375] Cys Ala Lys Glu Lys Ala Gly Thr Thr Gly Asp Tyr Tyr Tyr Asn Val
[6376] 565 570 575
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[6398] Ala Arg Asp Arg Ala Val Ala Gly Ala Phe Asp Ile Trp Gly Gln Gly
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[6402] Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
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[6404] Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
[6405] 145 150 155 160
[6406] Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
[6407] 165 170 175
[6408] Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
[6409] 180 185 190
[6410] Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
[6411] 195 200 205
[6412] Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
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[6486] 145 150 155 160

[6487] Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

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[6489] Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

[6490] 180 185 190

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[6492] 195 200 205

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[6494] 210 215 220

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[6532] 515 520 525
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[6552] Ala Met Thr Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
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[6555] 50 55 60
[6556] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
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[6560] Ala Lys Glu Gly Ser Ser Glu Thr Asp Asp His Tyr Tyr Asn Val Asp
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[6572] Glu Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val Lys Gly Arg Phe Thr
[6573] 195 200 205
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[6575] 210 215 220
[6576] Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Asp Arg Ala
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[6578] Val Ala Gly Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val
[6579] 245 250 255
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[6581] 260 265 270
[6582] Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys
[6583] 275 280 285
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[6594] Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe
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[6596] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
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[6598] Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
[6599] 405 410 415
[6600] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
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[6603] 435 440 445
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[6605] 450 455 460
[6606] Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
[6607] 465 470 475 480
[6608] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
[6609] 485 490 495
[6610] Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
[6611] 500 505 510
[6612] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
[6613] 515 520 525
[6614] Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[6615] 530 535 540
[6616] Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
[6617] 545 550 555 560
[6618] Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
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[6630] 1 5 10 15
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[6633] Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile
[6634] 35 40 45
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[6636] 50 55 60
[6637] Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
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[6639] Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Gly Ser Ser Arg
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[6647] Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
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[6650] 165 170 175
[6651] Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
[6652] 180 185 190
[6653] Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
[6654] 195 200 205
[6655] Phe Asn Arg Gly Glu Cys Glu Pro Lys Ser Ser Asp Lys Thr His Thr
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[6662] 260 265 270
[6663] Gly Leu Glu Trp Val Ser Ser Ile Ser Gly Ser Gly Val Ser Thr Tyr
[6664] 275 280 285
[6665] Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
[6666] 290 295 300
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[6682] 420 425 430
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[6685] Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
[6686] 450 455 460
[6687] Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
[6688] 465 470 475 480
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[6690] 485 490 495
[6691] Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
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[6693] Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
[6694] 515 520 525
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[6698] 545 550 555 560
[6699] Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
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[6718] <400> 274
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[6720] 1 5
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[6727] <400> 275
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[6729] 1 5
[6730] <210> 276
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[6732] <212> PRT
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[6741] <212> PRT
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[6744] <223> GS_15
[6745] <400> 277
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[6747] 1 5 10 15

[6748] <210> 278

[6749] <211> 20

[6750] <212> PRT

[6751] <213> Artificial Sequence

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[6753] <223> GS_20

[6754] <400> 278

[6755] Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly

[6756] 1 5 10 15

[6757] Gly Gly Gly Ser

[6758] 20

[6759] <210> 279

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[6761] <212> PRT

[6762] <213> Artificial Sequence

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[6764] <223> GS_25

[6765] <400> 279

[6766] Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly

[6767] 1 5 10 15

[6768] Gly Gly Gly Ser Gly Gly Gly Gly Ser

[6769] 20 25

[6770] <210> 280

[6771] <211> 15

[6772] <212> PRT

[6773] <213> Artificial Sequence

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[6775] <223> 人IgG1铰链

[6776] <400> 280

[6777] Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro

[6778] 1 5 10 15

[6779] <210> 281

[6780] <211> 15

[6781] <212> PRT

[6782] <213> Artificial Sequence

[6783] <220>

[6784] <223> 人IgG1铰链 (C220S)

[6785] <400> 281

[6786] Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro
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[6788] <210> 282
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[6793] <223> H1_15
[6794] <400> 282
[6795] Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro
[6796] 1 5 10 15
[6797] <210> 283
[6798] <211> 15
[6799] <212> PRT
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[6802] <223> G5-LH
[6803] <400> 283
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[6805] 1 5 10 15
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[6807] <211> 17
[6808] <212> PRT
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[6811] <223> H1_15-RT
[6812] <400> 284
[6813] Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro Arg
[6814] 1 5 10 15
[6815] Thr
[6816] <210> 285
[6817] <211> 18
[6818] <212> PRT
[6819] <213> Artificial Sequence
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[6821] <223> L-GS_15-RT
[6822] <400> 285
[6823] Leu Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
[6824] 1 5 10 15

[6825] Arg Thr
[6826] <210> 286
[6827] <211> 18
[6828] <212> PRT
[6829] <213> Artificial Sequence
[6830] <220>
[6831] <223> L-H1_15-RT
[6832] <400> 286
[6833] Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro Pro
[6834] 1 5 10 15
[6835] Arg Thr
[6836] <210> 287
[6837] <211> 19
[6838] <212> PRT
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[6841] <223> KL-H1_15-RT
[6842] <400> 287
[6843] Lys Leu Glu Pro Lys Ser Ser Asp Lys Thr His Thr Pro Pro Pro Pro
[6844] 1 5 10 15
[6845] Pro Arg Thr
[6846] <210> 288
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[6856] <210> 289
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[6861] <223> RT-GS_5-KL
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[6863] Arg Thr Gly Gly Gly Gly Ser Lys Leu

[6864] 1 5
[6865] <210> 290
[6866] <211> 19
[6867] <212> PRT
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[6870] <223> RT-GS_15-KL
[6871] <400> 290
[6872] Arg Thr Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
[6873] 1 5 10 15
[6874] Ser Lys Leu
[6875] <210> 291
[6876] <211> 29
[6877] <212> PRT
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[6880] <223> RT-GS_25-KL
[6881] <400> 291
[6882] Arg Thr Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
[6883] 1 5 10 15
[6884] Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Lys Leu
[6885] 20 25
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[6891] <223> EPKSSD
[6892] <400> 292
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[6894] 1 5
[6895] <210> 293
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[6900] <223> AS-GS_15
[6901] <400> 293
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[6903] 1 5 10 15

[6904] Ser

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[6909] <220>

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[6911] Chothia

[6912] <400> 294

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[6914] 1 5 10 15

[6915] Ser Leu Arg Leu Ser Cys Ala Ala Ser

[6916] 20 25

[6917] <210> 295

[6918] <211> 25

[6919] <212> PRT

[6920] <213> Artificial Sequence

[6921] <220>

[6922] <223> PR007287 HFWR1 Chothia

[6923] <400> 295

[6924] Glu Val Gln Leu Glu Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly

[6925] 1 5 10 15

[6926] Ser Leu Arg Leu Ser Cys Ala Ala Ser

[6927] 20 25

[6928] <210> 296

[6929] <211> 25

[6930] <212> PRT

[6931] <213> Artificial Sequence

[6932] <220>

[6933] <223> PR007290 HFWR1 Chothia

[6934] <400> 296

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[6936] 1 5 10 15

[6937] Ser Leu Arg Leu Ser Cys Ala Ala Ser

[6938] 20 25

[6939] <210> 297

[6940] <211> 25

[6941] <212> PRT

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[6944] <223> PR007291 HFWR1 Chothia
[6945] <400> 297
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[6947] 1 5 10 15
[6948] Ser Leu Arg Leu Ser Cys Val Thr Ser
[6949] 20 25
[6950] <210> 298
[6951] <211> 25
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[6955] <223> PR007294 HFWR1 Chothia, PR007296 HFWR1 Chothia
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[6958] 1 5 10 15
[6959] Ser Leu Arg Leu Ser Cys Val Ala Ser
[6960] 20 25
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[6966] <223> PR007300 HFWR1 Chothia
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[6969] 1 5 10 15
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[6971] 20 25
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[6991] 1 5 10 15

[6992] Ser Tyr Ile

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[7002] 1 5 10 15

[7003] Ser Tyr Ile

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[7012] 1 5 10 15

[7013] Ser Tyr Ile

[7014] <210> 304

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[7021] Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

[7022] 1 5 10 15

[7023] Ser Tyr Ile

[7024] <210> 305

[7025] <211> 19

[7026] <212> PRT

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[7029] <223> PR007299 HFWR2 Chothia

[7030] <400> 305

[7031] Gln Met Ser Trp Leu Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

[7032] 1 5 10 15

[7033] Ser Tyr Ile

[7034] <210> 306

[7035] <211> 19

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[7039] <223> PR007300 HFWR2 Chothia

[7040] <400> 306

[7041] Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

[7042] 1 5 10 15

[7043] Ser Tyr Ile

[7044] <210> 307

[7045] <211> 19

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[7048] <220>

[7049] <223> PR007381 HFWR2 Chothia

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[7052] 1 5 10 15

[7053] Ser Ser Ile

[7054] <210> 308

[7055] <211> 6

[7056] <212> PRT

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[7058] <220>

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[7062] Ser Ser Ser Gly Ser Thr
[7063] 1 5
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[7070] <400> 309
[7071] Ser Ser Ser Gly Ser Ile
[7072] 1 5
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[7078] <223> PR007288 HCDR2 Chothia
[7079] <400> 310
[7080] Ser Gly Ser Gly Ser Ile
[7081] 1 5
[7082] <210> 311
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[7088] <400> 311
[7089] Ser Ser Ser Gly Thr Thr
[7090] 1 5
[7091] <210> 312
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[7097] <400> 312

[7098] Ser Gly Asn Gly Ser Thr
[7099] 1 5
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[7105] <223> PR007293 HCDR2 Chothia
[7106] <400> 313
[7107] Asn Ser Ser Gly Ser Thr
[7108] 1 5
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[7114] <223> PR007294 HCDR2 Chothia, PR007296 HCDR2 Chothia
[7115] <400> 314
[7116] Ser Gly Ser Gly Thr Thr
[7117] 1 5
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[7123] <223> PR007295 HCDR2 Chothia, PR007300 HCDR2 Chothia
[7124] <400> 315
[7125] Ser Asn Asn Gly Ser Thr
[7126] 1 5
[7127] <210> 316
[7128] <211> 6
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[7132] <223> PR007297 HCDR2 Chothia
[7133] <400> 316
[7134] Ser Arg Ser Gly Ser Thr
[7135] 1 5
[7136] <210> 317

[7137] <211> 6
[7138] <212> PRT
[7139] <213> Artificial Sequence
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[7141] <223> PR007299 HCDR2 Chothia
[7142] <400> 317
[7143] Ser Ser Ser Gly Arg Thr
[7144] 1 5
[7145] <210> 318
[7146] <211> 41
[7147] <212> PRT
[7148] <213> Artificial Sequence
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[7150] <223> PR007286 HFWR3 Chothia, PR007291 HFWR3 Chothia, PR007295 HFWR3
[7151] Chothia
[7152] <400> 318
[7153] Ile Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
[7154] 1 5 10 15
[7155] Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
[7156] 20 25 30
[7157] Asp Thr Ala Val Tyr Tyr Cys Ala Arg
[7158] 35 40
[7159] <210> 319
[7160] <211> 41
[7161] <212> PRT
[7162] <213> Artificial Sequence
[7163] <220>
[7164] <223> PR007287 HFWR3 Chothia
[7165] <400> 319
[7166] Thr Asp Tyr Ala Asp Ala Val Lys Gly Arg Phe Asn Ile Ser Arg Asp
[7167] 1 5 10 15
[7168] Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
[7169] 20 25 30
[7170] Asp Thr Ala Val Tyr Tyr Cys Ala Arg
[7171] 35 40
[7172] <210> 320
[7173] <211> 41
[7174] <212> PRT
[7175] <213> Artificial Sequence

[7176] <220>
[7177] <223> PR007288 HFWR3 Chothia
[7178] <400> 320
[7179] Ile Asp Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
[7180] 1 5 10 15
[7181] Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
[7182] 20 25 30
[7183] Asp Thr Ala Val Tyr Tyr Cys Ser Arg
[7184] 35 40
[7185] <210> 321
[7186] <211> 41
[7187] <212> PRT
[7188] <213> Artificial Sequence
[7189] <220>
[7190] <223> PR007289 HFWR3 Chothia
[7191] <400> 321
[7192] Gln Asp Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
[7193] 1 5 10 15
[7194] Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
[7195] 20 25 30
[7196] Asp Thr Ala Val Tyr Tyr Cys Ala Arg
[7197] 35 40
[7198] <210> 322
[7199] <211> 41
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[7203] <223> PR007290 HFWR3 Chothia, PR007292 HFWR3 Chothia, PR007294 HFWR3
[7204] Chothia
[7205] <400> 322
[7206] Ile Asp Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
[7207] 1 5 10 15
[7208] Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
[7209] 20 25 30
[7210] Asp Thr Ala Val Tyr Tyr Cys Ala Arg
[7211] 35 40
[7212] <210> 323
[7213] <211> 41
[7214] <212> PRT

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[7217] <223> PR007293 HFWR3 Chothia
[7218] <400> 323
[7219] Ile Tyr Tyr Glu Tyr Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
[7220] 1 5 10 15
[7221] Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu
[7222] 20 25 30
[7223] Asp Thr Ala Val Tyr Tyr Cys Ala Arg
[7224] 35 40
[7225] <210> 324
[7226] <211> 41
[7227] <212> PRT
[7228] <213> Artificial Sequence
[7229] <220>
[7230] <223> PR007298 HFWR3 Chothia
[7231] <400> 324
[7232] Ile Asp Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
[7233] 1 5 10 15
[7234] Asn Ala Lys Asn Ser Leu Phe Leu Glu Met Asn Ser Leu Arg Ala Glu
[7235] 20 25 30
[7236] Asp Thr Ala Val Tyr Tyr Cys Ala Arg
[7237] 35 40
[7238] <210> 325
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[7240] <212> PRT
[7241] <213> Artificial Sequence
[7242] <220>
[7243] <223> PR007299 HFWR3 Chothia
[7244] <400> 325
[7245] Ile Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp
[7246] 1 5 10 15
[7247] Asn Ala Lys Asn Ser Val Ser Leu Gln Met Asn Ser Leu Arg Ala Glu
[7248] 20 25 30
[7249] Asp Thr Ala Val Tyr Tyr Cys Ala Arg
[7250] 35 40
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[7252] <211> 13
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[7255] <220>

[7256] <223> PR007286 HCDR3 Chothia

[7257] <400> 326

[7258] Val Lys Pro Val Ala Gly Thr Trp Asp Trp Phe Asp Pro

[7259] 1 5 10

[7260] <210> 327

[7261] <211> 13

[7262] <212> PRT

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[7264] <220>

[7265] <223> PR007287 HCDR3 Chothia, PR007296 HCDR3 Chothia

[7266] <400> 327

[7267] Glu Arg Glu Ala Val Ala Gly Thr Leu Asp Phe Asp Asn

[7268] 1 5 10

[7269] <210> 328

[7270] <211> 13

[7271] <212> PRT

[7272] <213> Artificial Sequence

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[7274] <223> PR007288 HCDR3 Chothia

[7275] <400> 328

[7276] Glu Arg Glu Ala Val Ala Gly Thr Leu Asp Phe Asp Tyr

[7277] 1 5 10

[7278] <210> 329

[7279] <211> 13

[7280] <212> PRT

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[7282] <220>

[7283] <223> PR007289 HCDR3 Chothia, PR007294 HCDR3 Chothia

[7284] <400> 329

[7285] Glu Arg Glu Pro Val Ala Gly Thr Leu Asp Phe Asp Asn

[7286] 1 5 10

[7287] <210> 330

[7288] <211> 13

[7289] <212> PRT

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[7291] <220>

[7292] <223> PR007290 HCDR3 Chothia, PR007293 HCDR3 Chothia

[7293] <400> 330

[7294] Glu Arg Glu Glu Val Ala Gly Thr Leu Asp Phe Asp Tyr

[7295] 1 5 10

[7296] <210> 331

[7297] <211> 15

[7298] <212> PRT

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[7301] <223> PR007291 HCDR3 Chothia, PR007295 HCDR3 Chothia, PR007297 HCDR3

[7302] Chothia

[7303] <400> 331

[7304] Val Arg Pro Gly Gly Ser Gly Asn Tyr Trp Asp Trp Phe Asp Pro

[7305] 1 5 10 15

[7306] <210> 332

[7307] <211> 13

[7308] <212> PRT

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[7311] <223> PR007292 HCDR3 Chothia

[7312] <400> 332

[7313] Glu Arg Glu Glu Val Ala Gly Thr Leu Asp Tyr Asp Asn

[7314] 1 5 10

[7315] <210> 333

[7316] <211> 13

[7317] <212> PRT

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[7319] <220>

[7320] <223> PR007298 HCDR3 Chothia

[7321] <400> 333

[7322] Glu Arg Glu Glu Val Ala Gly Thr Leu Asp Phe Asp Asn

[7323] 1 5 10

[7324] <210> 334

[7325] <211> 5

[7326] <212> PRT

[7327] <213> Artificial Sequence

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[7329] <223> PR007299 HCDR3 Chothia

[7330] <400> 334

[7331] Glu Gly Arg Phe Phe

[7332] 1 5

[7333] <210> 335

[7334] <211> 11

[7335] <212> PRT

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[7338] <223> PR007286 HFWR4 Chothia, PR007289 HFWR4 Chothia, PR007290 HFWR4

[7339] Chothia

[7340] <400> 335

[7341] Trp Gly Gln Gly Thr Pro Val Thr Val Ser Ser

[7342] 1 5 10

[7343] <210> 336

[7344] <211> 11

[7345] <212> PRT

[7346] <213> Artificial Sequence

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[7348] <223> PR007299 HFWR4 Chothia

[7349] <400> 336

[7350] Pro Gly Gln Gly Thr Pro Val Thr Val Ser Ser

[7351] 1 5 10

[7352] <210> 337

[7353] <211> 122

[7354] <212> PRT

[7355] <213> Artificial Sequence

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[7357] <223> PR007286 VH

[7358] <400> 337

[7359] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly

[7360] 1 5 10 15

[7361] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr

[7362] 20 25 30

[7363] Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

[7364] 35 40 45

[7365] Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val

[7366] 50 55 60

[7367] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr

[7368] 65 70 75 80

[7369] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

[7370] 85 90 95

[7371] Ala Arg Val Lys Pro Val Ala Gly Thr Trp Asp Trp Phe Asp Pro Trp
[7372] 100 105 110
[7373] Gly Gln Gly Thr Pro Val Thr Val Ser Ser
[7374] 115 120
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[7377] <212> PRT
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[7380] <223> PR007287 VH
[7381] <400> 338
[7382] Glu Val Gln Leu Glu Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
[7383] 1 5 10 15
[7384] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[7385] 20 25 30
[7386] Tyr Met Ser Trp Phe Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[7387] 35 40 45
[7388] Ser Tyr Ile Ser Ser Ser Gly Ser Ile Thr Asp Tyr Ala Asp Ala Val
[7389] 50 55 60
[7390] Lys Gly Arg Phe Asn Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[7391] 65 70 75 80
[7392] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[7393] 85 90 95
[7394] Ala Arg Glu Arg Glu Ala Val Ala Gly Thr Leu Asp Phe Asp Asn Trp
[7395] 100 105 110
[7396] Gly Gln Gly Thr Leu Val Thr Val Ser Ser
[7397] 115 120
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[7400] <212> PRT
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[7403] <223> PR007288 VH
[7404] <400> 339
[7405] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
[7406] 1 5 10 15
[7407] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[7408] 20 25 30
[7409] Tyr Met Ser Trp Phe Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

[7410] 35 40 45
[7411] Ser Tyr Ile Ser Gly Ser Gly Ser Ile Ile Asp Tyr Ala Asp Ser Val
[7412] 50 55 60
[7413] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[7414] 65 70 75 80
[7415] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[7416] 85 90 95
[7417] Ser Arg Glu Arg Glu Ala Val Ala Gly Thr Leu Asp Phe Asp Tyr Trp
[7418] 100 105 110
[7419] Gly Gln Gly Thr Leu Val Thr Val Ser Ser
[7420] 115 120
[7421] <210> 340
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[7423] <212> PRT
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[7426] <223> PR007289 VH
[7427] <400> 340
[7428] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
[7429] 1 5 10 15
[7430] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[7431] 20 25 30
[7432] Tyr Met Ser Trp Phe Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[7433] 35 40 45
[7434] Ser Tyr Ile Ser Ser Ser Gly Ser Thr Gln Asp Tyr Ala Asp Ser Val
[7435] 50 55 60
[7436] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[7437] 65 70 75 80
[7438] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[7439] 85 90 95
[7440] Ala Arg Glu Arg Glu Pro Val Ala Gly Thr Leu Asp Phe Asp Asn Trp
[7441] 100 105 110
[7442] Gly Gln Gly Thr Pro Val Thr Val Ser Ser
[7443] 115 120
[7444] <210> 341
[7445] <211> 122
[7446] <212> PRT
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[7449] <223> PR007290 VH
[7450] <400> 341
[7451] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
[7452] 1 5 10 15
[7453] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[7454] 20 25 30
[7455] Tyr Met Ser Trp Phe Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[7456] 35 40 45
[7457] Ser Tyr Ile Ser Ser Ser Gly Thr Thr Ile Asp Tyr Ala Asp Ser Val
[7458] 50 55 60
[7459] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[7460] 65 70 75 80
[7461] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[7462] 85 90 95
[7463] Ala Arg Glu Arg Glu Glu Val Ala Gly Thr Leu Asp Phe Asp Tyr Trp
[7464] 100 105 110
[7465] Gly Gln Gly Thr Pro Val Thr Val Ser Ser
[7466] 115 120
[7467] <210> 342
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[7469] <212> PRT
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[7472] <223> PR007291 VH
[7473] <400> 342
[7474] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
[7475] 1 5 10 15
[7476] Ser Leu Arg Leu Ser Cys Val Thr Ser Gly Phe Thr Phe Ser Asp Tyr
[7477] 20 25 30
[7478] Tyr Met Asn Trp Ile Arg Gln Ala Pro Gly Lys Gly Gln Glu Trp Val
[7479] 35 40 45
[7480] Ser Tyr Ile Ser Gly Asn Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
[7481] 50 55 60
[7482] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[7483] 65 70 75 80
[7484] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[7485] 85 90 95
[7486] Ala Arg Val Arg Pro Gly Gly Ser Gly Asn Tyr Trp Asp Trp Phe Asp
[7487] 100 105 110

[7488] Pro Trp Gly Gln Gly Thr Pro Val Thr Val Ser Ser
[7489] 115 120
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[7497] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
[7498] 1 5 10 15
[7499] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[7500] 20 25 30
[7501] Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[7502] 35 40 45
[7503] Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Asp Tyr Ala Asp Ser Val
[7504] 50 55 60
[7505] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[7506] 65 70 75 80
[7507] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[7508] 85 90 95
[7509] Ala Arg Glu Arg Glu Glu Val Ala Gly Thr Leu Asp Tyr Asp Asn Trp
[7510] 100 105 110
[7511] Gly Gln Gly Thr Leu Val Thr Val Ser Ser
[7512] 115 120
[7513] <210> 344
[7514] <211> 122
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[7518] <223> PR007293 VH
[7519] <400> 344
[7520] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
[7521] 1 5 10 15
[7522] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[7523] 20 25 30
[7524] Tyr Met Ser Trp Phe Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[7525] 35 40 45
[7526] Ser Tyr Ile Asn Ser Ser Gly Ser Thr Ile Tyr Tyr Glu Tyr Ser Val

[7527] 50 55 60

[7528] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr

[7529] 65 70 75 80

[7530] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

[7531] 85 90 95

[7532] Ala Arg Glu Arg Glu Glu Val Ala Gly Thr Leu Asp Phe Asp Tyr Trp

[7533] 100 105 110

[7534] Gly Gln Gly Thr Leu Val Thr Val Ser Ser

[7535] 115 120

[7536] <210> 345

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[7538] <212> PRT

[7539] <213> Artificial Sequence

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[7541] <223> PR007294 VH

[7542] <400> 345

[7543] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly

[7544] 1 5 10 15

[7545] Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Tyr

[7546] 20 25 30

[7547] Tyr Met Ser Trp Phe Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

[7548] 35 40 45

[7549] Ser Tyr Ile Ser Gly Ser Gly Thr Thr Ile Asp Tyr Ala Asp Ser Val

[7550] 50 55 60

[7551] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr

[7552] 65 70 75 80

[7553] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

[7554] 85 90 95

[7555] Ala Arg Glu Arg Glu Pro Val Ala Gly Thr Leu Asp Phe Asp Asn Trp

[7556] 100 105 110

[7557] Gly Gln Gly Thr Leu Val Thr Val Ser Ser

[7558] 115 120

[7559] <210> 346

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[7561] <212> PRT

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[7564] <223> PR007295 VH

[7565] <400> 346

[7566] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
[7567] 1 5 10 15
[7568] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[7569] 20 25 30
[7570] Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[7571] 35 40 45
[7572] Ser Tyr Ile Ser Asn Asn Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
[7573] 50 55 60
[7574] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[7575] 65 70 75 80
[7576] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[7577] 85 90 95
[7578] Ala Arg Val Arg Pro Gly Gly Ser Gly Asn Tyr Trp Asp Trp Phe Asp
[7579] 100 105 110
[7580] Pro Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
[7581] 115 120
[7582] <210> 347
[7583] <211> 122
[7584] <212> PRT
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[7588] <400> 347
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[7590] 1 5 10 15
[7591] Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[7592] 20 25 30
[7593] Tyr Met Ser Trp Phe Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[7594] 35 40 45
[7595] Ser Tyr Ile Ser Gly Ser Gly Thr Thr Ile Asp Tyr Ala Asp Ser Val
[7596] 50 55 60
[7597] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[7598] 65 70 75 80
[7599] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[7600] 85 90 95
[7601] Ala Arg Glu Arg Glu Ala Val Ala Gly Thr Leu Asp Phe Asp Asn Trp
[7602] 100 105 110
[7603] Gly Gln Gly Thr Pro Val Thr Val Ser Ser
[7604] 115 120

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[7607] <212> PRT
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[7610] <223> PR007297 VH
[7611] <400> 348
[7612] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
[7613] 1 5 10 15
[7614] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[7615] 20 25 30
[7616] Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[7617] 35 40 45
[7618] Ser Tyr Ile Ser Arg Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
[7619] 50 55 60
[7620] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[7621] 65 70 75 80
[7622] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[7623] 85 90 95
[7624] Ala Arg Val Arg Pro Gly Gly Ser Gly Asn Tyr Trp Asp Trp Phe Asp
[7625] 100 105 110
[7626] Pro Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
[7627] 115 120
[7628] <210> 349
[7629] <211> 122
[7630] <212> PRT
[7631] <213> Artificial Sequence
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[7633] <223> PR007298 VH
[7634] <400> 349
[7635] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
[7636] 1 5 10 15
[7637] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[7638] 20 25 30
[7639] Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[7640] 35 40 45
[7641] Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Asp Tyr Ala Asp Ser Val
[7642] 50 55 60
[7643] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe

[7644] 65 70 75 80
[7645] Leu Glu Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[7646] 85 90 95
[7647] Ala Arg Glu Arg Glu Glu Val Ala Gly Thr Leu Asp Phe Asp Asn Trp
[7648] 100 105 110
[7649] Gly Gln Gly Thr Leu Val Thr Val Ser Ser
[7650] 115 120
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[7653] <212> PRT
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[7656] <223> PR007299 VH
[7657] <400> 350
[7658] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
[7659] 1 5 10 15
[7660] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[7661] 20 25 30
[7662] Gln Met Ser Trp Leu Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[7663] 35 40 45
[7664] Ser Tyr Ile Ser Ser Ser Gly Arg Thr Ile Tyr Tyr Ala Asp Ser Val
[7665] 50 55 60
[7666] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Val Ser
[7667] 65 70 75 80
[7668] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[7669] 85 90 95
[7670] Ala Arg Glu Gly Arg Phe Phe Pro Gly Gln Gly Thr Pro Val Thr Val
[7671] 100 105 110
[7672] Ser Ser
[7673] <210> 351
[7674] <211> 124
[7675] <212> PRT
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[7678] <223> PR007300 VH
[7679] <400> 351
[7680] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
[7681] 1 5 10 15
[7682] Ser Leu Arg Leu Ser Cys Thr Thr Ser Gly Phe Thr Phe Ser Asp Tyr

[7683] 20 25 30
[7684] Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[7685] 35 40 45
[7686] Ser Tyr Ile Ser Asn Asn Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
[7687] 50 55 60
[7688] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[7689] 65 70 75 80
[7690] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[7691] 85 90 95
[7692] Ala Arg Val Arg Pro Gly Gly Ser Gly Asn Tyr Trp Asp Trp Phe Asp
[7693] 100 105 110
[7694] Pro Trp Gly Gln Gly Thr Pro Val Thr Val Ser Ser
[7695] 115 120
[7696] <210> 352
[7697] <211> 124
[7698] <212> PRT
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[7701] <223> PR007381 VH
[7702] <400> 352
[7703] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[7704] 1 5 10 15
[7705] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
[7706] 20 25 30
[7707] Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[7708] 35 40 45
[7709] Ser Ser Ile Asp Ala Ser Gly Gly Asp Thr Tyr Tyr Ala Asp Ser Val
[7710] 50 55 60
[7711] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[7712] 65 70 75 80
[7713] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[7714] 85 90 95
[7715] Ala Lys Glu Gly Ser His Gly Thr Asp Asp Ser His Tyr Asp Val Asp
[7716] 100 105 110
[7717] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
[7718] 115 120
[7719] <210> 353
[7720] <211> 354
[7721] <212> PRT

[7722] <213> Artificial Sequence
[7723] <220>
[7724] <223> PR007286 HC
[7725] <400> 353
[7726] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
[7727] 1 5 10 15
[7728] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[7729] 20 25 30
[7730] Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[7731] 35 40 45
[7732] Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
[7733] 50 55 60
[7734] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[7735] 65 70 75 80
[7736] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[7737] 85 90 95
[7738] Ala Arg Val Lys Pro Val Ala Gly Thr Trp Asp Trp Phe Asp Pro Trp
[7739] 100 105 110
[7740] Gly Gln Gly Thr Pro Val Thr Val Ser Ser Glu Pro Lys Ser Ser Asp
[7741] 115 120 125
[7742] Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
[7743] 130 135 140
[7744] Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
[7745] 145 150 155 160
[7746] Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
[7747] 165 170 175
[7748] Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
[7749] 180 185 190
[7750] Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
[7751] 195 200 205
[7752] Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
[7753] 210 215 220
[7754] Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
[7755] 225 230 235 240
[7756] Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
[7757] 245 250 255
[7758] Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
[7759] 260 265 270
[7760] Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp

[7761] 275 280 285
[7762] Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
[7763] 290 295 300
[7764] Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
[7765] 305 310 315 320
[7766] Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
[7767] 325 330 335
[7768] Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
[7769] 340 345 350
[7770] Gly Lys
[7771] <210> 354
[7772] <211> 354
[7773] <212> PRT
[7774] <213> Artificial Sequence
[7775] <220>
[7776] <223> PR007287 HC
[7777] <400> 354
[7778] Glu Val Gln Leu Glu Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
[7779] 1 5 10 15
[7780] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[7781] 20 25 30
[7782] Tyr Met Ser Trp Phe Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[7783] 35 40 45
[7784] Ser Tyr Ile Ser Ser Ser Gly Ser Ile Thr Asp Tyr Ala Asp Ala Val
[7785] 50 55 60
[7786] Lys Gly Arg Phe Asn Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[7787] 65 70 75 80
[7788] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[7789] 85 90 95
[7790] Ala Arg Glu Arg Glu Ala Val Ala Gly Thr Leu Asp Phe Asp Asn Trp
[7791] 100 105 110
[7792] Gly Gln Gly Thr Leu Val Thr Val Ser Ser Glu Pro Lys Ser Ser Asp
[7793] 115 120 125
[7794] Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
[7795] 130 135 140
[7796] Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
[7797] 145 150 155 160
[7798] Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
[7799] 165 170 175

[7800] Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
[7801] 180 185 190
[7802] Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
[7803] 195 200 205
[7804] Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
[7805] 210 215 220
[7806] Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
[7807] 225 230 235 240
[7808] Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
[7809] 245 250 255
[7810] Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
[7811] 260 265 270
[7812] Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
[7813] 275 280 285
[7814] Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
[7815] 290 295 300
[7816] Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
[7817] 305 310 315 320
[7818] Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
[7819] 325 330 335
[7820] Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
[7821] 340 345 350
[7822] Gly Lys
[7823] <210> 355
[7824] <211> 354
[7825] <212> PRT
[7826] <213> Artificial Sequence
[7827] <220>
[7828] <223> PR007288 HC
[7829] <400> 355
[7830] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
[7831] 1 5 10 15
[7832] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[7833] 20 25 30
[7834] Tyr Met Ser Trp Phe Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[7835] 35 40 45
[7836] Ser Tyr Ile Ser Gly Ser Gly Ser Ile Ile Asp Tyr Ala Asp Ser Val
[7837] 50 55 60
[7838] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr

[7839] 65 70 75 80
[7840] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[7841] 85 90 95
[7842] Ser Arg Glu Arg Glu Ala Val Ala Gly Thr Leu Asp Phe Asp Tyr Trp
[7843] 100 105 110
[7844] Gly Gln Gly Thr Leu Val Thr Val Ser Ser Glu Pro Lys Ser Ser Asp
[7845] 115 120 125
[7846] Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
[7847] 130 135 140
[7848] Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
[7849] 145 150 155 160
[7850] Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
[7851] 165 170 175
[7852] Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
[7853] 180 185 190
[7854] Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
[7855] 195 200 205
[7856] Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
[7857] 210 215 220
[7858] Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
[7859] 225 230 235 240
[7860] Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
[7861] 245 250 255
[7862] Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
[7863] 260 265 270
[7864] Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
[7865] 275 280 285
[7866] Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
[7867] 290 295 300
[7868] Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
[7869] 305 310 315 320
[7870] Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
[7871] 325 330 335
[7872] Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
[7873] 340 345 350
[7874] Gly Lys
[7875] <210> 356
[7876] <211> 354
[7877] <212> PRT

[7878] <213> Artificial Sequence
[7879] <220>
[7880] <223> PR007289 HC
[7881] <400> 356
[7882] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
[7883] 1 5 10 15
[7884] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[7885] 20 25 30
[7886] Tyr Met Ser Trp Phe Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[7887] 35 40 45
[7888] Ser Tyr Ile Ser Ser Ser Gly Ser Thr Gln Asp Tyr Ala Asp Ser Val
[7889] 50 55 60
[7890] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[7891] 65 70 75 80
[7892] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[7893] 85 90 95
[7894] Ala Arg Glu Arg Glu Pro Val Ala Gly Thr Leu Asp Phe Asp Asn Trp
[7895] 100 105 110
[7896] Gly Gln Gly Thr Pro Val Thr Val Ser Ser Glu Pro Lys Ser Ser Asp
[7897] 115 120 125
[7898] Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
[7899] 130 135 140
[7900] Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
[7901] 145 150 155 160
[7902] Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
[7903] 165 170 175
[7904] Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
[7905] 180 185 190
[7906] Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
[7907] 195 200 205
[7908] Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
[7909] 210 215 220
[7910] Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
[7911] 225 230 235 240
[7912] Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
[7913] 245 250 255
[7914] Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
[7915] 260 265 270
[7916] Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp

[7917] 275 280 285
[7918] Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
[7919] 290 295 300
[7920] Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
[7921] 305 310 315 320
[7922] Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
[7923] 325 330 335
[7924] Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
[7925] 340 345 350
[7926] Gly Lys
[7927] <210> 357
[7928] <211> 354
[7929] <212> PRT
[7930] <213> Artificial Sequence
[7931] <220>
[7932] <223> PR007290 HC
[7933] <400> 357
[7934] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
[7935] 1 5 10 15
[7936] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[7937] 20 25 30
[7938] Tyr Met Ser Trp Phe Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[7939] 35 40 45
[7940] Ser Tyr Ile Ser Ser Ser Gly Thr Thr Ile Asp Tyr Ala Asp Ser Val
[7941] 50 55 60
[7942] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[7943] 65 70 75 80
[7944] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[7945] 85 90 95
[7946] Ala Arg Glu Arg Glu Glu Val Ala Gly Thr Leu Asp Phe Asp Tyr Trp
[7947] 100 105 110
[7948] Gly Gln Gly Thr Pro Val Thr Val Ser Ser Glu Pro Lys Ser Ser Asp
[7949] 115 120 125
[7950] Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
[7951] 130 135 140
[7952] Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
[7953] 145 150 155 160
[7954] Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
[7955] 165 170 175

[7956] Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
[7957] 180 185 190
[7958] Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
[7959] 195 200 205
[7960] Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
[7961] 210 215 220
[7962] Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
[7963] 225 230 235 240
[7964] Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
[7965] 245 250 255
[7966] Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
[7967] 260 265 270
[7968] Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
[7969] 275 280 285
[7970] Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
[7971] 290 295 300
[7972] Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
[7973] 305 310 315 320
[7974] Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
[7975] 325 330 335
[7976] Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
[7977] 340 345 350
[7978] Gly Lys
[7979] <210> 358
[7980] <211> 356
[7981] <212> PRT
[7982] <213> Artificial Sequence
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[7984] <223> PR007291 HC
[7985] <400> 358
[7986] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
[7987] 1 5 10 15
[7988] Ser Leu Arg Leu Ser Cys Val Thr Ser Gly Phe Thr Phe Ser Asp Tyr
[7989] 20 25 30
[7990] Tyr Met Asn Trp Ile Arg Gln Ala Pro Gly Lys Gly Gln Glu Trp Val
[7991] 35 40 45
[7992] Ser Tyr Ile Ser Gly Asn Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
[7993] 50 55 60
[7994] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr

[7995] 65 70 75 80
[7996] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[7997] 85 90 95
[7998] Ala Arg Val Arg Pro Gly Gly Ser Gly Asn Tyr Trp Asp Trp Phe Asp
[7999] 100 105 110
[8000] Pro Trp Gly Gln Gly Thr Pro Val Thr Val Ser Ser Glu Pro Lys Ser
[8001] 115 120 125
[8002] Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
[8003] 130 135 140
[8004] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
[8005] 145 150 155 160
[8006] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
[8007] 165 170 175
[8008] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
[8009] 180 185 190
[8010] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
[8011] 195 200 205
[8012] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
[8013] 210 215 220
[8014] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
[8015] 225 230 235 240
[8016] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
[8017] 245 250 255
[8018] Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
[8019] 260 265 270
[8020] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[8021] 275 280 285
[8022] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
[8023] 290 295 300
[8024] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
[8025] 305 310 315 320
[8026] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
[8027] 325 330 335
[8028] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
[8029] 340 345 350
[8030] Ser Pro Gly Lys
[8031] 355
[8032] <210> 359
[8033] <211> 354

[8034] <212> PRT

[8035] <213> Artificial Sequence

[8036] <220>

[8037] <223> PR007292 HC

[8038] <400> 359

[8039] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly

[8040] 1 5 10 15

[8041] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr

[8042] 20 25 30

[8043] Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

[8044] 35 40 45

[8045] Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Asp Tyr Ala Asp Ser Val

[8046] 50 55 60

[8047] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr

[8048] 65 70 75 80

[8049] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

[8050] 85 90 95

[8051] Ala Arg Glu Arg Glu Glu Val Ala Gly Thr Leu Asp Tyr Asp Asn Trp

[8052] 100 105 110

[8053] Gly Gln Gly Thr Leu Val Thr Val Ser Ser Glu Pro Lys Ser Ser Asp

[8054] 115 120 125

[8055] Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly

[8056] 130 135 140

[8057] Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile

[8058] 145 150 155 160

[8059] Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu

[8060] 165 170 175

[8061] Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His

[8062] 180 185 190

[8063] Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg

[8064] 195 200 205

[8065] Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys

[8066] 210 215 220

[8067] Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu

[8068] 225 230 235 240

[8069] Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr

[8070] 245 250 255

[8071] Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu

[8072] 260 265 270

[8073] Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
[8074] 275 280 285
[8075] Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
[8076] 290 295 300
[8077] Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
[8078] 305 310 315 320
[8079] Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
[8080] 325 330 335
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[8084] <210> 360
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[8090] <400> 360
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[8092] 1 5 10 15
[8093] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[8094] 20 25 30
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[8096] 35 40 45
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[8098] 50 55 60
[8099] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[8100] 65 70 75 80
[8101] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[8102] 85 90 95
[8103] Ala Arg Glu Arg Glu Glu Val Ala Gly Thr Leu Asp Phe Asp Tyr Trp
[8104] 100 105 110
[8105] Gly Gln Gly Thr Leu Val Thr Val Ser Ser Glu Pro Lys Ser Ser Asp
[8106] 115 120 125
[8107] Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
[8108] 130 135 140
[8109] Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
[8110] 145 150 155 160
[8111] Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu

[8112] 165 170 175
[8113] Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
[8114] 180 185 190
[8115] Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
[8116] 195 200 205
[8117] Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
[8118] 210 215 220
[8119] Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
[8120] 225 230 235 240
[8121] Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
[8122] 245 250 255
[8123] Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
[8124] 260 265 270
[8125] Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
[8126] 275 280 285
[8127] Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
[8128] 290 295 300
[8129] Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
[8130] 305 310 315 320
[8131] Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
[8132] 325 330 335
[8133] Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
[8134] 340 345 350
[8135] Gly Lys
[8136] <210> 361
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[8142] <400> 361
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[8144] 1 5 10 15
[8145] Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[8146] 20 25 30
[8147] Tyr Met Ser Trp Phe Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[8148] 35 40 45
[8149] Ser Tyr Ile Ser Gly Ser Gly Thr Thr Ile Asp Tyr Ala Asp Ser Val
[8150] 50 55 60

[8151] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[8152] 65 70 75 80
[8153] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[8154] 85 90 95
[8155] Ala Arg Glu Arg Glu Pro Val Ala Gly Thr Leu Asp Phe Asp Asn Trp
[8156] 100 105 110
[8157] Gly Gln Gly Thr Leu Val Thr Val Ser Ser Glu Pro Lys Ser Ser Asp
[8158] 115 120 125
[8159] Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
[8160] 130 135 140
[8161] Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
[8162] 145 150 155 160
[8163] Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
[8164] 165 170 175
[8165] Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
[8166] 180 185 190
[8167] Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
[8168] 195 200 205
[8169] Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
[8170] 210 215 220
[8171] Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
[8172] 225 230 235 240
[8173] Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
[8174] 245 250 255
[8175] Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
[8176] 260 265 270
[8177] Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
[8178] 275 280 285
[8179] Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
[8180] 290 295 300
[8181] Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
[8182] 305 310 315 320
[8183] Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
[8184] 325 330 335
[8185] Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
[8186] 340 345 350
[8187] Gly Lys
[8188] <210> 362
[8189] <211> 356

[8190] <212> PRT

[8191] <213> Artificial Sequence

[8192] <220>

[8193] <223> PR007295 HC

[8194] <400> 362

[8195] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly

[8196] 1 5 10 15

[8197] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr

[8198] 20 25 30

[8199] Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

[8200] 35 40 45

[8201] Ser Tyr Ile Ser Asn Asn Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val

[8202] 50 55 60

[8203] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr

[8204] 65 70 75 80

[8205] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

[8206] 85 90 95

[8207] Ala Arg Val Arg Pro Gly Gly Ser Gly Asn Tyr Trp Asp Trp Phe Asp

[8208] 100 105 110

[8209] Pro Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Glu Pro Lys Ser

[8210] 115 120 125

[8211] Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu

[8212] 130 135 140

[8213] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu

[8214] 145 150 155 160

[8215] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser

[8216] 165 170 175

[8217] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu

[8218] 180 185 190

[8219] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr

[8220] 195 200 205

[8221] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn

[8222] 210 215 220

[8223] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro

[8224] 225 230 235 240

[8225] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln

[8226] 245 250 255

[8227] Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val

[8228] 260 265 270

[8229] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[8230] 275 280 285
[8231] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
[8232] 290 295 300
[8233] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
[8234] 305 310 315 320
[8235] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
[8236] 325 330 335
[8237] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
[8238] 340 345 350
[8239] Ser Pro Gly Lys
[8240] 355
[8241] <210> 363
[8242] <211> 354
[8243] <212> PRT
[8244] <213> Artificial Sequence
[8245] <220>
[8246] <223> PR007296 HC
[8247] <400> 363
[8248] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
[8249] 1 5 10 15
[8250] Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[8251] 20 25 30
[8252] Tyr Met Ser Trp Phe Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[8253] 35 40 45
[8254] Ser Tyr Ile Ser Gly Ser Gly Thr Thr Ile Asp Tyr Ala Asp Ser Val
[8255] 50 55 60
[8256] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[8257] 65 70 75 80
[8258] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[8259] 85 90 95
[8260] Ala Arg Glu Arg Glu Ala Val Ala Gly Thr Leu Asp Phe Asp Asn Trp
[8261] 100 105 110
[8262] Gly Gln Gly Thr Pro Val Thr Val Ser Ser Glu Pro Lys Ser Ser Asp
[8263] 115 120 125
[8264] Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
[8265] 130 135 140
[8266] Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
[8267] 145 150 155 160

[8268] Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
[8269] 165 170 175
[8270] Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
[8271] 180 185 190
[8272] Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
[8273] 195 200 205
[8274] Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
[8275] 210 215 220
[8276] Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
[8277] 225 230 235 240
[8278] Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
[8279] 245 250 255
[8280] Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
[8281] 260 265 270
[8282] Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
[8283] 275 280 285
[8284] Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
[8285] 290 295 300
[8286] Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
[8287] 305 310 315 320
[8288] Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
[8289] 325 330 335
[8290] Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
[8291] 340 345 350
[8292] Gly Lys
[8293] <210> 364
[8294] <211> 356
[8295] <212> PRT
[8296] <213> Artificial Sequence
[8297] <220>
[8298] <223> PR007297 HC
[8299] <400> 364
[8300] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
[8301] 1 5 10 15
[8302] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[8303] 20 25 30
[8304] Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[8305] 35 40 45
[8306] Ser Tyr Ile Ser Arg Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val

[8307] 50 55 60
[8308] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[8309] 65 70 75 80
[8310] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[8311] 85 90 95
[8312] Ala Arg Val Arg Pro Gly Gly Ser Gly Asn Tyr Trp Asp Trp Phe Asp
[8313] 100 105 110
[8314] Pro Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Glu Pro Lys Ser
[8315] 115 120 125
[8316] Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
[8317] 130 135 140
[8318] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
[8319] 145 150 155 160
[8320] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
[8321] 165 170 175
[8322] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
[8323] 180 185 190
[8324] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
[8325] 195 200 205
[8326] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
[8327] 210 215 220
[8328] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
[8329] 225 230 235 240
[8330] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
[8331] 245 250 255
[8332] Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
[8333] 260 265 270
[8334] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[8335] 275 280 285
[8336] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
[8337] 290 295 300
[8338] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
[8339] 305 310 315 320
[8340] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
[8341] 325 330 335
[8342] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
[8343] 340 345 350
[8344] Ser Pro Gly Lys
[8345] 355

[8346] <210> 365
[8347] <211> 354
[8348] <212> PRT
[8349] <213> Artificial Sequence
[8350] <220>
[8351] <223> PR007298 HC
[8352] <400> 365
[8353] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
[8354] 1 5 10 15
[8355] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[8356] 20 25 30
[8357] Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[8358] 35 40 45
[8359] Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Asp Tyr Ala Asp Ser Val
[8360] 50 55 60
[8361] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
[8362] 65 70 75 80
[8363] Leu Glu Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[8364] 85 90 95
[8365] Ala Arg Glu Arg Glu Glu Val Ala Gly Thr Leu Asp Phe Asp Asn Trp
[8366] 100 105 110
[8367] Gly Gln Gly Thr Leu Val Thr Val Ser Ser Glu Pro Lys Ser Ser Asp
[8368] 115 120 125
[8369] Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
[8370] 130 135 140
[8371] Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
[8372] 145 150 155 160
[8373] Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
[8374] 165 170 175
[8375] Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
[8376] 180 185 190
[8377] Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
[8378] 195 200 205
[8379] Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
[8380] 210 215 220
[8381] Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
[8382] 225 230 235 240
[8383] Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
[8384] 245 250 255

[8385] Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
[8386] 260 265 270
[8387] Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
[8388] 275 280 285
[8389] Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
[8390] 290 295 300
[8391] Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
[8392] 305 310 315 320
[8393] Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
[8394] 325 330 335
[8395] Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
[8396] 340 345 350
[8397] Gly Lys
[8398] <210> 366
[8399] <211> 346
[8400] <212> PRT
[8401] <213> Artificial Sequence
[8402] <220>
[8403] <223> PR007299 HC
[8404] <400> 366
[8405] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
[8406] 1 5 10 15
[8407] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[8408] 20 25 30
[8409] Gln Met Ser Trp Leu Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[8410] 35 40 45
[8411] Ser Tyr Ile Ser Ser Ser Gly Arg Thr Ile Tyr Tyr Ala Asp Ser Val
[8412] 50 55 60
[8413] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Val Ser
[8414] 65 70 75 80
[8415] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[8416] 85 90 95
[8417] Ala Arg Glu Gly Arg Phe Phe Pro Gly Gln Gly Thr Pro Val Thr Val
[8418] 100 105 110
[8419] Ser Ser Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys
[8420] 115 120 125
[8421] Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
[8422] 130 135 140
[8423] Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys

[8424] 145 150 155 160
[8425] Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
[8426] 165 170 175
[8427] Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
[8428] 180 185 190
[8429] Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
[8430] 195 200 205
[8431] His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
[8432] 210 215 220
[8433] Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
[8434] 225 230 235 240
[8435] Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
[8436] 245 250 255
[8437] Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
[8438] 260 265 270
[8439] Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
[8440] 275 280 285
[8441] Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
[8442] 290 295 300
[8443] Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
[8444] 305 310 315 320
[8445] Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
[8446] 325 330 335
[8447] Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[8448] 340 345
[8449] <210> 367
[8450] <211> 356
[8451] <212> PRT
[8452] <213> Artificial Sequence
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[8454] <223> PR007300 HC
[8455] <400> 367
[8456] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
[8457] 1 5 10 15
[8458] Ser Leu Arg Leu Ser Cys Thr Thr Ser Gly Phe Thr Phe Ser Asp Tyr
[8459] 20 25 30
[8460] Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[8461] 35 40 45
[8462] Ser Tyr Ile Ser Asn Asn Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val

[8463] 50 55 60

[8464] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr

[8465] 65 70 75 80

[8466] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

[8467] 85 90 95

[8468] Ala Arg Val Arg Pro Gly Gly Ser Gly Asn Tyr Trp Asp Trp Phe Asp

[8469] 100 105 110

[8470] Pro Trp Gly Gln Gly Thr Pro Val Thr Val Ser Ser Glu Pro Lys Ser

[8471] 115 120 125

[8472] Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu

[8473] 130 135 140

[8474] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu

[8475] 145 150 155 160

[8476] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser

[8477] 165 170 175

[8478] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu

[8479] 180 185 190

[8480] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr

[8481] 195 200 205

[8482] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn

[8483] 210 215 220

[8484] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro

[8485] 225 230 235 240

[8486] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln

[8487] 245 250 255

[8488] Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val

[8489] 260 265 270

[8490] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val

[8491] 275 280 285

[8492] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro

[8493] 290 295 300

[8494] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr

[8495] 305 310 315 320

[8496] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val

[8497] 325 330 335

[8498] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu

[8499] 340 345 350

[8500] Ser Pro Gly Lys

[8501] 355

[8502] <210> 368
[8503] <211> 356
[8504] <212> PRT
[8505] <213> Artificial Sequence
[8506] <220>
[8507] <223> PR007381 HC
[8508] <400> 368

[8509] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
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[8511] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
[8512] 20 25 30
[8513] Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[8514] 35 40 45
[8515] Ser Ser Ile Asp Ala Ser Gly Gly Asp Thr Tyr Tyr Ala Asp Ser Val
[8516] 50 55 60
[8517] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[8518] 65 70 75 80
[8519] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[8520] 85 90 95
[8521] Ala Lys Glu Gly Ser His Gly Thr Asp Asp Ser His Tyr Asp Val Asp
[8522] 100 105 110
[8523] Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Glu Pro Lys Ser
[8524] 115 120 125
[8525] Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
[8526] 130 135 140
[8527] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
[8528] 145 150 155 160
[8529] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
[8530] 165 170 175
[8531] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
[8532] 180 185 190
[8533] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
[8534] 195 200 205
[8535] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
[8536] 210 215 220
[8537] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
[8538] 225 230 235 240
[8539] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
[8540] 245 250 255

[8541] Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
[8542] 260 265 270
[8543] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[8544] 275 280 285
[8545] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
[8546] 290 295 300
[8547] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
[8548] 305 310 315 320
[8549] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
[8550] 325 330 335
[8551] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
[8552] 340 345 350
[8553] Ser Pro Gly Lys
[8554] 355
[8555] <210> 369
[8556] <211> 578
[8557] <212> PRT
[8558] <213> Artificial Sequence
[8559] <220>
[8560] <223> PR007130链
[8561] <400> 369
[8562] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[8563] 1 5 10 15
[8564] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
[8565] 20 25 30
[8566] Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[8567] 35 40 45
[8568] Ala Asn Ile Lys Gln Glu Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
[8569] 50 55 60
[8570] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[8571] 65 70 75 80
[8572] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[8573] 85 90 95
[8574] Ala Arg Asp Arg Ala Val Ala Gly Ala Phe Asp Ile Trp Gly Gln Gly
[8575] 100 105 110
[8576] Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
[8577] 115 120 125
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[8579] 130 135 140

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[8595] 260 265 270
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[8613] 405 410 415
[8614] Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
[8615] 420 425 430
[8616] Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[8617] 435 440 445
[8618] Gly Gly Ser Gly Gly Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly

[8619] 450 455 460
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[8622] Phe Thr Phe Ser Asn Tyr Ala Met Ser Trp Phe Arg Gln Pro Pro Glu
[8623] 485 490 495
[8624] Thr Gly Leu Lys Trp Val Ser Ser Ile Asp Ala Ser Gly Gly Asp Thr
[8625] 500 505 510
[8626] Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
[8627] 515 520 525
[8628] Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
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[8630] Thr Ala Val Tyr Tyr Cys Ala Lys Glu Gly Ser His Gly Thr Asp Asp
[8631] 545 550 555 560
[8632] Ser His Tyr Asp Val Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val
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[8665] 180 185 190
[8666] Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
[8667] 195 200 205
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[8675] 260 265 270
[8676] Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
[8677] 275 280 285
[8678] Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
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[8685] 340 345 350
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[8687] 355 360 365
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[8693] 405 410 415
[8694] Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
[8695] 420 425 430
[8696] Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly

[8697] 435 440 445
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[8699] 450 455 460
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[8702] Phe Thr Phe Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly
[8703] 485 490 495
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[8707] 515 520 525
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[8710] Thr Ala Val Tyr Tyr Cys Ala Arg Val Lys Pro Val Ala Gly Thr Trp
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[8712] Asp Trp Phe Asp Pro Trp Gly Gln Gly Thr Pro Val Thr Val Ser Ser
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[8726] 35 40 45
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[8736] 115 120 125
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[8738] 130 135 140
[8739] Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
[8740] 145 150 155 160
[8741] Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
[8742] 165 170 175
[8743] Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
[8744] 180 185 190
[8745] Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
[8746] 195 200 205
[8747] Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
[8748] 210 215 220
[8749] Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro
[8750] 225 230 235 240
[8751] Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
[8752] 245 250 255
[8753] Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
[8754] 260 265 270
[8755] Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
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[8759] Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
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[8761] Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
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[8763] Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
[8764] 340 345 350
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[8766] 355 360 365
[8767] Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
[8768] 370 375 380
[8769] Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
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[8772] 405 410 415
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[8775] Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[8776] 435 440 445
[8777] Gly Gly Ser Gly Gly Ser Glu Val Gln Leu Glu Glu Ser Gly Gly Gly
[8778] 450 455 460
[8779] Leu Val Lys Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
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[8781] Phe Thr Phe Ser Asp Tyr Tyr Met Ser Trp Phe Arg Gln Ala Pro Gly
[8782] 485 490 495
[8783] Lys Gly Leu Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser Ile Thr
[8784] 500 505 510
[8785] Asp Tyr Ala Asp Ala Val Lys Gly Arg Phe Asn Ile Ser Arg Asp Asn
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[8805] 35 40 45
[8806] Ala Asn Ile Lys Gln Glu Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
[8807] 50 55 60
[8808] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
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[8811] 85 90 95
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[8826] Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
[8827] 210 215 220
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[8833] 260 265 270
[8834] Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
[8835] 275 280 285
[8836] Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
[8837] 290 295 300
[8838] Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
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[8840] Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
[8841] 325 330 335
[8842] Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
[8843] 340 345 350
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[8845] 355 360 365
[8846] Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
[8847] 370 375 380
[8848] Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
[8849] 385 390 395 400
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[8851] 405 410 415
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[8853] 420 425 430
[8854] Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
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[8858] Leu Val Lys Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
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[8864] Asp Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
[8865] 515 520 525
[8866] Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
[8867] 530 535 540
[8868] Thr Ala Val Tyr Tyr Cys Ser Arg Glu Arg Glu Ala Val Ala Gly Thr
[8869] 545 550 555 560
[8870] Leu Asp Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
[8871] 565 570 575
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[8884] 35 40 45
[8885] Ala Asn Ile Lys Gln Glu Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
[8886] 50 55 60
[8887] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
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[8890] 85 90 95
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[8906] 210 215 220
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[8912] 260 265 270
[8913] Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
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[8916] 290 295 300
[8917] Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
[8918] 305 310 315 320
[8919] Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
[8920] 325 330 335
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[8926] 370 375 380
[8927] Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
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[8933] Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
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[8936] 450 455 460
[8937] Leu Val Lys Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
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[8944] 515 520 525
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[8947] Thr Ala Val Tyr Tyr Cys Ala Arg Glu Arg Glu Pro Val Ala Gly Thr
[8948] 545 550 555 560
[8949] Leu Asp Phe Asp Asn Trp Gly Gln Gly Thr Pro Val Thr Val Ser Ser
[8950] 565 570 575
[8951] <210> 374
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[8963] 35 40 45
[8964] Ala Asn Ile Lys Gln Glu Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
[8965] 50 55 60
[8966] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
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[8969] 85 90 95

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[8983] 195 200 205
[8984] Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
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[8991] 260 265 270
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[8995] 290 295 300
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[8997] 305 310 315 320
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[9004] Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
[9005] 370 375 380
[9006] Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
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[9012] Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
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[9015] 450 455 460
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[9017] 465 470 475 480
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[9019] 485 490 495
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[9021] 500 505 510
[9022] Asp Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
[9023] 515 520 525
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[9025] 530 535 540
[9026] Thr Ala Val Tyr Tyr Cys Ala Arg Glu Arg Glu Glu Val Ala Gly Thr
[9027] 545 550 555 560
[9028] Leu Asp Phe Asp Tyr Trp Gly Gln Gly Thr Pro Val Thr Val Ser Ser
[9029] 565 570 575
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[9042] 35 40 45
[9043] Ala Asn Ile Lys Gln Glu Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
[9044] 50 55 60
[9045] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
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[9047] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

[9048] 85 90 95

[9049] Ala Arg Asp Arg Ala Val Ala Gly Ala Phe Asp Ile Trp Gly Gln Gly

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[9051] Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe

[9052] 115 120 125

[9053] Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

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[9056] 145 150 155 160

[9057] Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

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[9060] 180 185 190

[9061] Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

[9062] 195 200 205

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[9223] 210 215 220
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[9239] 340 345 350
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[9243] 370 375 380

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[9255] 465 470 475 480

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[9283] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr

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[9298] 180 185 190

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[9320] 355 360 365

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[9332] 450 455 460
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[9420] 515 520 525
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[9481] 370 375 380
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[9492] Leu Val Lys Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
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[9501] 530 535 540
[9502] Thr Ala Val Tyr Tyr Cys Ala Arg Val Arg Pro Gly Gly Ser Gly Asn
[9503] 545 550 555 560
[9504] Tyr Trp Asp Trp Phe Asp Pro Trp Gly Gln Gly Thr Leu Val Thr Val
[9505] 565 570 575
[9506] Ser Ser
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[9551] 290 295 300
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[9553] 305 310 315 320
[9554] Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys

[9555] 325 330 335
[9556] Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
[9557] 340 345 350
[9558] Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
[9559] 355 360 365
[9560] Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
[9561] 370 375 380
[9562] Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
[9563] 385 390 395 400
[9564] Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
[9565] 405 410 415
[9566] Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
[9567] 420 425 430
[9568] Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[9569] 435 440 445
[9570] Gly Gly Ser Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly
[9571] 450 455 460
[9572] Leu Val Lys Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly
[9573] 465 470 475 480
[9574] Phe Thr Phe Ser Asp Tyr Tyr Met Ser Trp Val Arg Gln Ala Pro Gly
[9575] 485 490 495
[9576] Lys Gly Leu Glu Trp Val Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile
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[9578] Asp Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
[9579] 515 520 525
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[9585] 565 570 575
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[9589] <213> Artificial Sequence
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[9593] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

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[9595] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
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[9597] Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[9598] 35 40 45
[9599] Ala Asn Ile Lys Gln Glu Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
[9600] 50 55 60
[9601] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[9602] 65 70 75 80
[9603] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[9604] 85 90 95
[9605] Ala Arg Asp Arg Ala Val Ala Gly Ala Phe Asp Ile Trp Gly Gln Gly
[9606] 100 105 110
[9607] Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
[9608] 115 120 125
[9609] Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
[9610] 130 135 140
[9611] Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
[9612] 145 150 155 160
[9613] Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
[9614] 165 170 175
[9615] Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
[9616] 180 185 190
[9617] Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
[9618] 195 200 205
[9619] Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
[9620] 210 215 220
[9621] Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Ala Pro
[9622] 225 230 235 240
[9623] Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
[9624] 245 250 255
[9625] Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
[9626] 260 265 270
[9627] Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
[9628] 275 280 285
[9629] Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
[9630] 290 295 300
[9631] Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
[9632] 305 310 315 320

[9633] Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
[9634] 325 330 335
[9635] Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
[9636] 340 345 350
[9637] Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
[9638] 355 360 365
[9639] Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
[9640] 370 375 380
[9641] Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
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[9643] Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
[9644] 405 410 415
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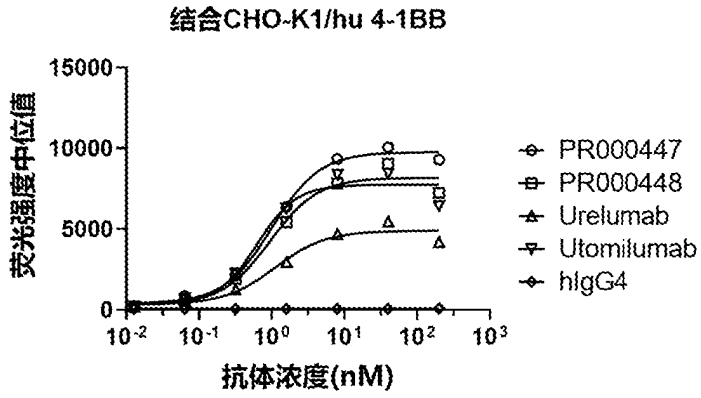
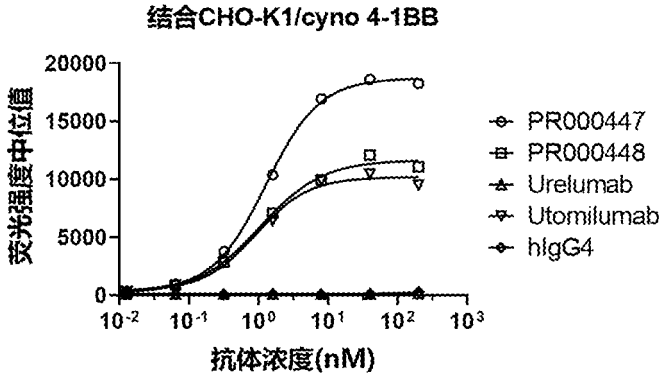
[9657] Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn
[9658] 515 520 525
[9659] Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
[9660] 530 535 540
[9661] Thr Ala Val Tyr Tyr Cys Ala Arg Val Arg Pro Gly Gly Ser Gly Asn
[9662] 545 550 555 560
[9663] Tyr Trp Asp Trp Phe Asp Pro Trp Gly Gln Gly Thr Pro Val Thr Val
[9664] 565 570 575
[9665] Ser Ser



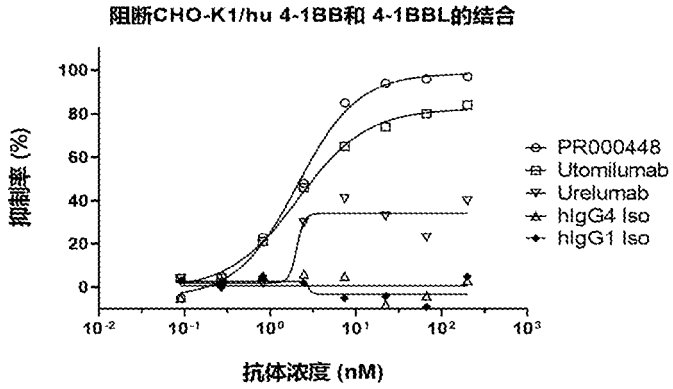
抗体	EC50 (nM)	最大结合值
PR000447	1.007	9768
PR000448	0.9473	8182
Urelumab	1.114	4898
Utomilumab	0.6271	7747

图1A



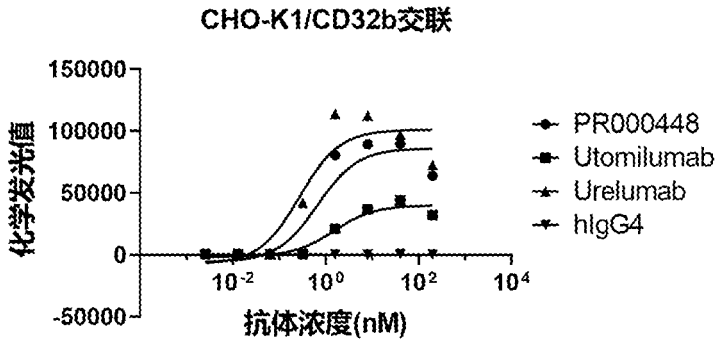
抗体	EC50 (nM)	最大结合值
PR000447	1.285	18715
PR000448	1.064	11657
Urelumab	不结合	
Utomilumab	0.9293	10188

图1B



抗体	IC50 (nM)	最大抑制率 (%)
PR000448	2.054	97
Utomilumab	2.103	84
Urelumab	n.d.	40

图2



抗体	EC50	最大值
PR000448	0.6632	86095
Utomilumab	1.489	40042
Urelumab	0.2728	101148

图3A

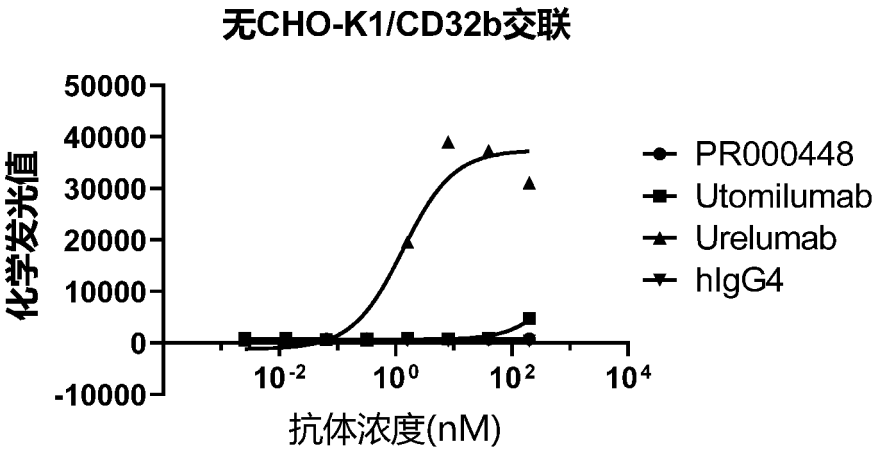


图3B

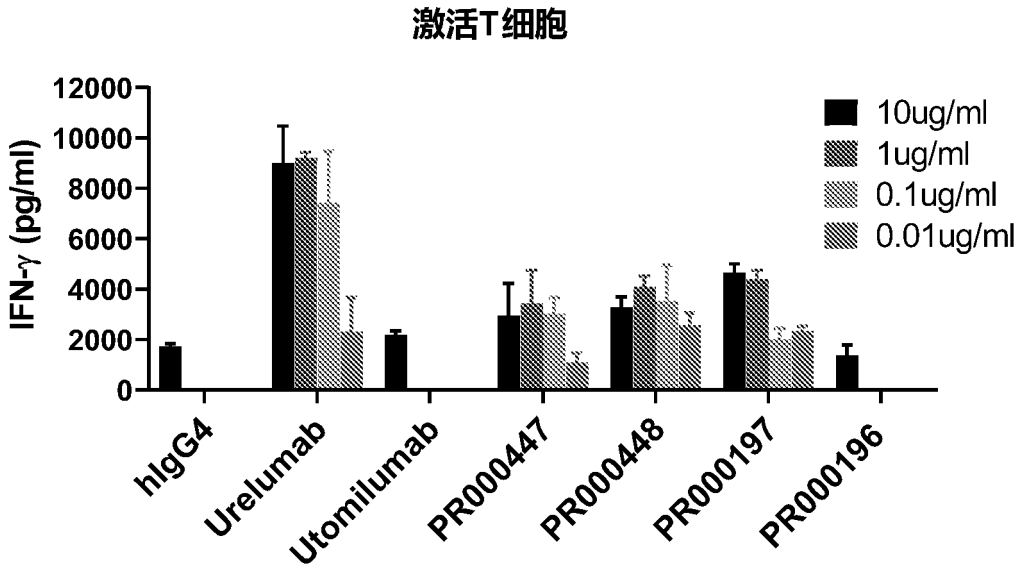


图4

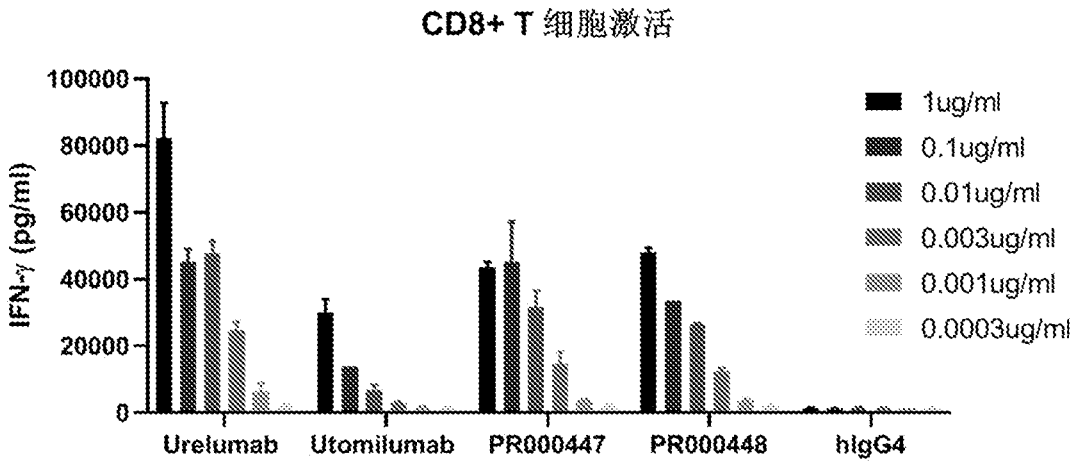

CD8+ T 细胞激活
IFN-γ (pg/ml)
100000
80000
60000
40000
20000
0
1ug/ml
0.1ug/ml
0.01ug/ml
0.003ug/ml
0.001ug/ml
0.0003ug/ml
Urelumab
Utomilumab
PR000447
PR000448
hIgG4

图5A

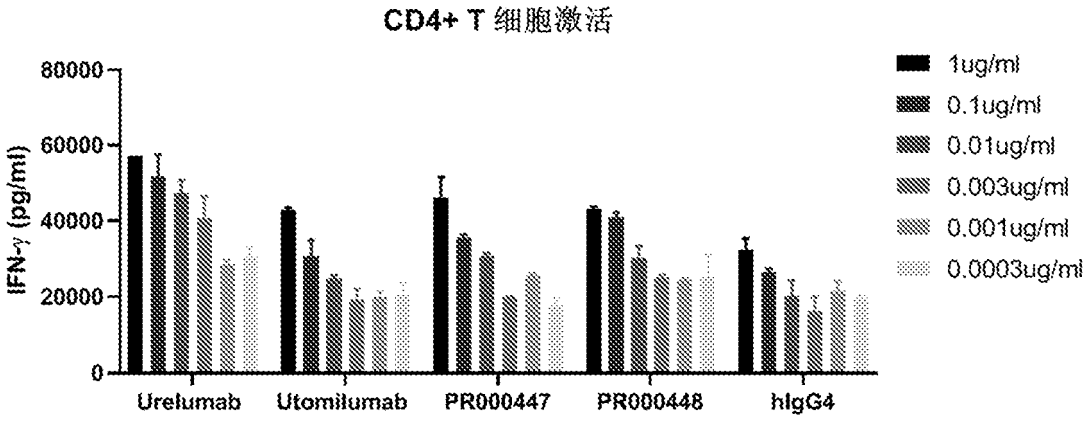

CD4+ T 细胞激活
IFN-γ (pg/ml)
80000
60000
40000
20000
0
1ug/ml
0.1ug/ml
0.01ug/ml
0.003ug/ml
0.001ug/ml
0.0003ug/ml
Urelumab
Utomilumab
PR000447
PR000448
hIgG4

图5B

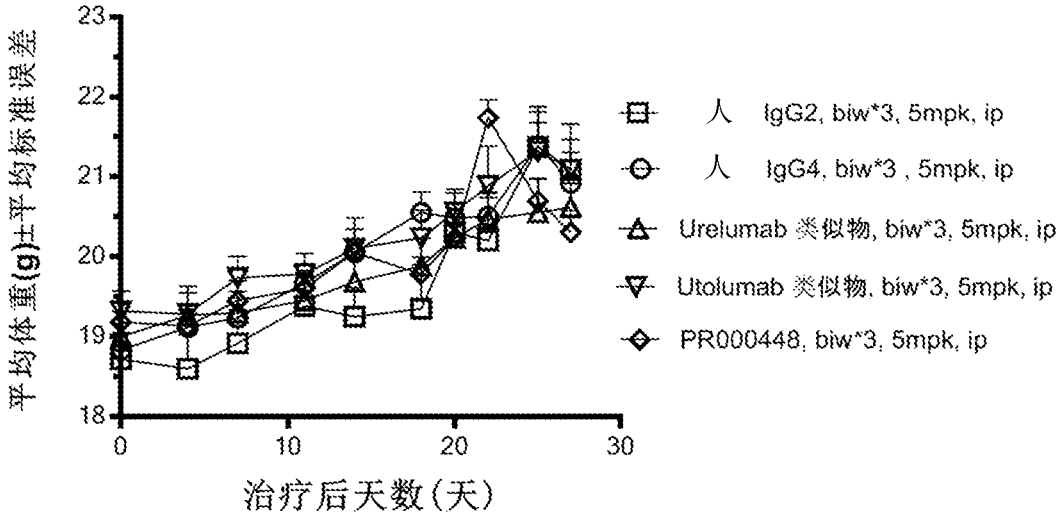

平均体重(g)±平均标准误差
23
22
21
20
19
18
0
10
20
30
治疗后天数(天)
人 IgG2, biw*3, 5mpk, ip
人 IgG4, biw*3 , 5mpk, ip
Urelumab 类似物, biw*3, 5mpk, ip
Utolumab 类似物, biw*3, 5mpk, ip
PR000448, biw*3, 5mpk, ip

图6A

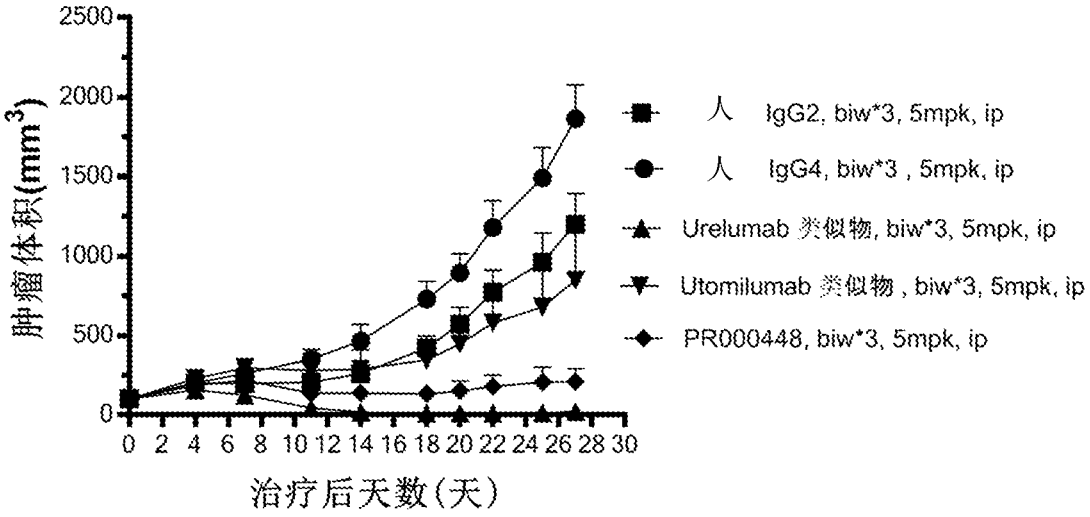

2500
2000
1500
1000
500
0
肿瘤体积(mm3)
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
治疗后天数(天)
人 IgG2, biw*3, 5mpk, ip
人 IgG4, biw*3 , 5mpk, ip
Urelumab 类似物, biw*3, 5mpk, ip
Utomilumab 类似物 , biw*3, 5mpk, ip
PR000448, biw*3, 5mpk, ip

图6B

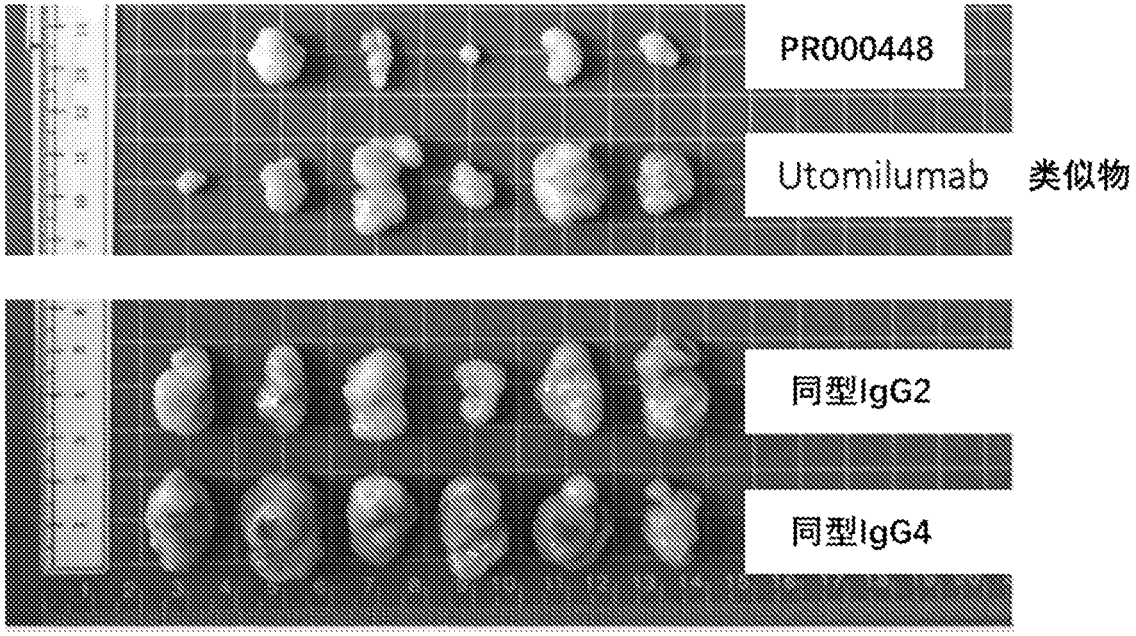

PR000448
Utomilumab 类似物
同型IgG2
同型IgG4

图6C

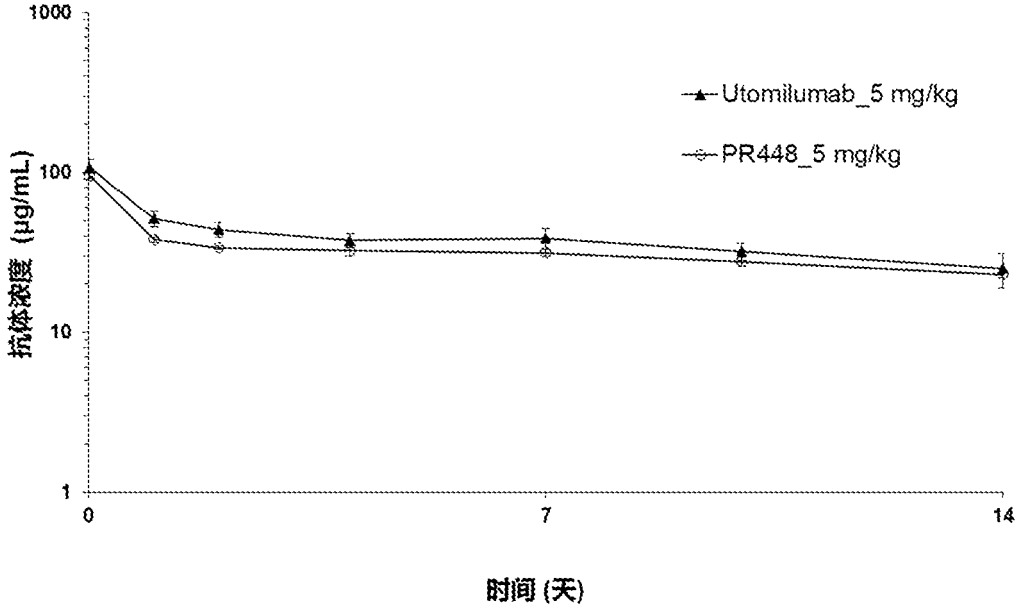

1000
100
10
1
抗体浓度 (μg/mL)
0
7
14
时间 (天)
Utomilumab_5 mg/kg
PR448_5 mg/kg

图7

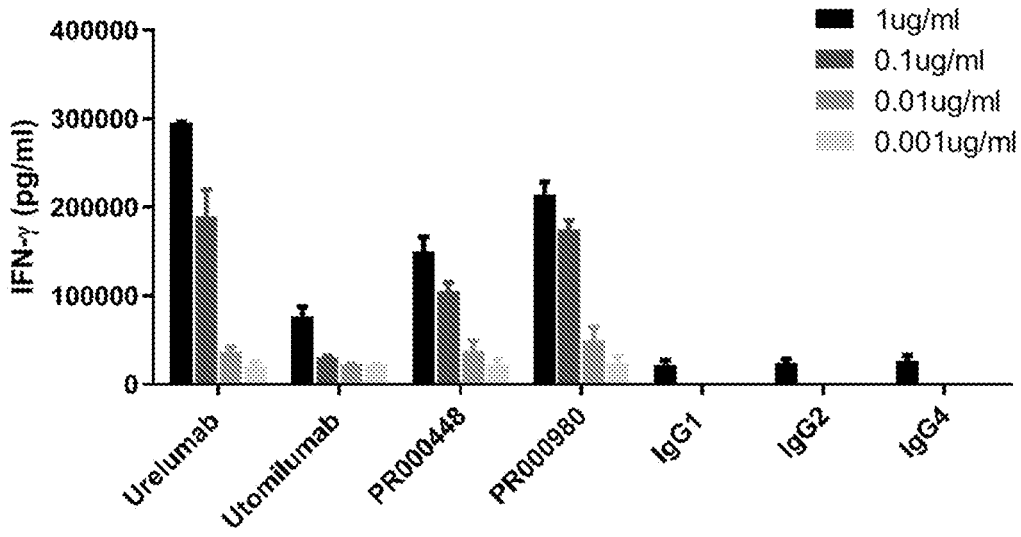

400000
300000
200000
100000
0
IFN-γ (pg/ml)
1ug/ml
0.1ug/ml
0.01ug/ml
0.001ug/ml
Urelumab
Utomilumab
PR000448
PR000980
IgG1
IgG2
IgG4

图8A

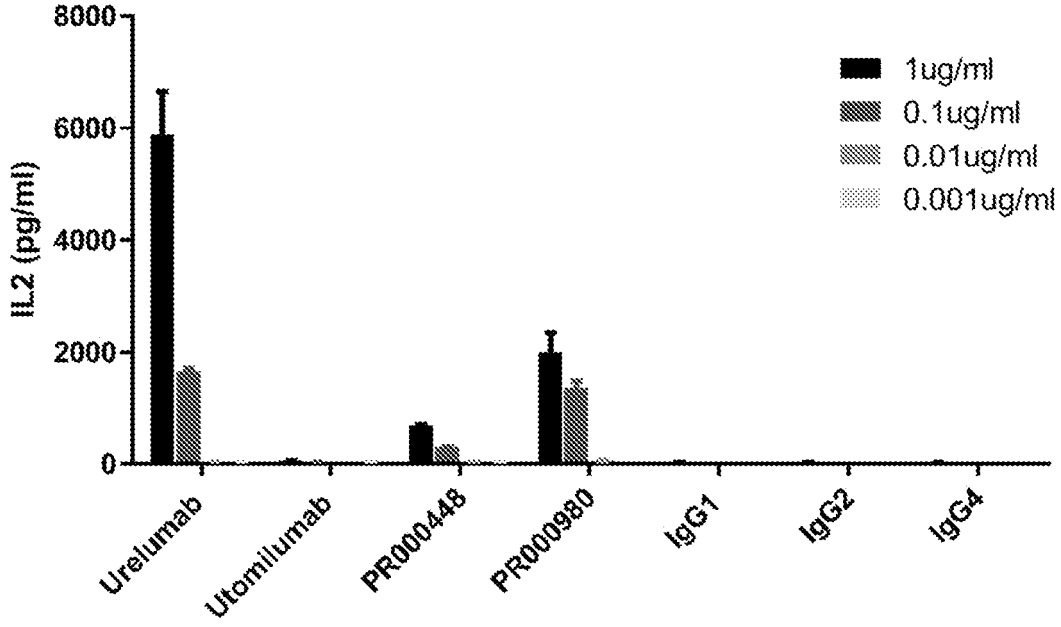

8000
6000
4000
2000
0
IL2 (pg/ml)
1ug/ml
0.1ug/ml
0.01ug/ml
0.001ug/ml
Urelumab
Utomilumab
PR000448
PR000980
IgG1
IgG2
IgG4

图8B

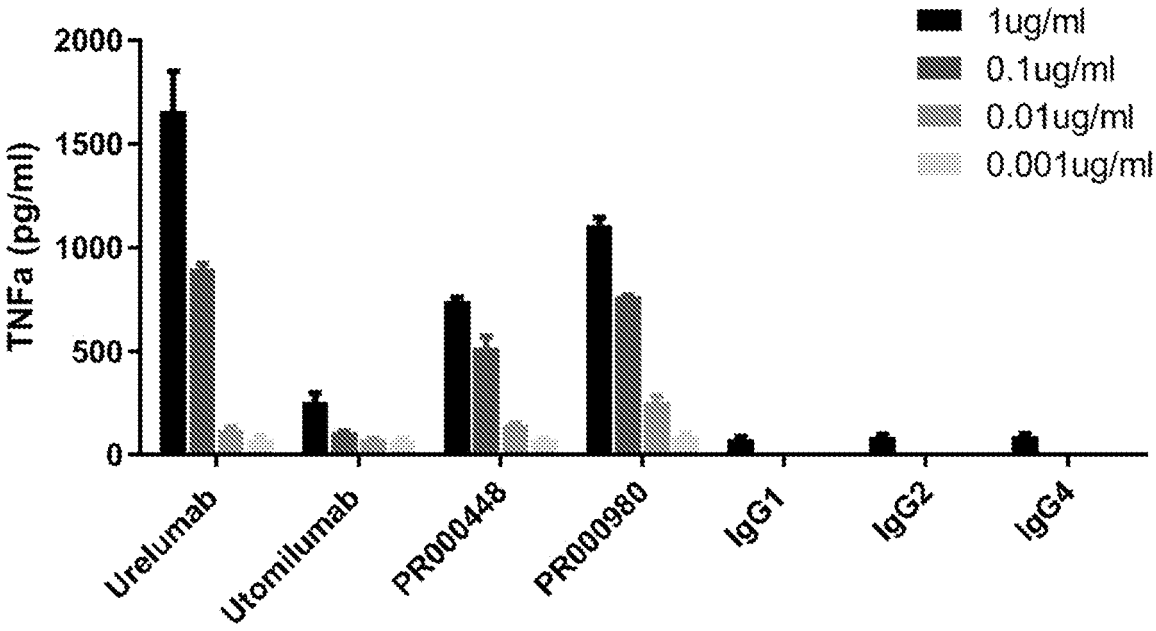

2000
1500
1000
500
0
TNFa (pg/ml)
1ug/ml
0.1ug/ml
0.01ug/ml
0.001ug/ml
Urelumab
Utomilumab
PR000448
PR000980
IgG1
IgG2
IgG4

图8C

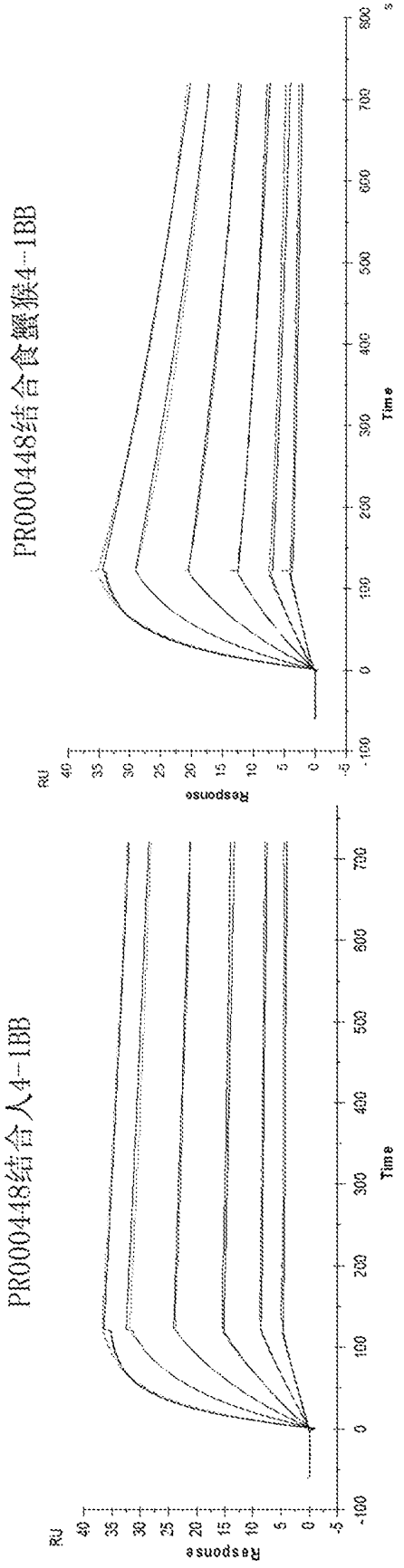


图9A

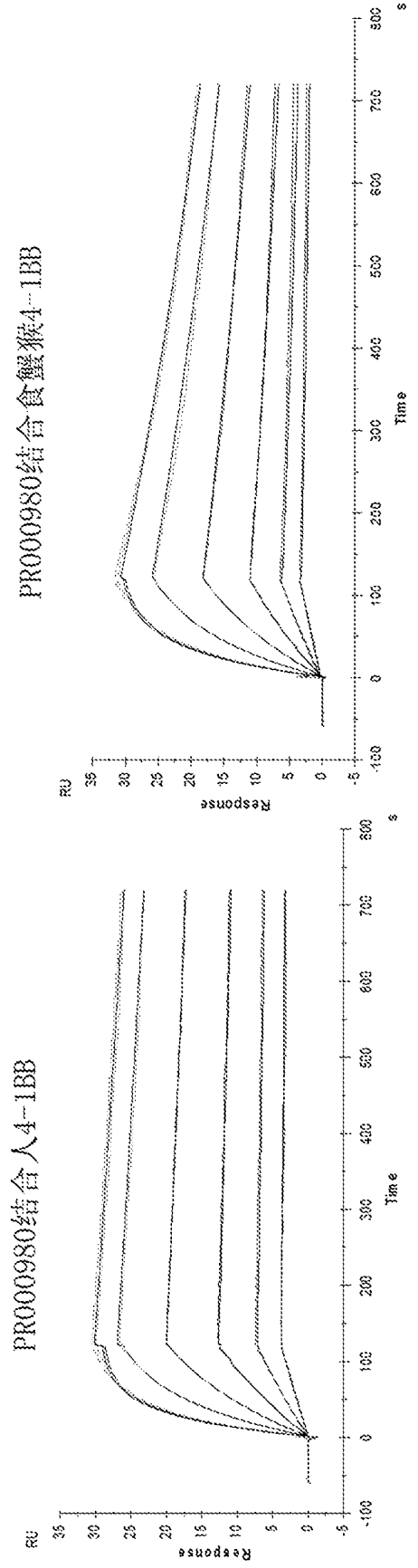


图9B

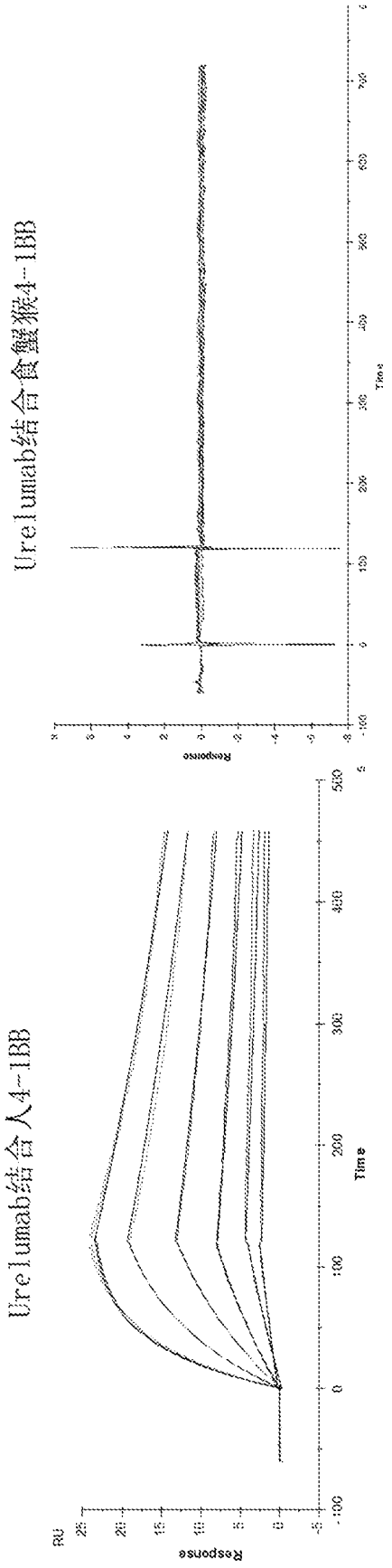

Urelumab结合食蟹猴4-1BB
Response
Time
Urelumab结合人4-1BB
RU
Response
Time

图9C

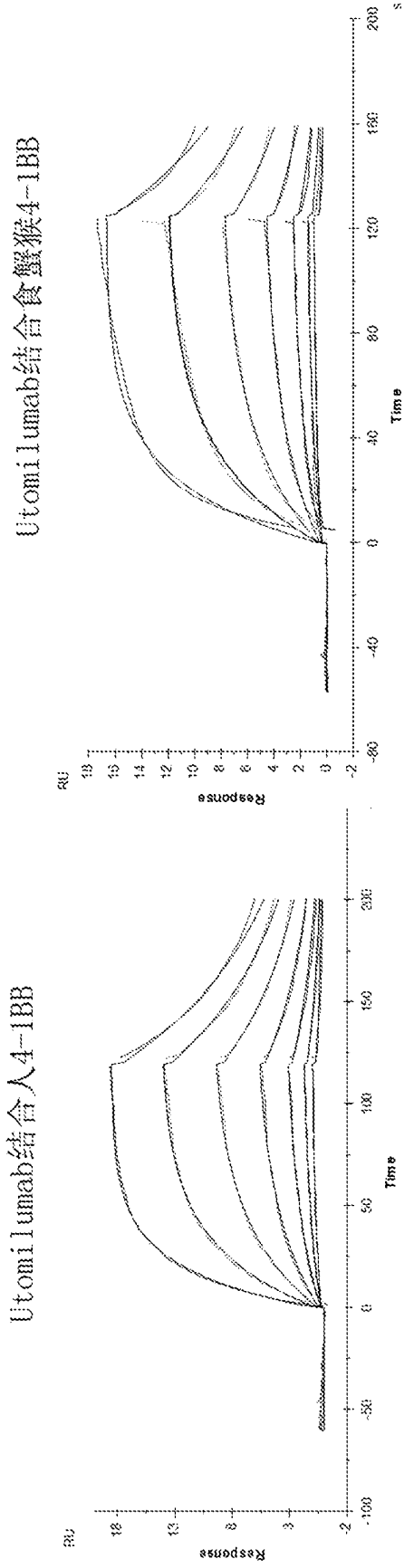


图9D

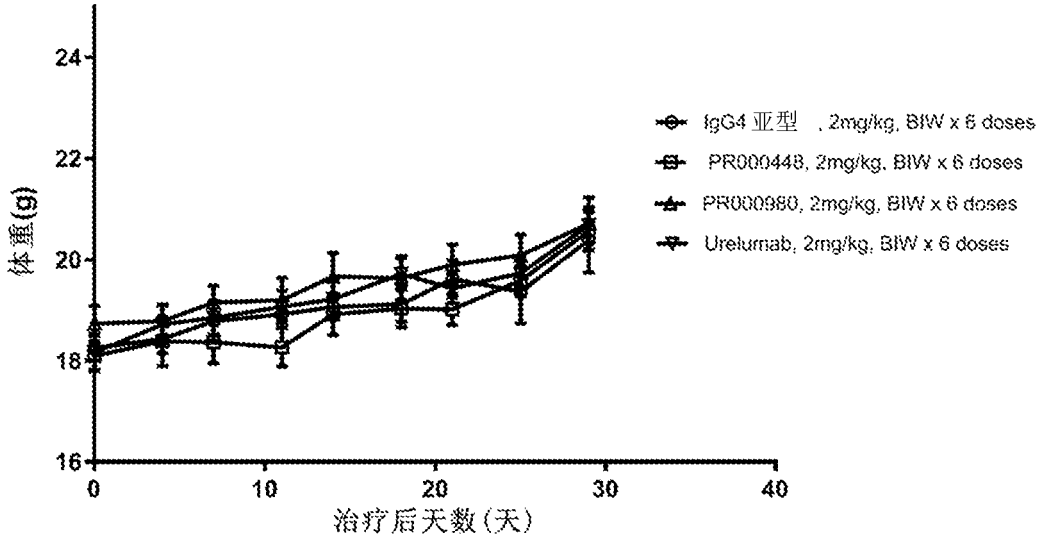


图10A

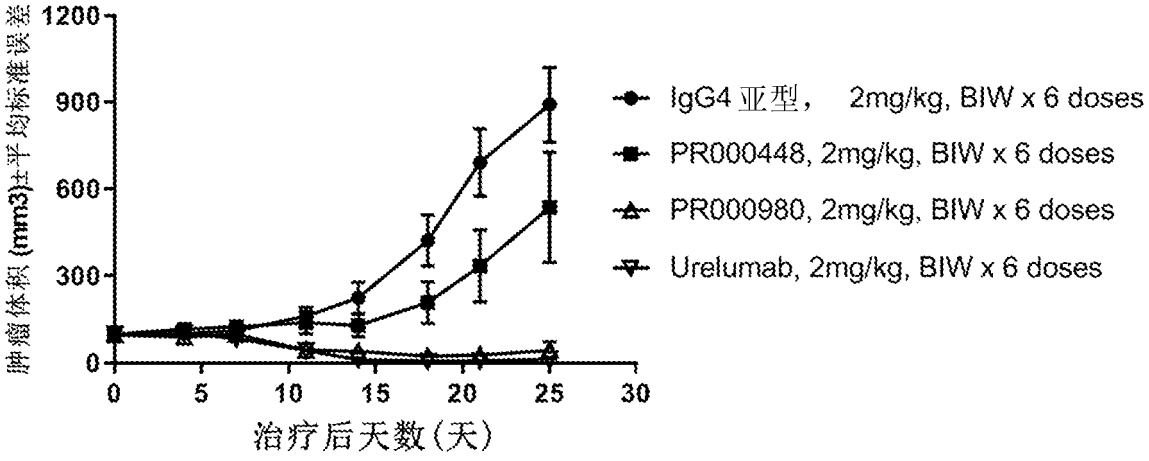
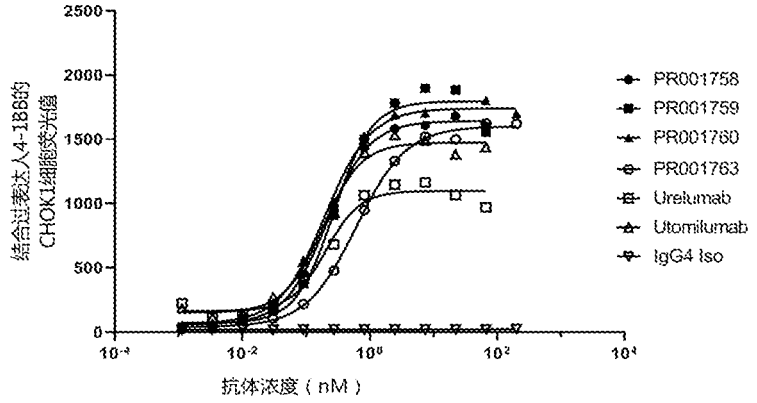
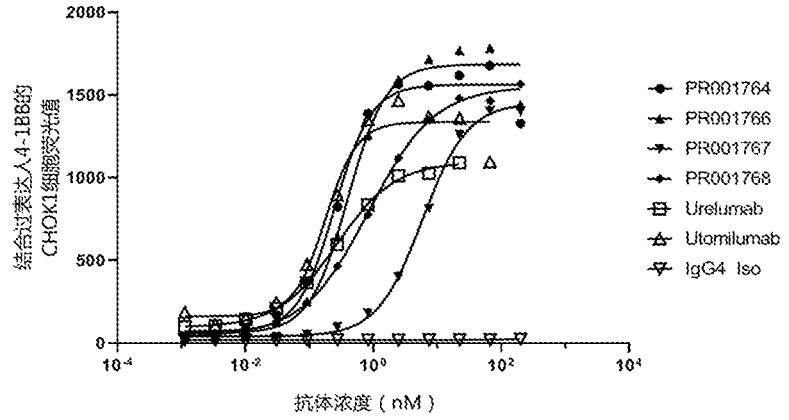


图10B



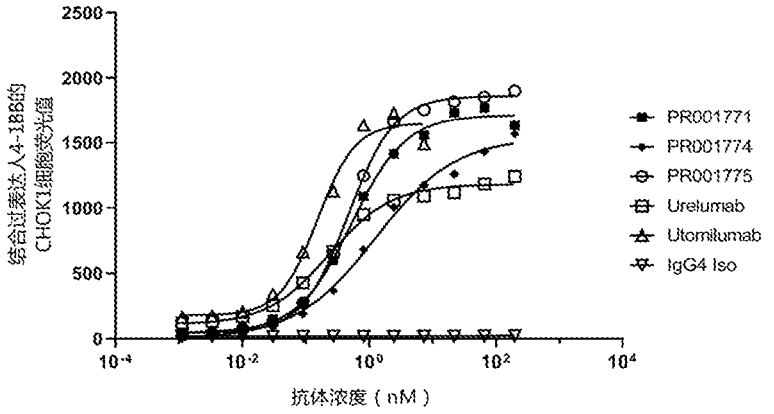
抗体	EC50 (nM)	荧光最大值
PR001758	0.2122	1644
PR001759	0.2742	1797
PR001760	0.1981	1742
PR001763	0.616	1602
Urelumab	0.2223	1381
Utomilumab	0.1297	1584

图11A



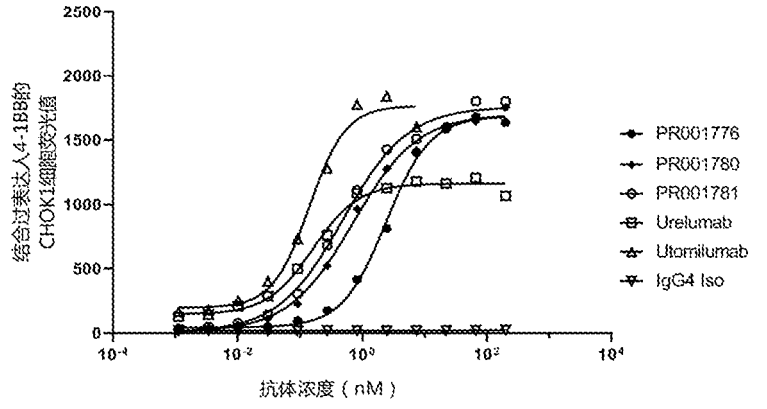
抗体	EC50 (nM)	荧光最大值
PR001764	0.2488	1562
PR001766	0.3991	1684
PR001767	5.874	1453
PR001768	0.846	1552
Urelumab	0.2223	1381
Utomilumab	0.1297	1584

图11B



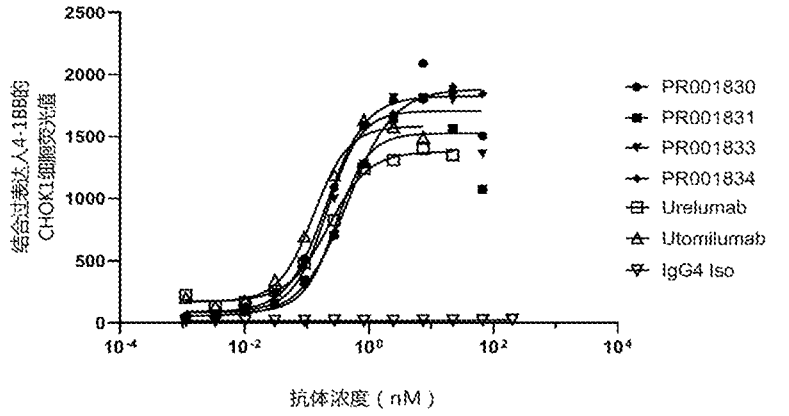
抗体	EC50 (nM)	荧光最大值
PR001771	0.5323	1716
PR001774	1.27	1544
PR001775	0.4773	1862
Urelumab	0.2223	1381
Utomilumab	0.1297	1584

图11C



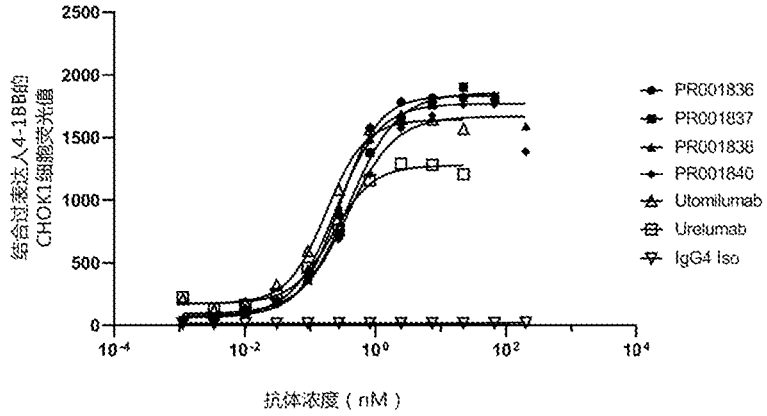
抗体	EC50 (nM)	荧光最大值
PR001776	2.428	1687
PR001780	0.7075	1703
PR001781	0.4917	1761
Urelumab	0.2223	1381
Utomilumab	0.1297	1584

图11D



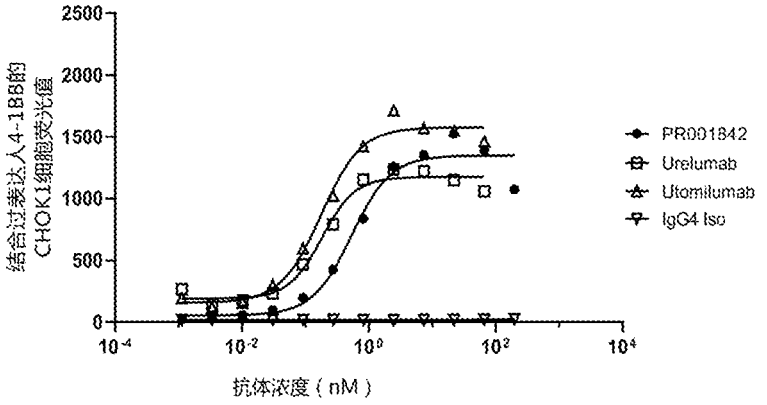
抗体	EC50 (nM)	荧光最大值
PR001830	0.2088	1826
PR001831	0.2965	1527
PR001833	0.2099	1708
PR001834	0.4487	1883
Urelumab	0.2223	1381
Utomilumab	0.1297	1584

图11E



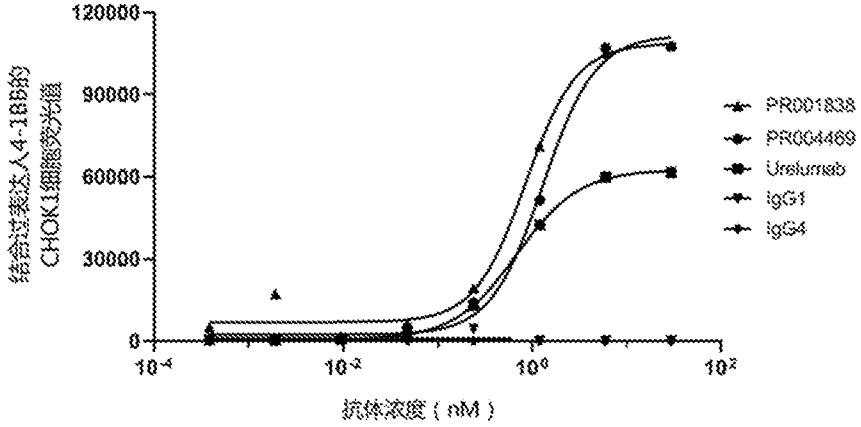
抗体	EC50 (nM)	荧光最大值
PR001836	0.2798	1833
PR001837	0.3856	1857
PR001838	0.2482	1770
PR001840	0.3696	1669
Urelumab	0.2223	1381
Utomilumab	0.1297	1584

图11F



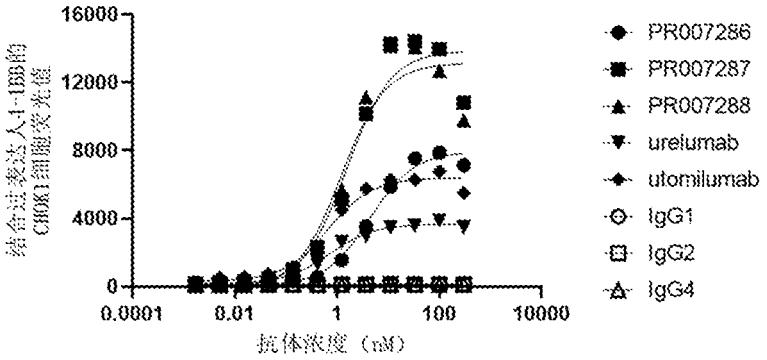
抗体	EC50 (nM)	荧光最大值
PR001842	0.5372	1346
Urelumab	0.2223	1381
Utomilumab	0.1297	1584

图11G



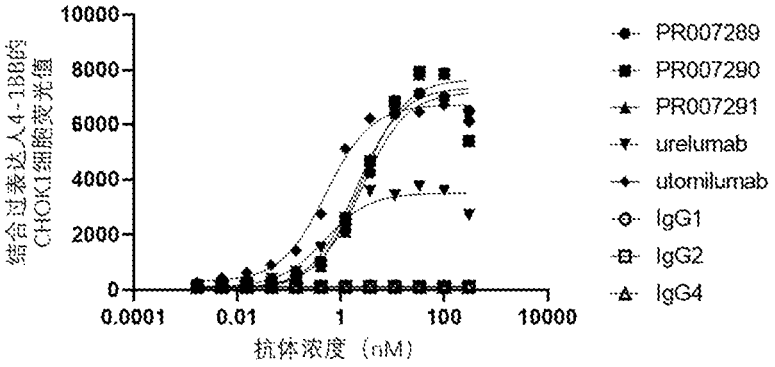
抗体	EC50 (nM)	荧光最大值
PR001838	0.8512	108600
PR004469	1.295	111597
Urelumab	0.6834	62510

图11H



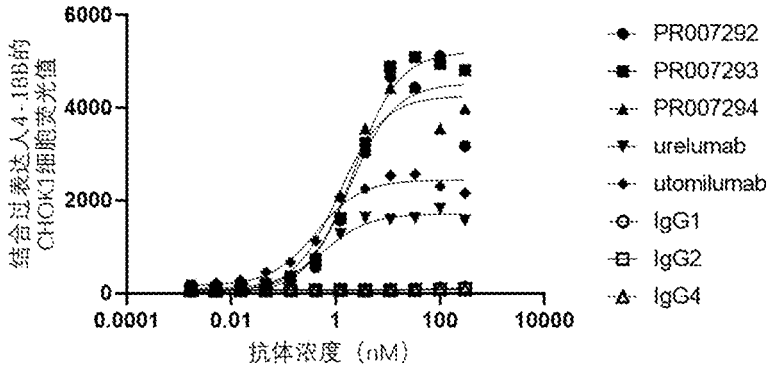
抗体	EC50(nM)	荧光最大值
PR007286	4.365	7875
PR007287	1.551	14416
PR007288	1.208	14156
urelumab	0.7123	3885
utomilumab	0.6668	6778

图11I



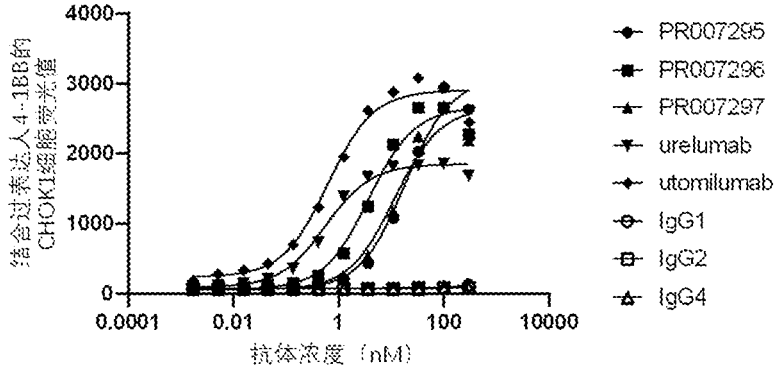
抗体	EC50(nM)	荧光最大值
PR007289	2.492	7134
PR007290	2.016	7950
PR007291	2.467	7946
urelumab	0.4859	3773
utomilumab	0.5235	6895

图11J



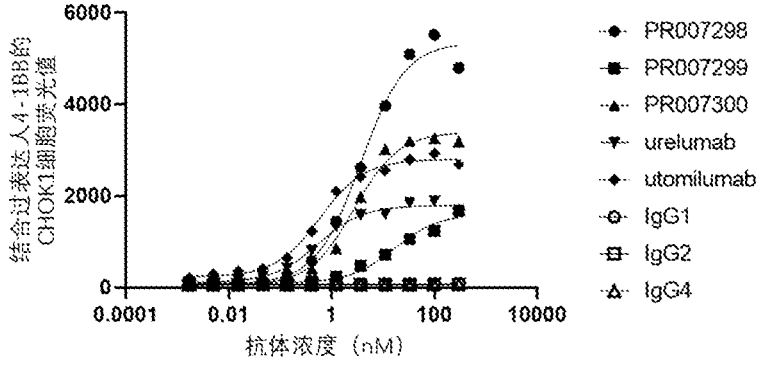
抗体	EC50(nM)	荧光最大值
PR007292	1.807	5124
PR007293	2.252	5095
PR007294	1.144	4446
urelumab	0.5833	1826
utomilumab	0.4163	2567

图11K



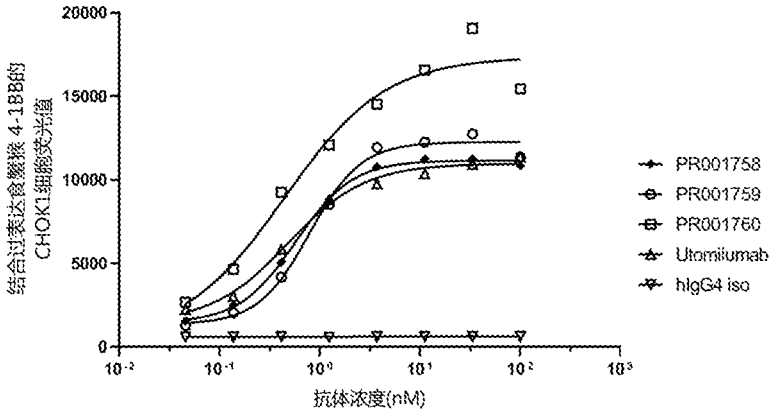
抗体	EC50(nM)	荧光最大值
PR007295	18.86	2946
PR007296	3.814	2654
PR007297	11.69	2678
urelumab	0.565	1853
utomilumab	0.6385	3074

图11L



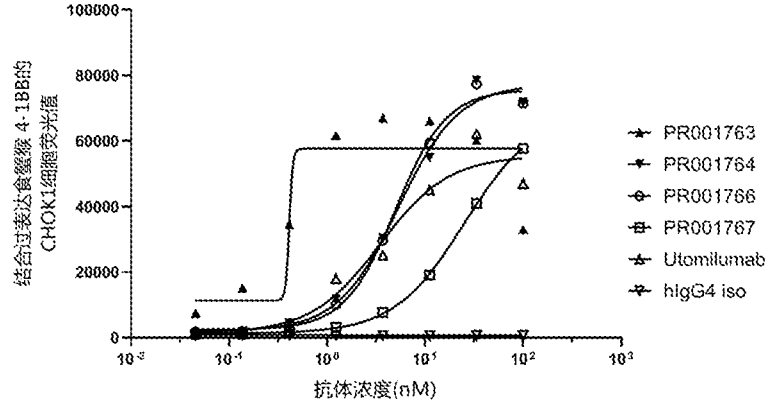
抗体	EC50(nM)	荧光最大值
PR007298	3.707	5522
PR007299	17.04	1674
PR007300	2.771	3263
urelumab	0.5502	1868
utomilumab	0.5922	2930

图11M



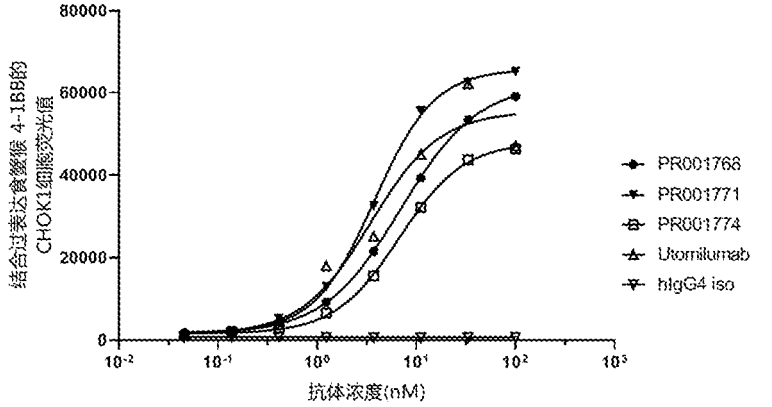
抗体	EC50 (nM)	荧光最大值
PR001758	0.5747	11167
PR001759	0.7885	12268
PR001760	0.4428	17361
Utomilumab	3.459	55506

图12A



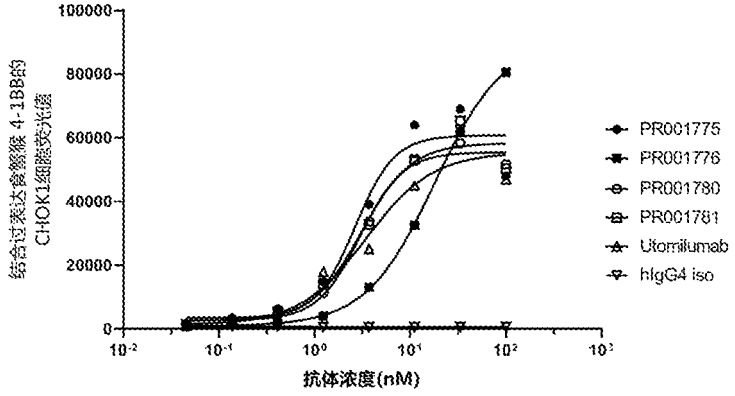
抗体	EC50 (nM)	荧光最大值
PR001763	~0.4114	57664
PR001764	5.325	77340
PR001766	4.986	75674
PR001767	25	68419
Utomilumab	3.459	55506

图12B



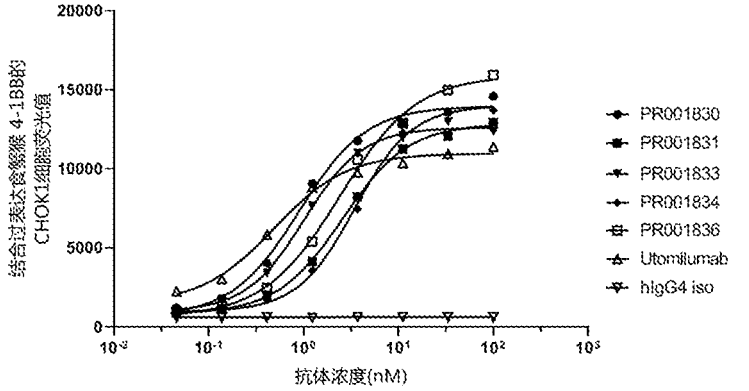
抗体	EC50 (nM)	荧光最大值
PR001768	6.969	62154
PR001771	3.77	65713
PR001774	6.728	48008
Utomilumab	3.459	55506

图12C



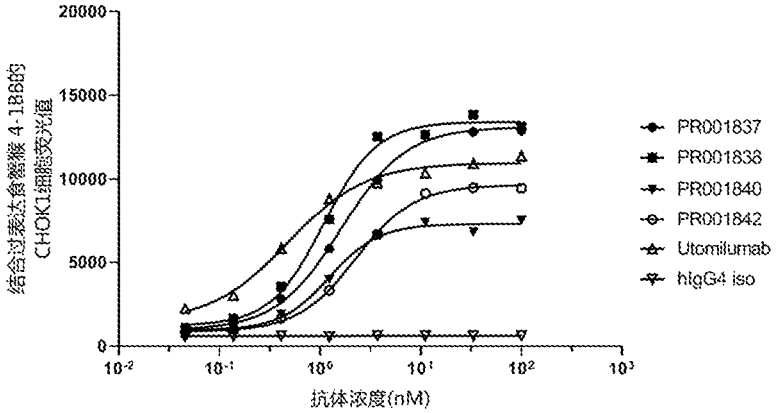
抗体	EC50 (nM)	荧光最大值
PR001775	2.656	60773
PR001776	18.05	90804
PR001780	2.99	55516
PR001781	3.099	58329
Utomilumab	3.459	55506

图12D



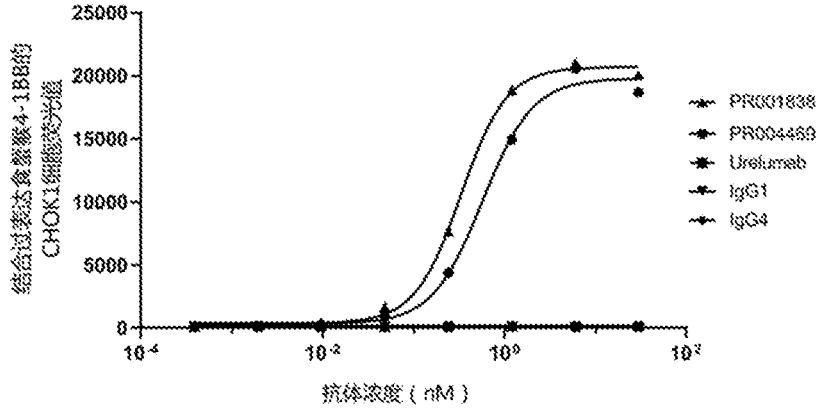
抗体	EC50 (nM)	荧光最大值
PR001830	0.8991	13968
PR001831	2.577	12856
PR001833	1.018	12610
PR001834	3.459	14006
PR001836	2.41	15913
Utomilumab	3.459	55506

图12E



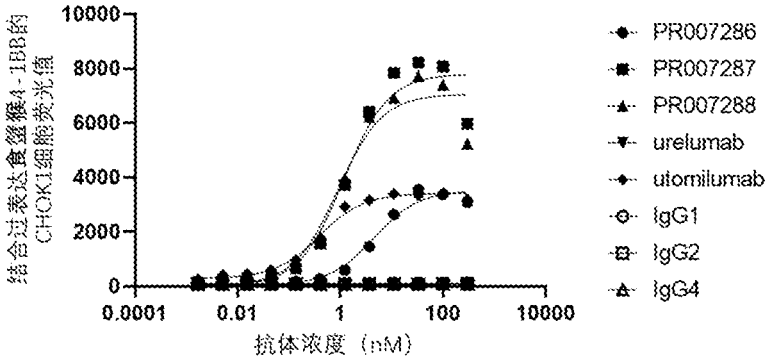
抗体	EC50 (nM)	荧光最大值
PR001837	1.627	13112
PR001838	1.089	13431
PR001840	1.246	7303
PR001842	2.285	9660
Utomilumab	3.459	55506

图12F



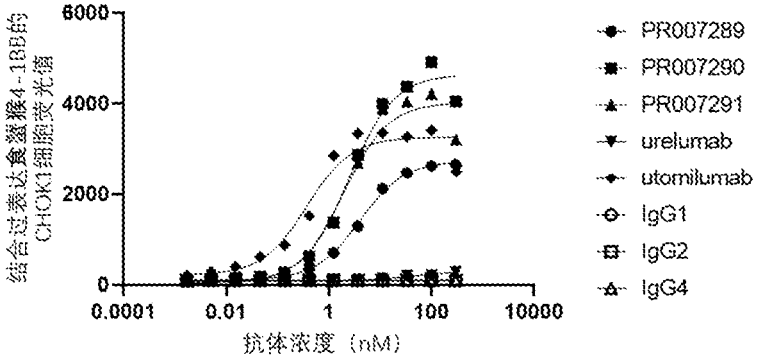
抗体	EC50 (nM)	荧光最大值
PR001838	0.3287	20591
PR004469	0.5878	19797
Urelumab	不结合	不结合

图12G



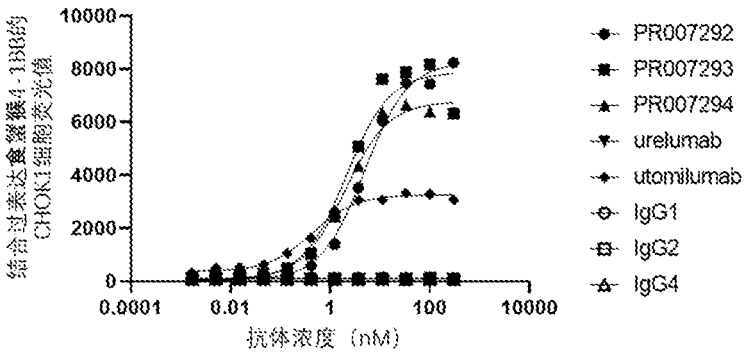
抗体	EC50(nM)	荧光最大值
PR007286	4.605	3552
PR007287	1.167	8229
PR007288	0.9034	7726
urelumab	/	/
utomilumab	0.3926	3429

图12H



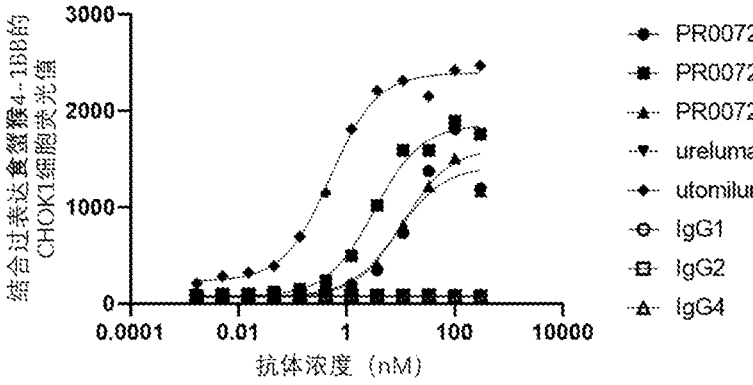
抗体	EC50(nM)	荧光最大值
PR007289	4.105	2639
PR007290	2.503	4920
PR007291	3.949	4223
urelumab	/	/
utomilumab	0.3778	3421

图12I



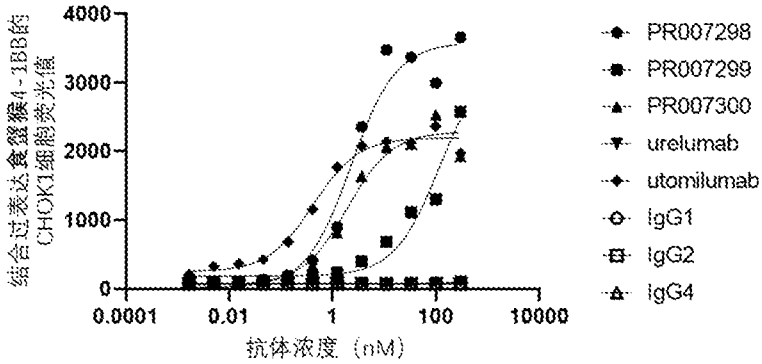
抗体	EC50(nM)	荧光最大值
PR007292	4.883	8242
PR007293	2.095	8183
PR007294	1.989	6655
urelumab	/	/
utomilumab	0.4346	3333

图12J



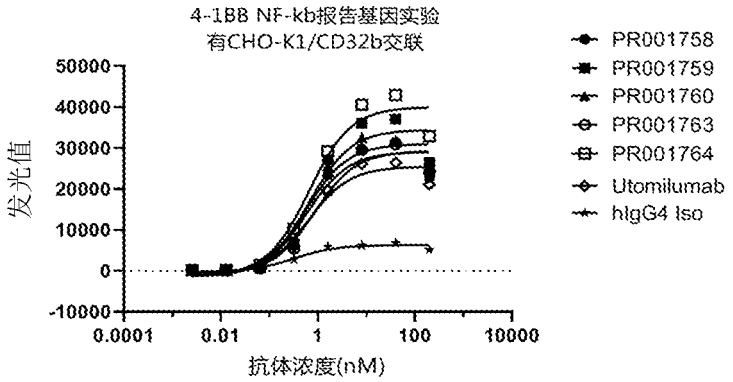
抗体	EC50(nM)	荧光最大值
PR007295	11.06	1815
PR007296	3.278	1902
PR007297	8.837	1513
urelumab	/	/
utomilumab	0.5027	2477

图12K



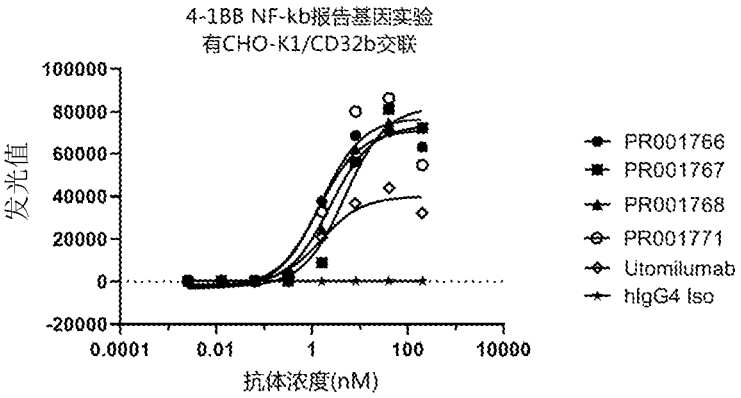
抗体	EC50(nM)	荧光最大值
PR007298	2.327	3665
PR007299	118	2574
PR007300	1.935	2536
urelumab	/	/
utomilumab	0.4254	2367

图12L



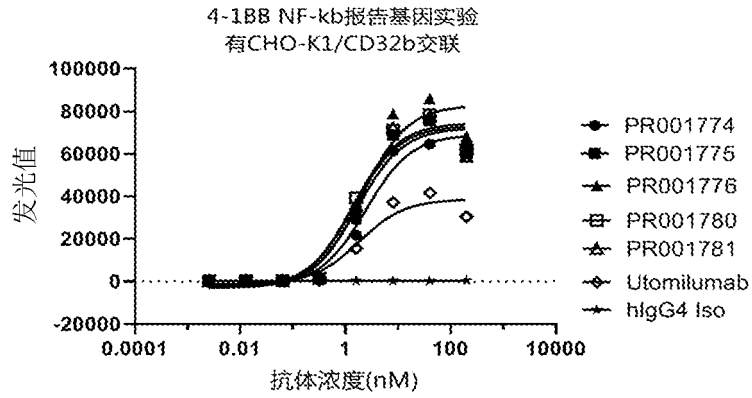
抗体	EC50 (nM)	最大信号值
PR001758	0.5792	29057
PR001759	0.6445	34468
PR001760	0.5603	30993
PR001763	0.8385	29264
PR001764	0.6532	40022
Utomilumab	0.6266	25460

图13A



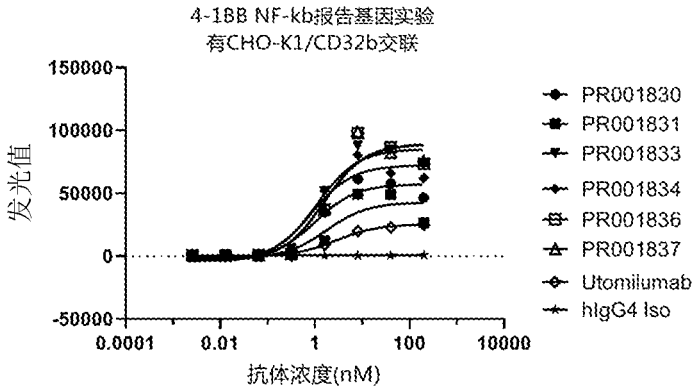
抗体	EC50 (nM)	最大信号值
PR001766	1.37	71169
PR001767	4.847	82421
PR001768	2.394	73239
PR001771	1.522	76879
Utomilumab	1.489	40042

图13B



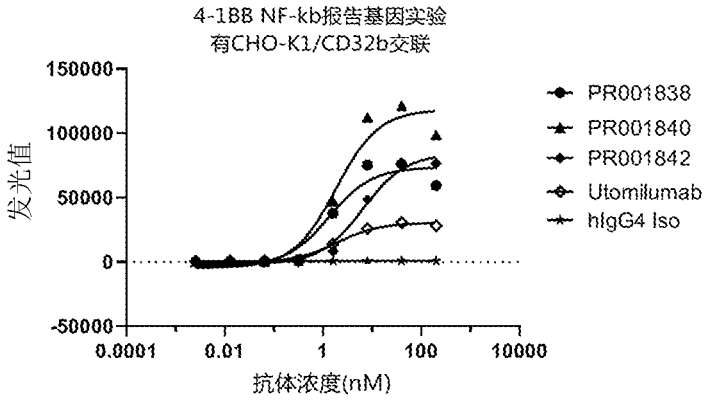
抗体	EC50 (nM)	最大信号值
PR001774	2.438	69123
PR001775	1.7	72267
PR001776	2.002	82841
PR001780	1.411	74515
PR001781	1.444	73253
Utomilumab	1.823	38653

图13C



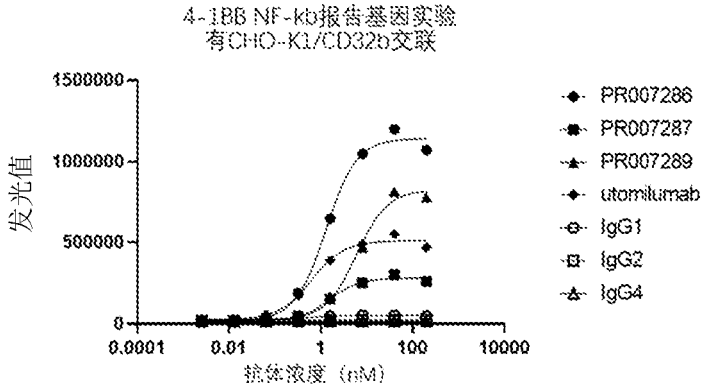
抗体	EC50 (nM)	最大信号值
PR001830	1.018	64969
PR001831	1.751	57947
PR001833	1.082	94253
PR001834	0.8521	78748
PR001836	1.541	102518
PR001837	1.522	99453
Utomilumab	2.848	25353

图13D



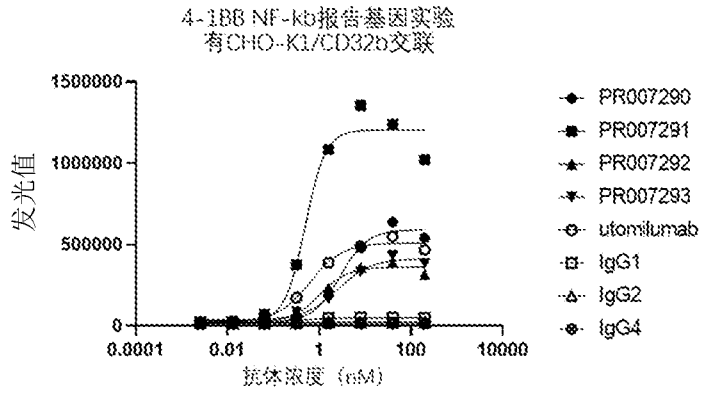
抗体	EC50 (nM)	最大信号值
PR001838	1.35	73495
PR001840	1.837	118258
PR001842	6.483	83951
Utomilumab	1.944	30515

图13E



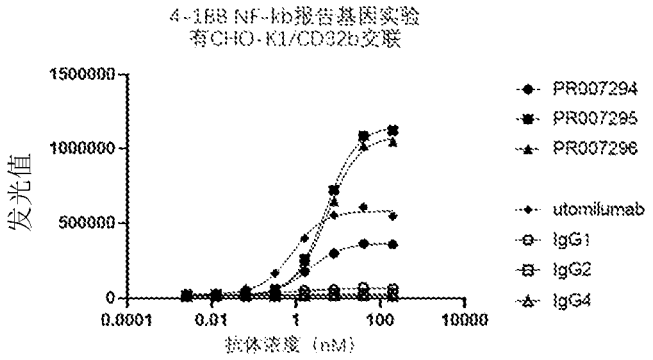
抗体	EC50(nM)	荧光最大值
PR007286	1.305	1198580
PR007287	1.569	300490
PR007288	5.999	811400
utomilumab	0.6241	550230

图13F



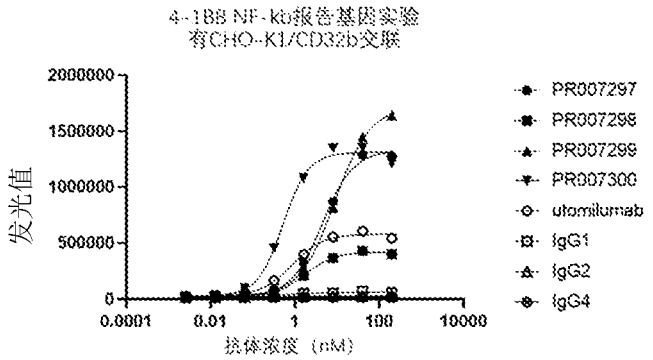
抗体	EC50(nM)	荧光最大值
PR007290	2.888	637190
PR007291	0.4984	1355320
PR007292	1.042	393660
PR007293	2.539	433560
utomilumab	0.6241	550230

图13G



抗体	EC50(nM)	荧光最大值
PR007294	2.888	361240
PR007295	0.4984	1119530
PR007296	1.042	1043940
utomilumab	0.1153	605920

图13H



抗体	EC50(nM)	荧光最大值
PR007297	4.488	1286820
PR007298	1.742	433930
PR007299	8.827	1643170
PR007300	0.5248	1356560
utomilumab	0.8343	605920

图13I

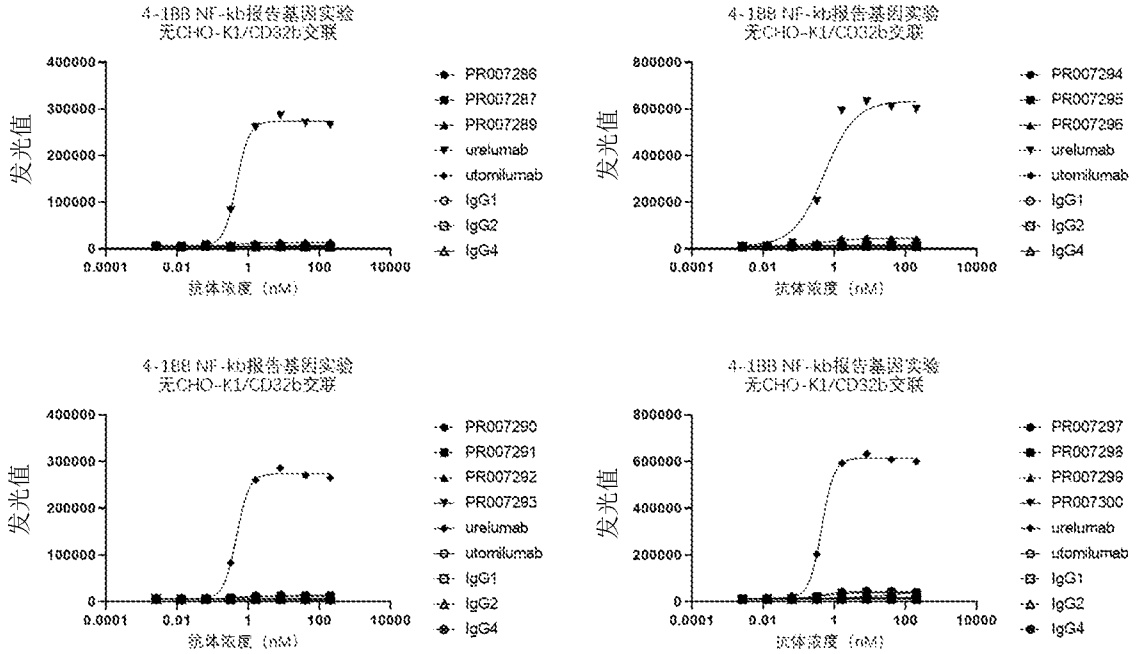
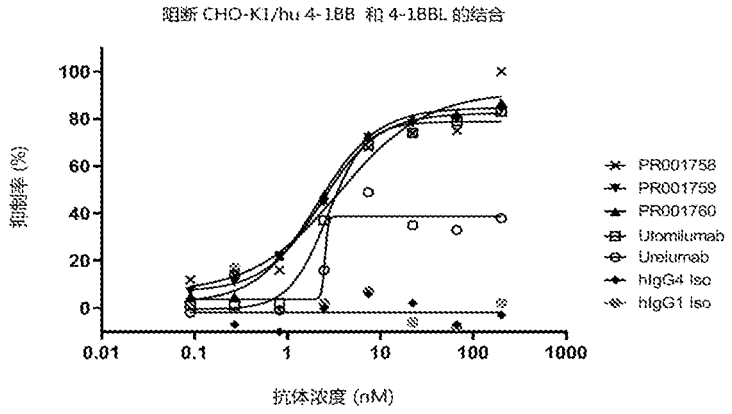
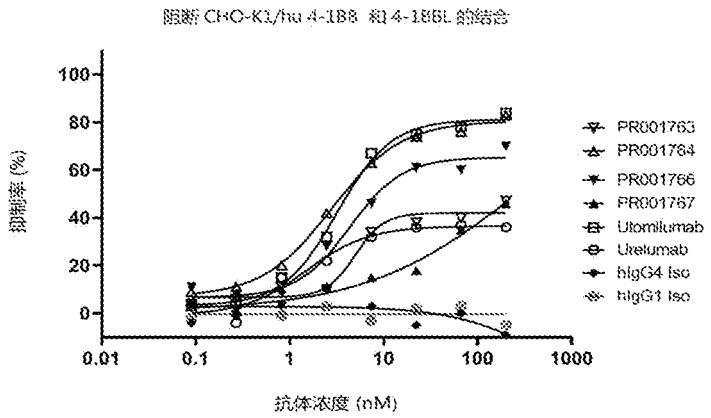


图13J



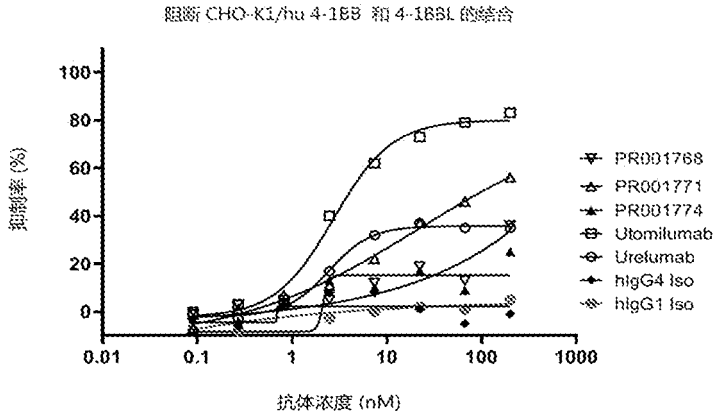
抗体	IC50 (nM)	最大抑制率 (%)
PR001758	3.606	100
PR001759	2.312	84
PR001760	2.050	87
Utomilumab	2.699	83
Urelumab	~2.531	38

图14A



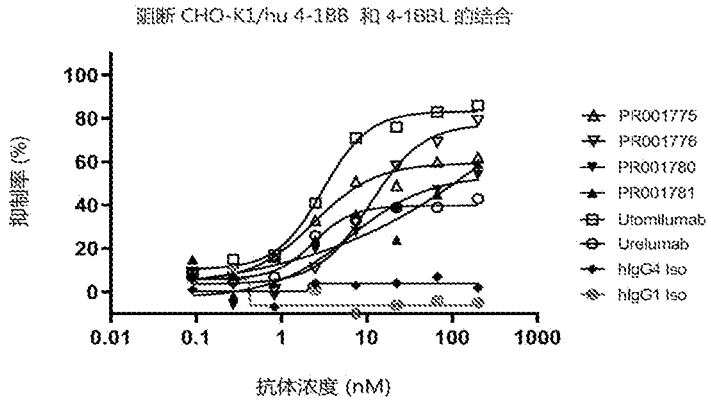
抗体	IC50 (nM)	最大抑制率 (%)
PR001763	4.985	47
PR001764	2.790	83
PR001766	4.344	70
PR001767	n.d.	46
Utomilumab	3.195	84
Urelumab	1.503	36

图14B



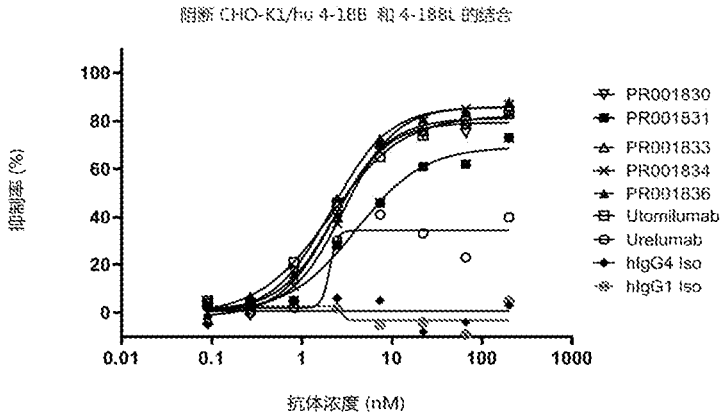
抗体	IC50 (nM)	最大抑制率 (%)
PR001768	n.d.	36
PR001771	21.56	56
PR001774	~2.122	25
Utomilumab	2.741	83
Urelumab	2.413	35

图14C



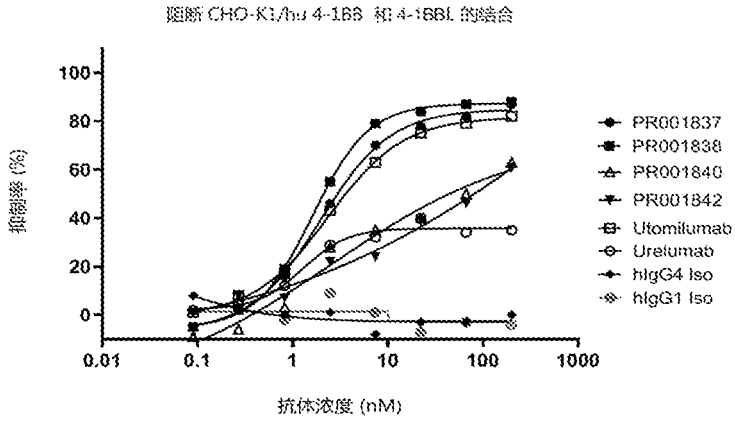
抗体	IC50 (nM)	最大抑制率 (%)
PR001775	2.404	62
PR001776	10.92	79
PR001780	6.335	54
PR001781	n.d.	59
Utomilumab	3.025	86
Urelumab	2.371	43

图14D



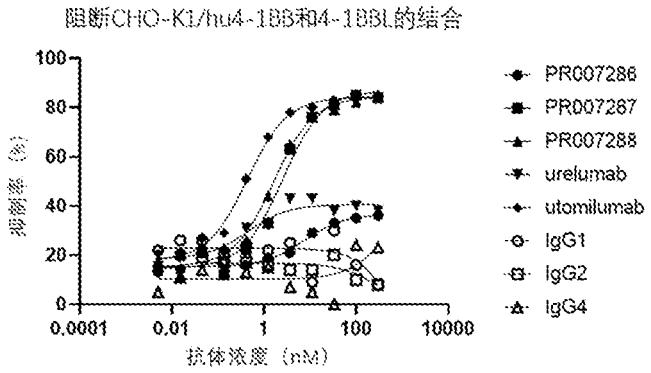
抗体	IC50 (nM)	最大抑制率 (%)
PR001830	2.316	84
PR001831	4.052	73
PR001833	2.307	83
PR001834	2.932	87
PR001836	2.122	88
Utomilumab	2.103	84
Urelumab	n.d.	40

图14E



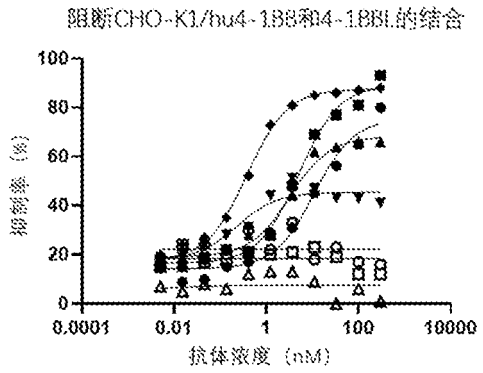
抗体	IC50 (nM)	最大抑制率 (%)
PR001837	1.957	87
PR001838	1.614	88
PR001840	2.583	63
PR001842	n.d.	61
Utomilumab	2.363	82
Urelumab	1.274	35

图14F



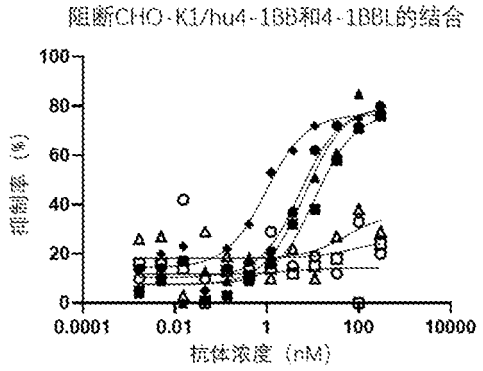
抗体	IC50(nM)	最大抑制率（%）
PR007286	7.537	36
PR007287	2.548	85
PR007288	1.627	85
urelumab	0.4472	43
utomilumab	0.4406	85

图14G



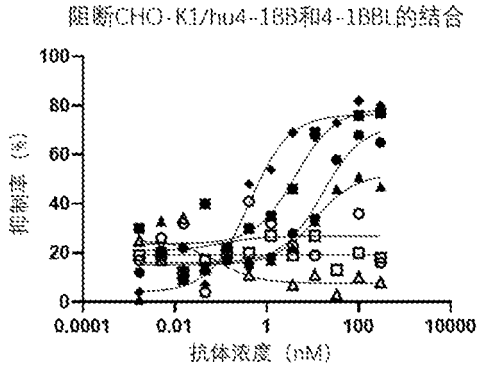
抗体	IC50(nM)	最大抑制率（%）
PR007289	11.03	80
PR007290	5.106	93
PR007291	3.285	66
urelumab	0.2322	51
utomilumab	0.3834	88

图14H



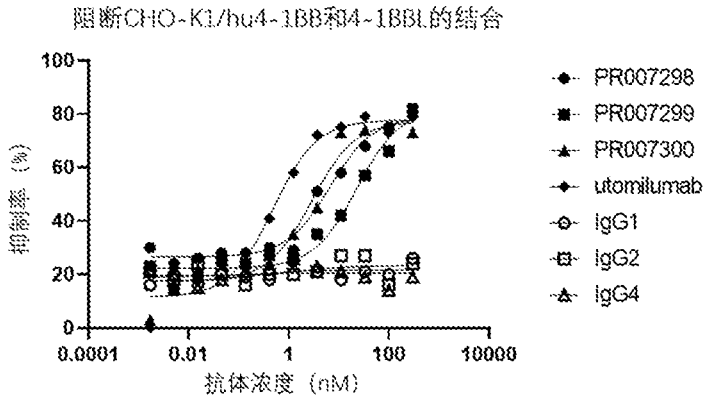
抗体	IC50(nM)	最大抑制率（%）
PR007292	5.374	80
PR007293	11.15	76
PR007294	6.606	85
utomilumab	0.973	80

图14I



抗体	IC50(nM)	最大抑制率（%）
PR007295	16.11	68
PR007296	4.194	137
PR007297	11.27	51
utomilumab	0.4154	82

图14J



抗体	IC50(nM)	最大抑制率（%）
PR007298	6.697	80
PR007299	23.14	82
PR007300	2.87	75
utomilumab	0.4896	79

图14K

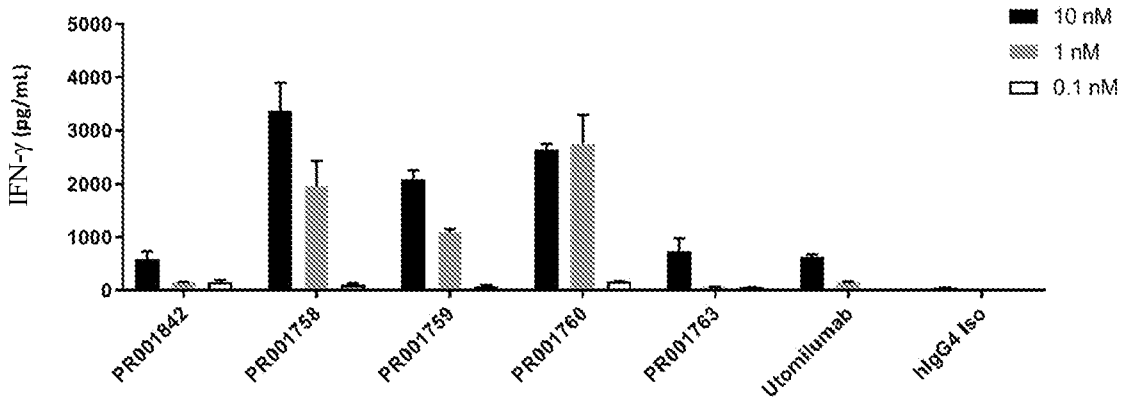


图15A

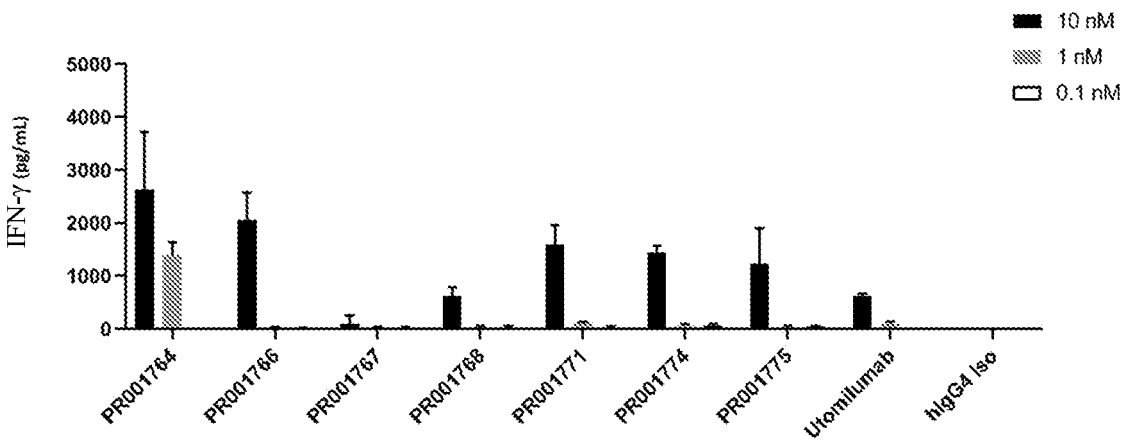


图15B

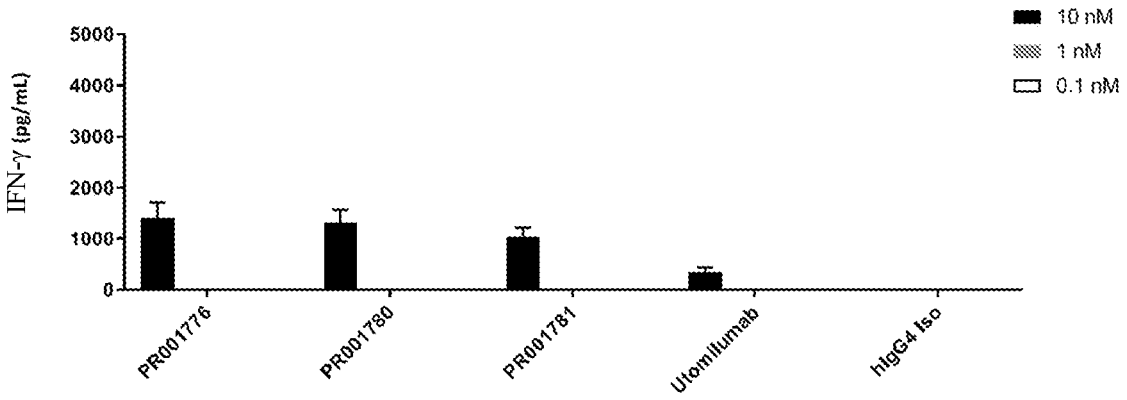


图15C

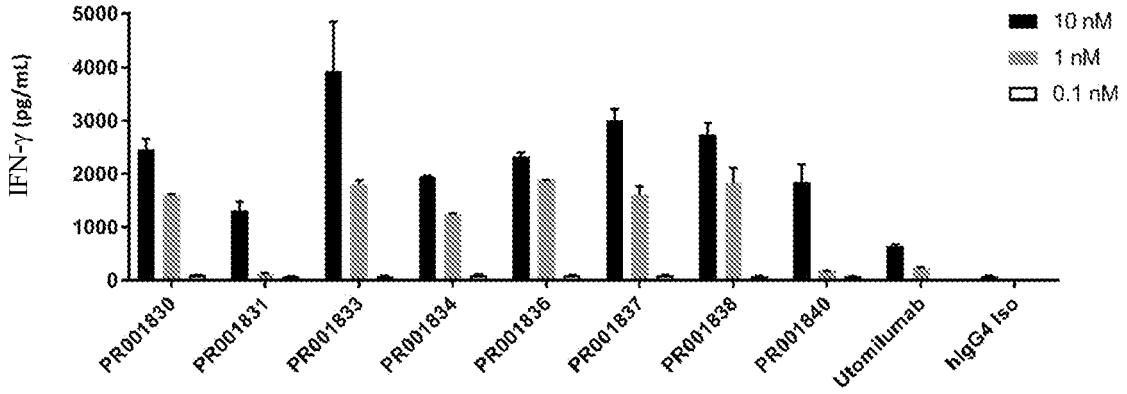
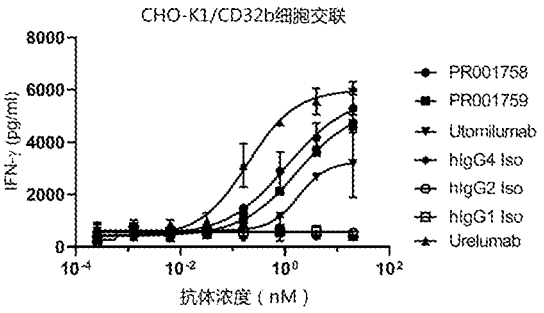
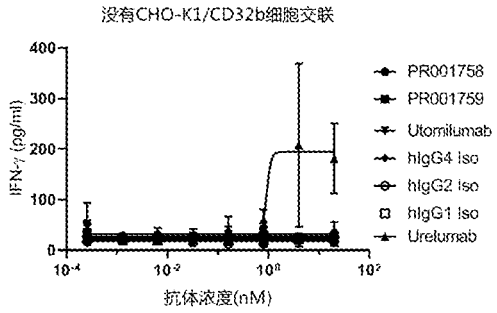


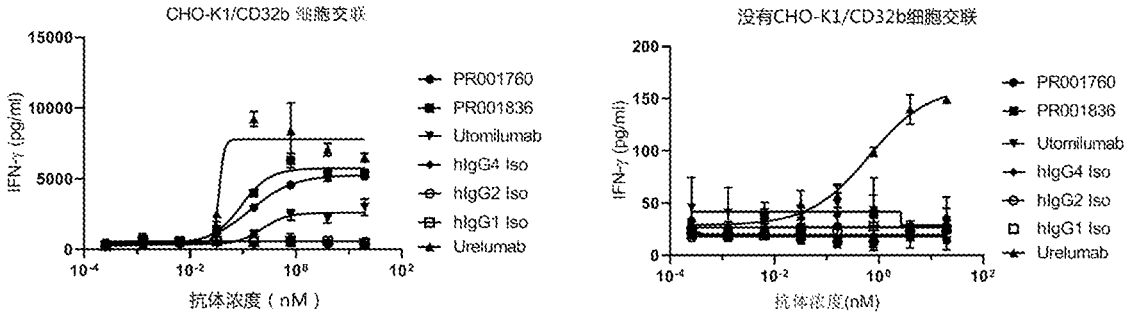
图15D





抗体	EC50(nM)	最大IFN gamma 释放值
PR001758	1.079	5753
PR001759	1.715	5312
Utomilumab	1.825	3254

图16A



抗体	EC50(nM)	最大IFN gamma释放值
PR001760	0.137	5272
PR001836	0.09331	5746
Utomilumab	0.2349	2604

图16B

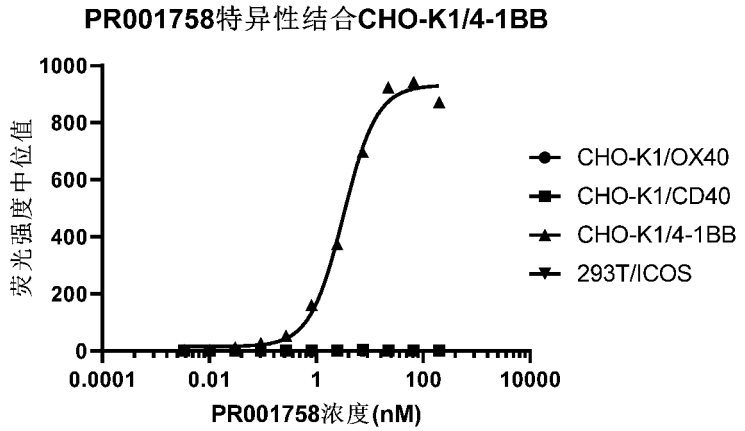


图17A

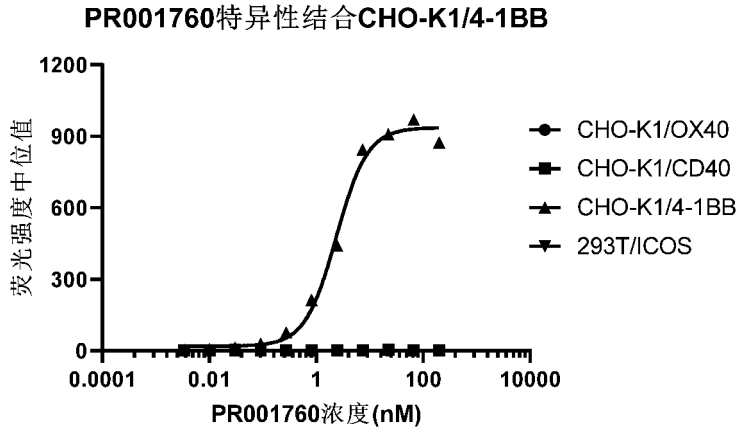


图17B

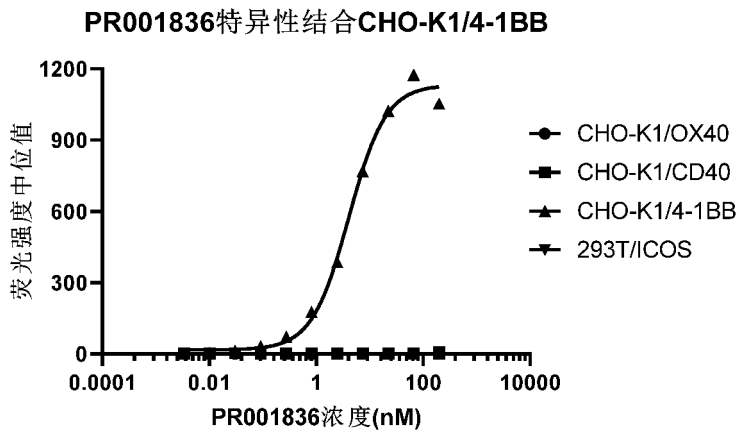

PR001836特异性结合CHO-K1/4-1BB
荧光强度中位值
1200
900
600
300
0
0.0001
0.01
1
100
10000
PR001836浓度(nM)
CHO-K1/OX40
CHO-K1/CD40
CHO-K1/4-1BB
293T/ICOS

图17C

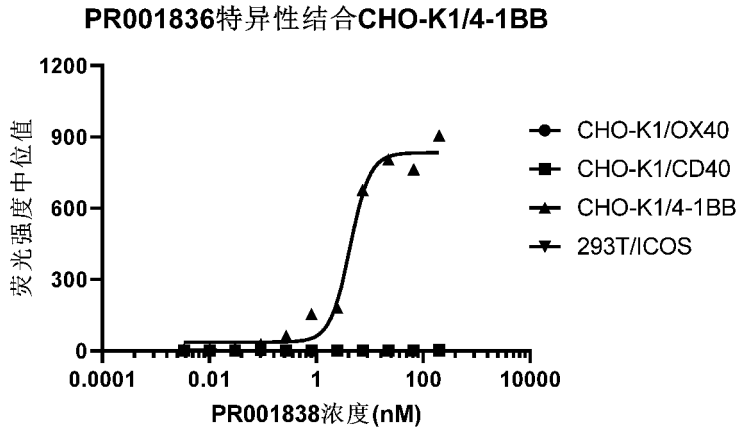

PR001836特异性结合CHO-K1/4-1BB
荧光强度中位值
1200
900
600
300
0
0.0001
0.01
1
100
10000
PR001838浓度(nM)
CHO-K1/OX40
CHO-K1/CD40
CHO-K1/4-1BB
293T/ICOS

图17D

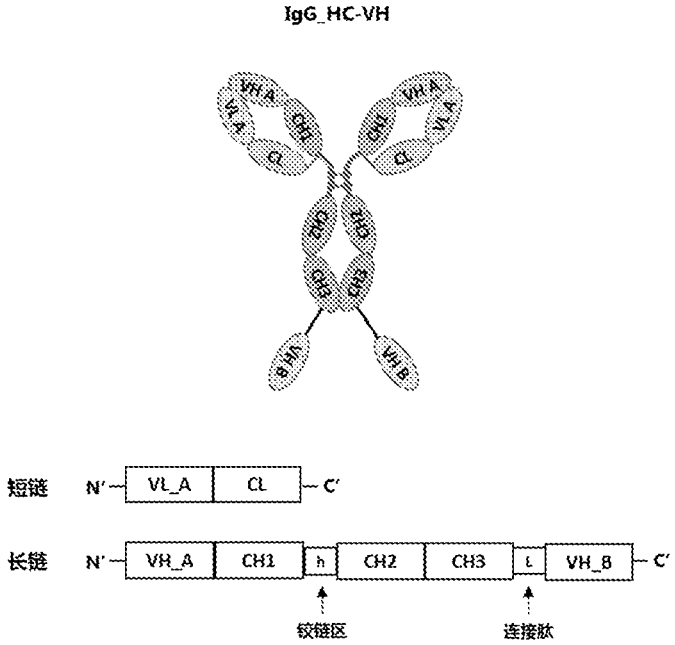

IgG_HC-VH
VH_A
VL_A
CH1
CL
VH_A
VL_A
CH1
CL
CH2
CH3
CH2
CH3
VL_B
VH_B
短链
N'
VL_A
CL
C'
长链
N'
VH_A
CH1
h
CH2
CH3
L
VH_B
C'
铰链区
连接肽

图18A

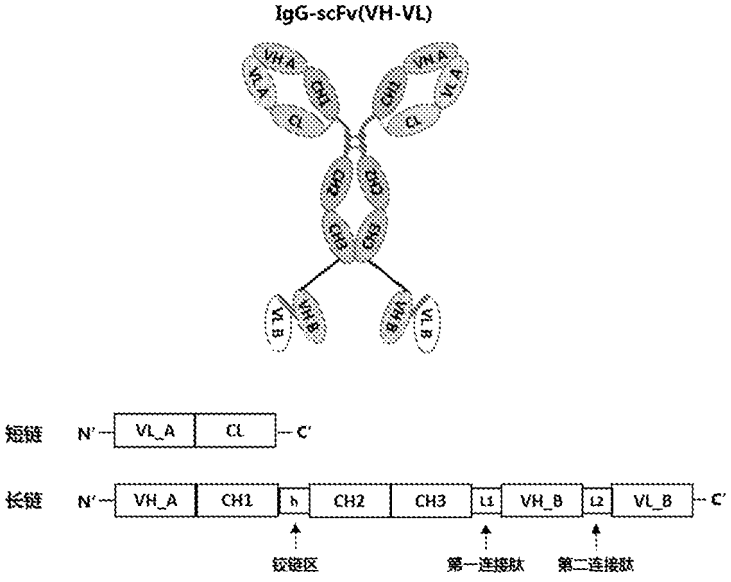

IgG-scFv(VH-VL)
短链
N'
VL_A
CL
C'
长链
N'
VH_A
CH1
h
CH2
CH3
L1
VH_B
L2
VL_B
C'
铰链区
第一连接肽
第二连接肽

图18B

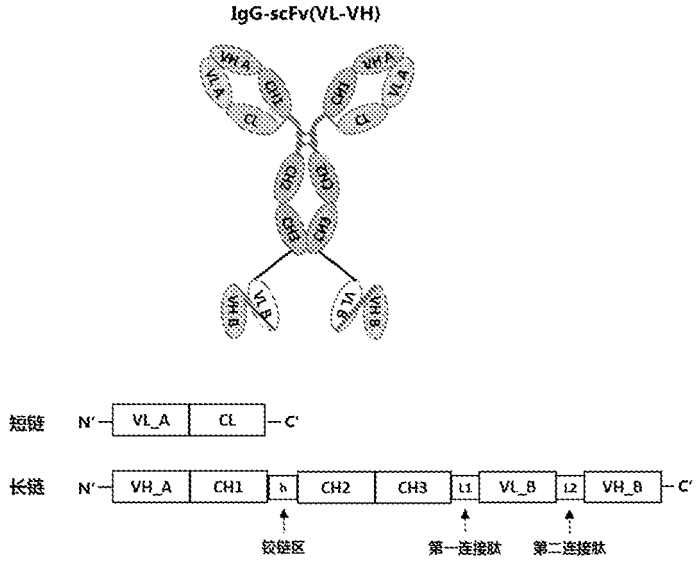
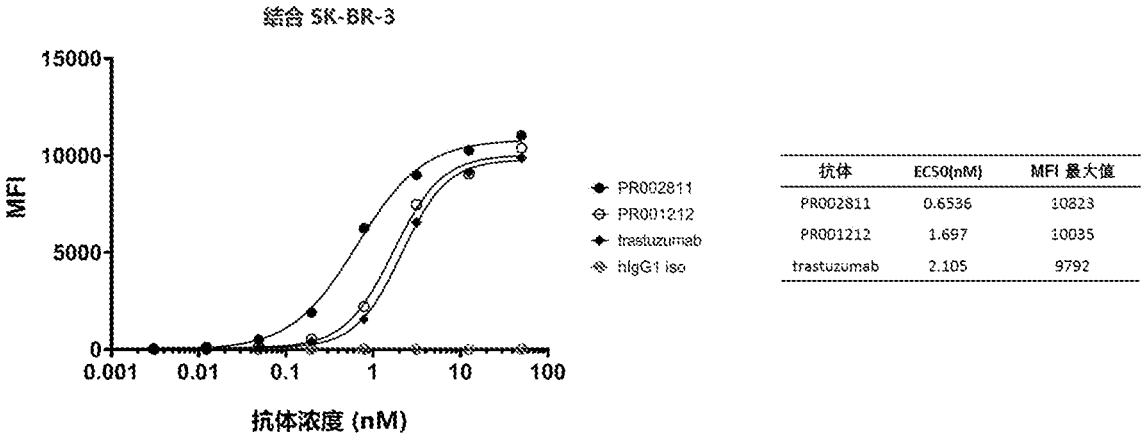
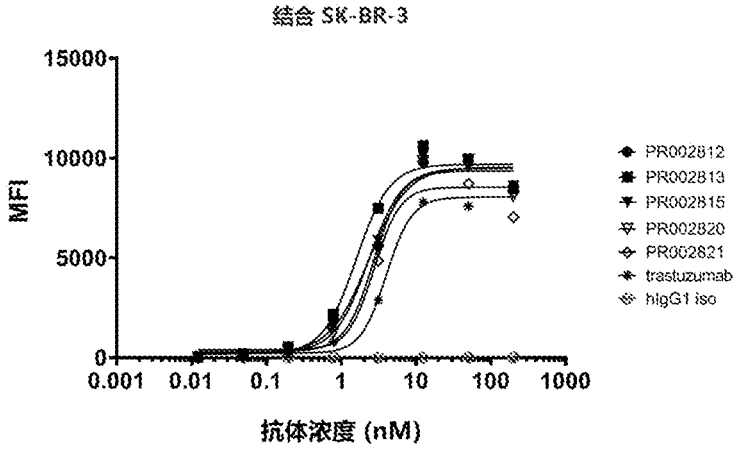


图18C



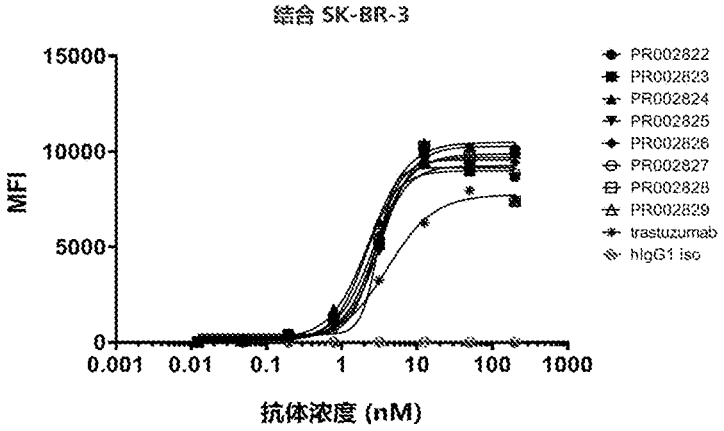
抗体	EC50(nM)	MFI 最大值
PR002811	0.6536	10823
PR001212	1.697	10035
trastuzumab	2.105	9792

图19A



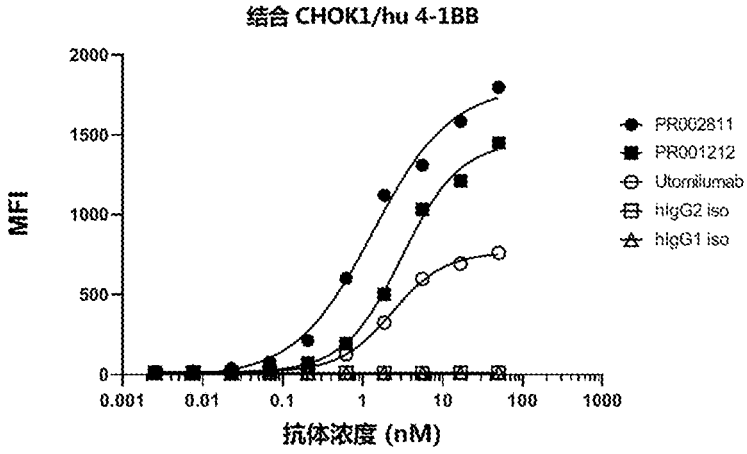
抗体	EC50 (nM)	MFI 最大值
PR002812	2.326	9539
PR002813	1.585	9687
PR002815	2.311	9485
PR002820	2.703	9357
PR002821	2.752	8546
trastuzumab	4	8046

图19B



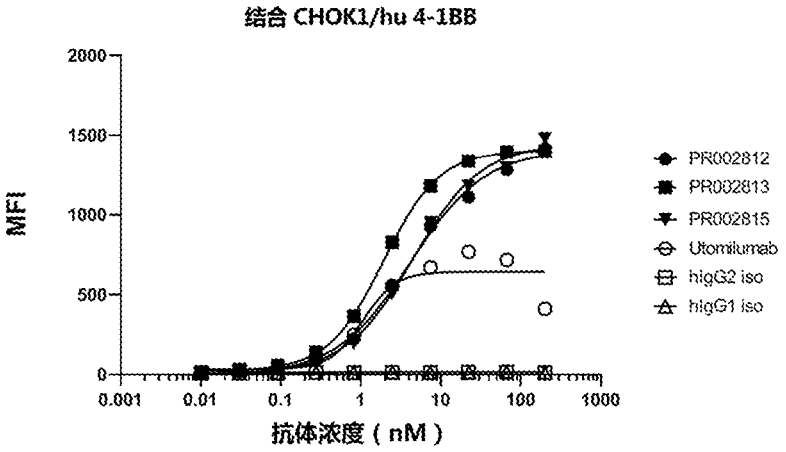
抗体	EC50 (nM)	MFI 最大值
PR002822	2.771	9251
PR002823	2.88	9705
PR002824	2.348	10480
PR002825	3.311	10265
PR002826	2.683	9867
PR002827	2.839	9567
PR002828	2.989	9149
PR002829	2.072	8991
trastuzumab	4.043	7740

图19C



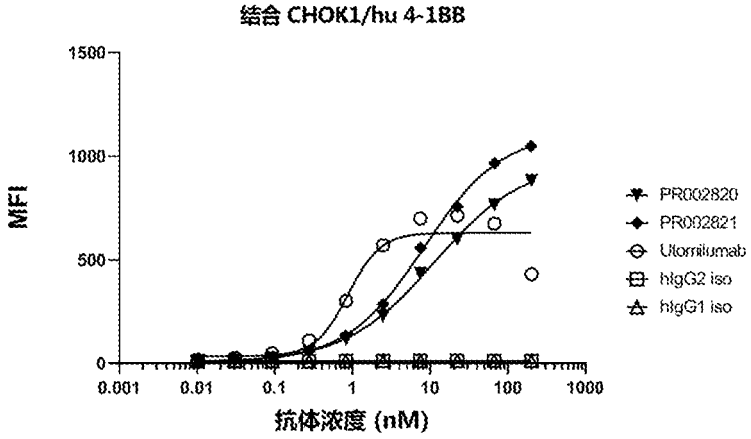
抗体	EC50 (nM)	MFI 最大值
PR002811	1.349	1803
PR001212	3.077	1457
Utomilumab	2.326	763.8

图20A



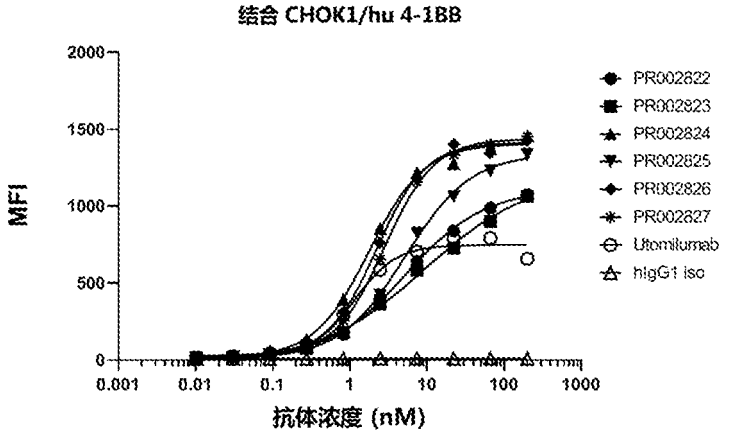
抗体	EC50 (nM)	MFI 最大值
PR002812	4.183	1410
PR002813	1.93	1404
PR002815	4.497	1446
Utomilumab	1.061	643.8

图20B



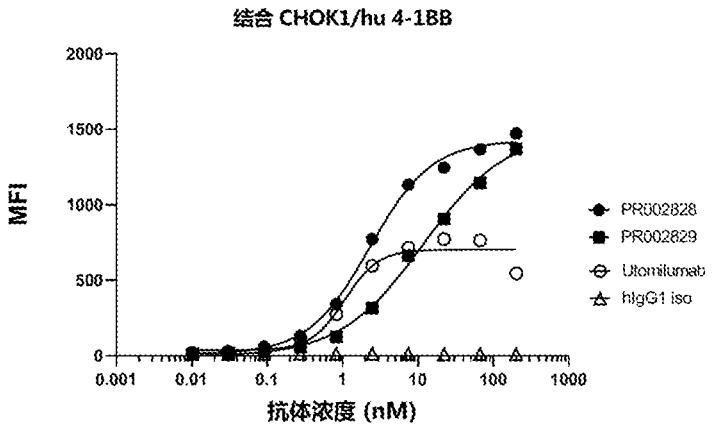
抗体	EC50 (nM)	MFI 最大值
PR002820	11.31	974.6
PR002821	8.362	1115
Utomilumab	0.5739	631

图20C



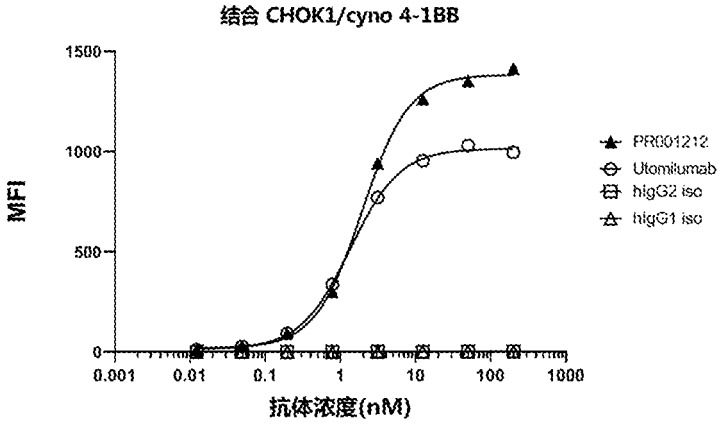
抗体	EC50 (nM)	MFI 最大值
PR002822	5.282	1111
PR002823	9.2	1192
PR002824	1.792	1403
PR002825	5.241	1339
PR002826	2.224	1410
PR002827	2.798	1434
Utomilumab	1.13	747.7

图20D



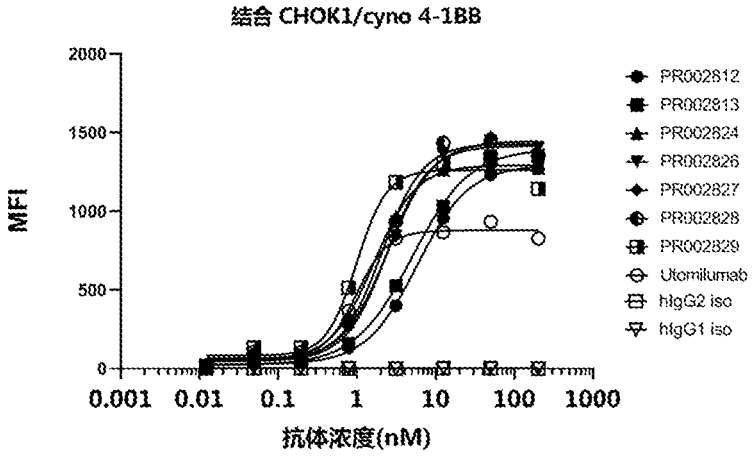
抗体	EC50 (nM)	MFI 最大值
PR002828	2.291	1427
PR002829	11.74	1485
Utomilumab	1.067	704.1

图20E



抗体	EC50 (nM)	MFI 最大值
PR001212	1.935	1385
Utomilumab	1.345	1016

图21A



抗体	EC50 (nM)	MFI 最大值
PR002812	5.848	1293
PR002813	5.019	1397
PR002824	1.643	1292
PR002826	2.467	1447
PR002827	2.405	1416
PR002828	2.079	1429
PR002829	0.9916	1263
Utomilumab	0.9841	879.2

图21B

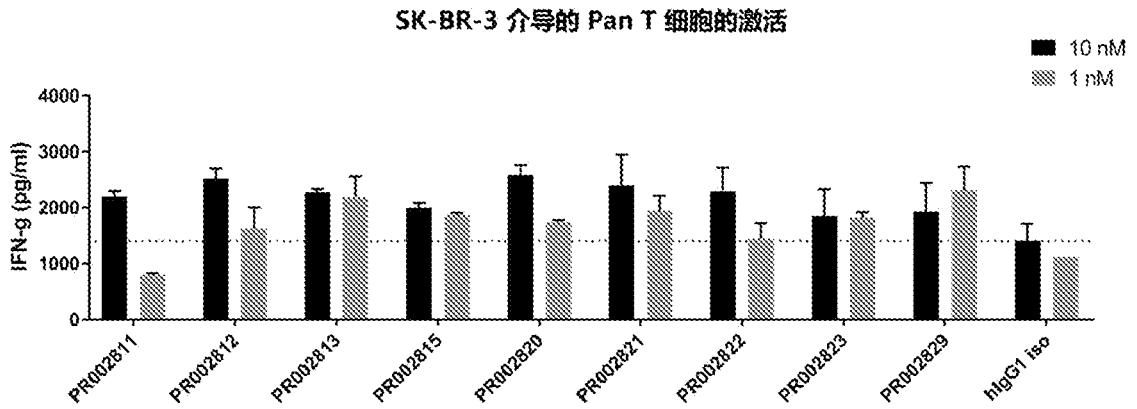


图22A

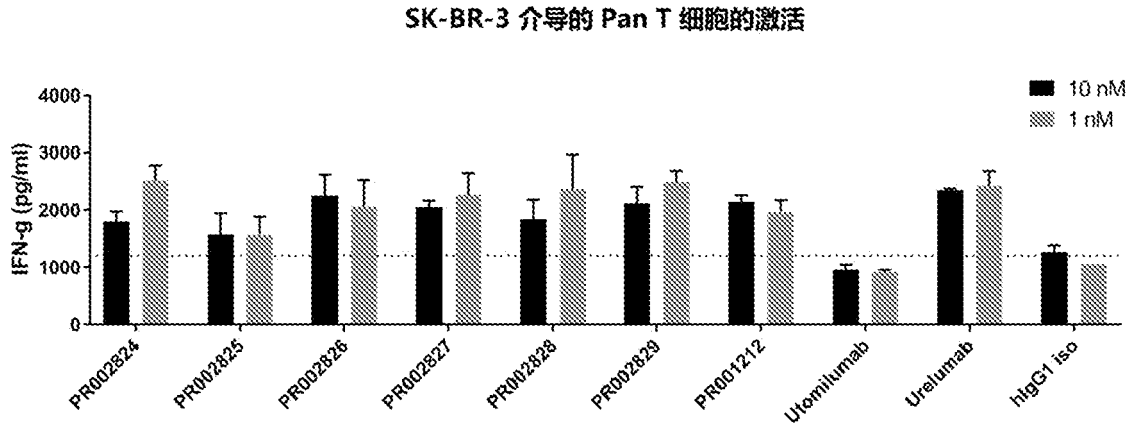
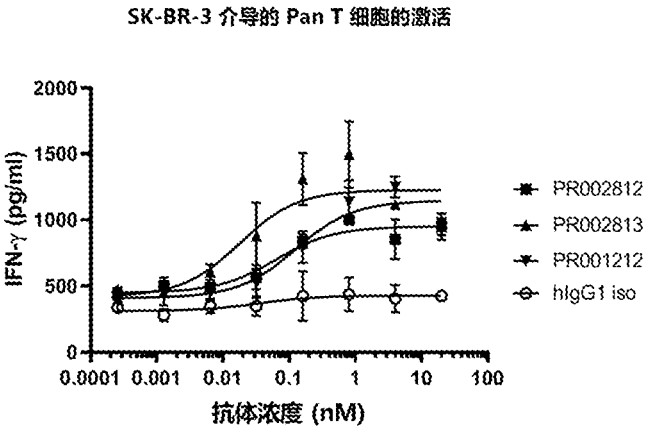
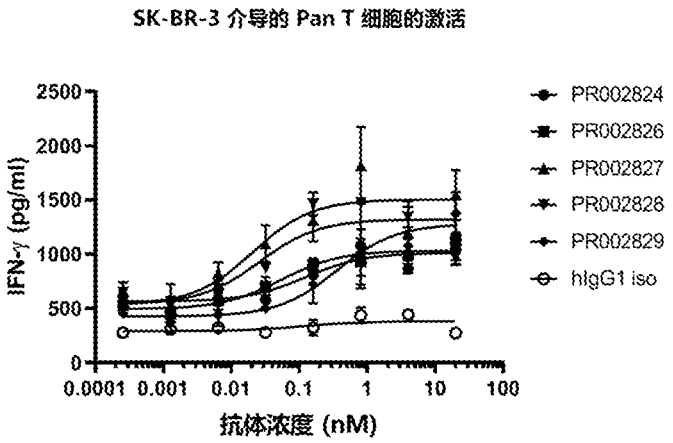


图22B



抗体	EC50 (nM)	IFN-γ 最大释放值
PR002812	0.06325	950
PR002813	0.01791	1226
PR001212	0.1249	1146

图22C



抗体	EC50 (nM)	IFN-γ 最大释放值
PR002824	0.124	1013
PR002826	0.05389	1033
PR002827	0.02068	1503
PR002828	0.02602	1321
PR002829	0.3622	1280

图22D

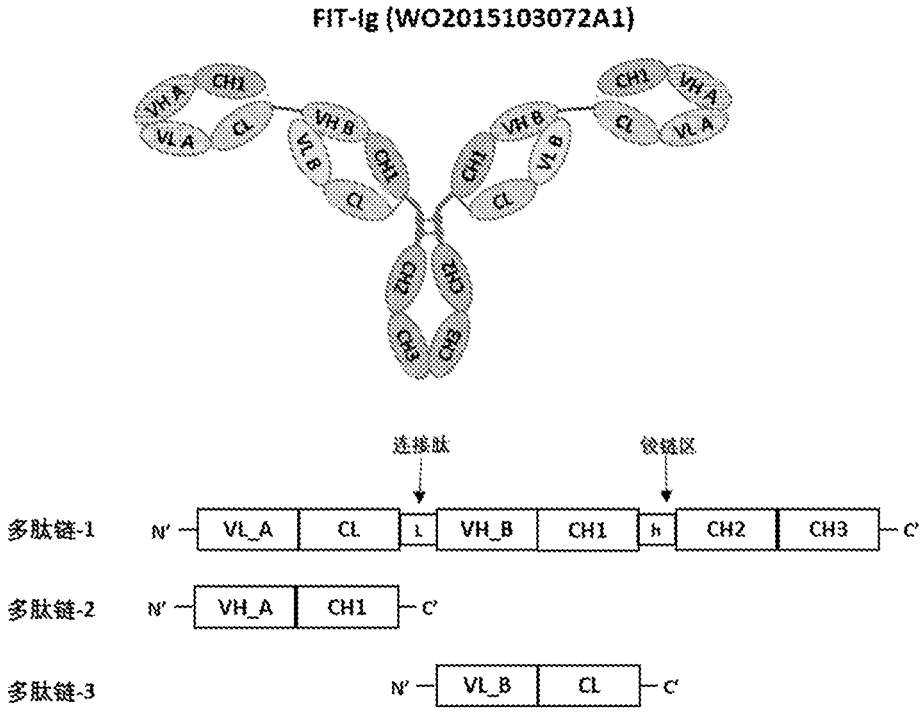


图23A

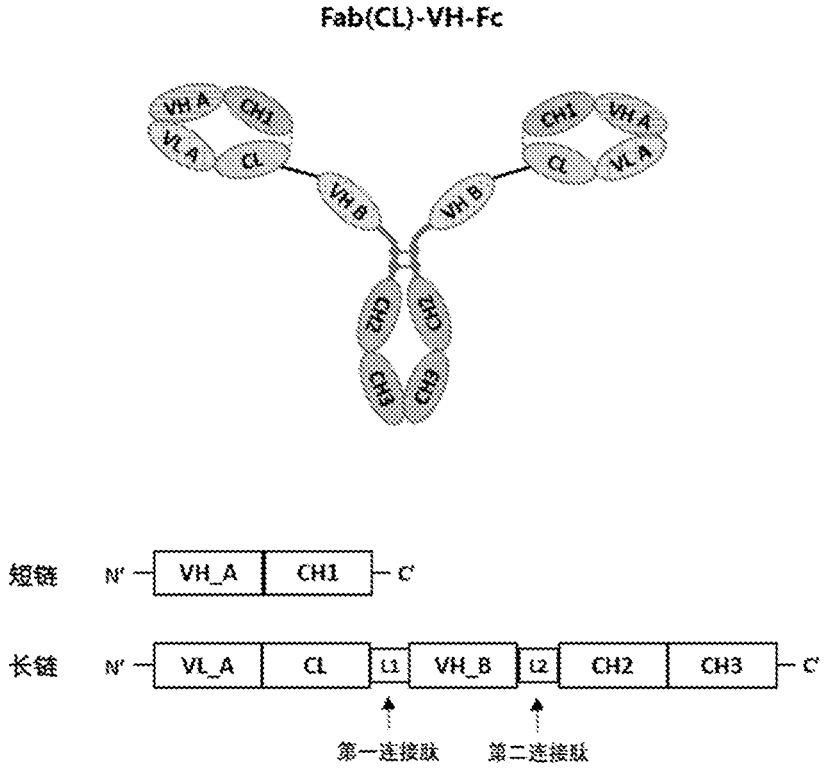

Fab(CL)-VH-Fc
VH_A
CH1
VL_A
CL
VH_B
CH1
VH_A
CL
VL_A
CH2
CH2
CH3
CH3
短链
N'
VH_A
CH1
C'
长链
N'
VL_A
CL
L1
VH_B
L2
CH2
CH3
C'
第一连接肽
第二连接肽

图23B

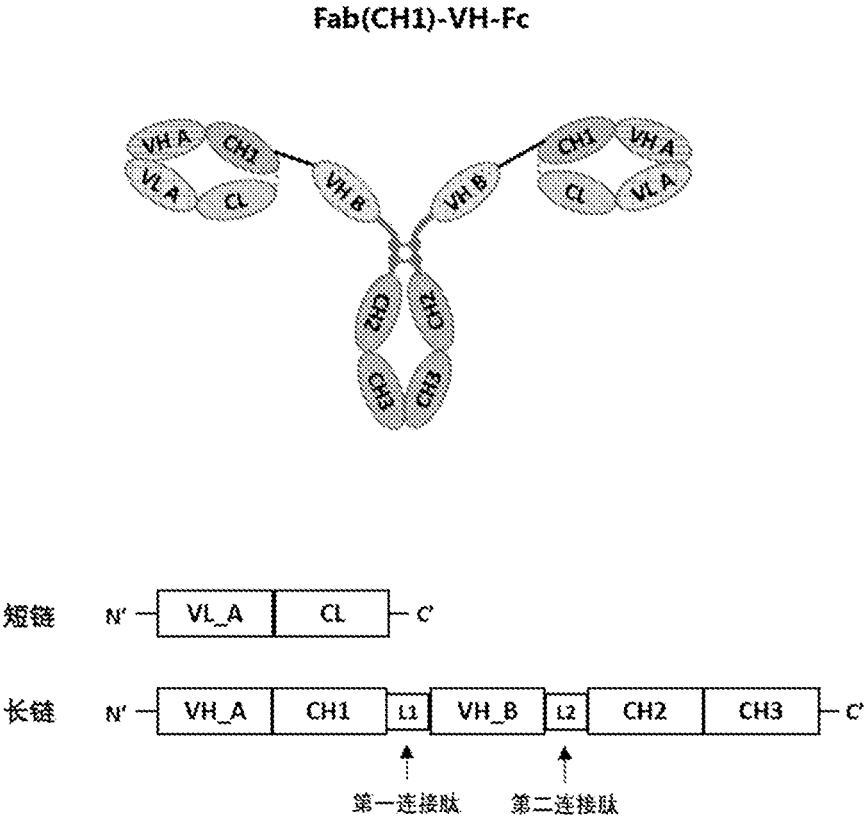

Fab(CH1)-VH-Fc
VH_A
CH1
VL_A
CL
VH_B
CH1
VH_A
CL
VL_A
CH2
CH2
CH3
CH3
短链
N'
VL_A
CL
C'
长链
N'
VH_A
CH1
L1
VH_B
L2
CH2
CH3
C'
第一连接肽
第二连接肽

图23C

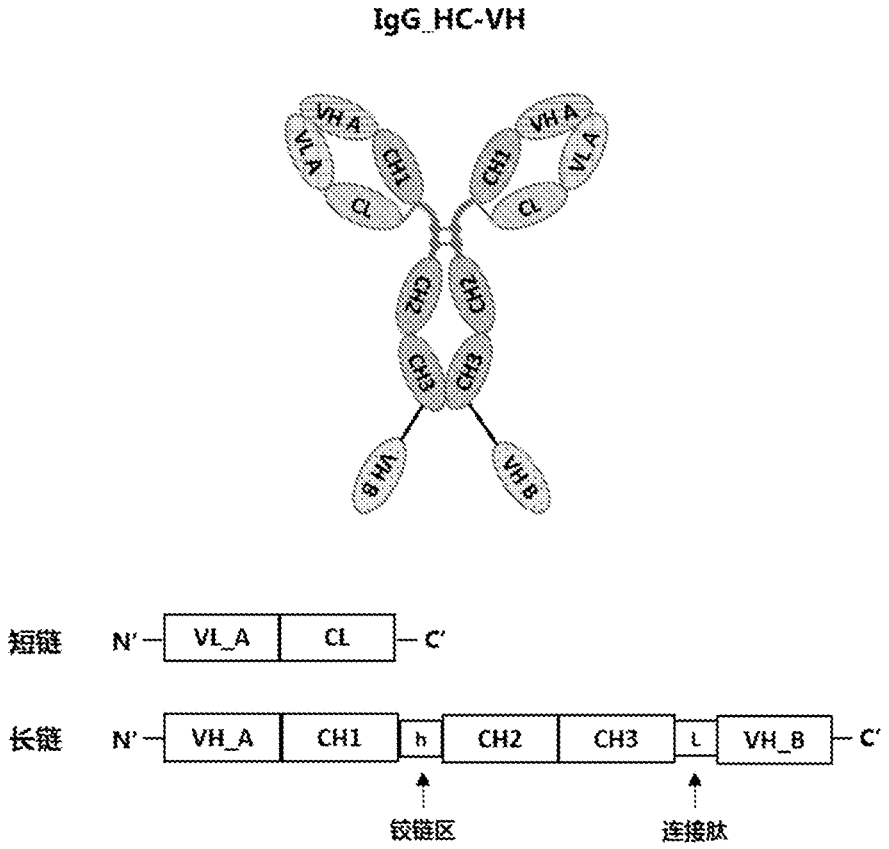

IgG_HC-VH
VH_A
VL_A
CH1
CL
CH2
CH3
VH_B
短链
N'
VL_A
CL
C'
长链
N'
VH_A
CH1
h
CH2
CH3
L
VH_B
C'
铰链区
连接肽

图23D

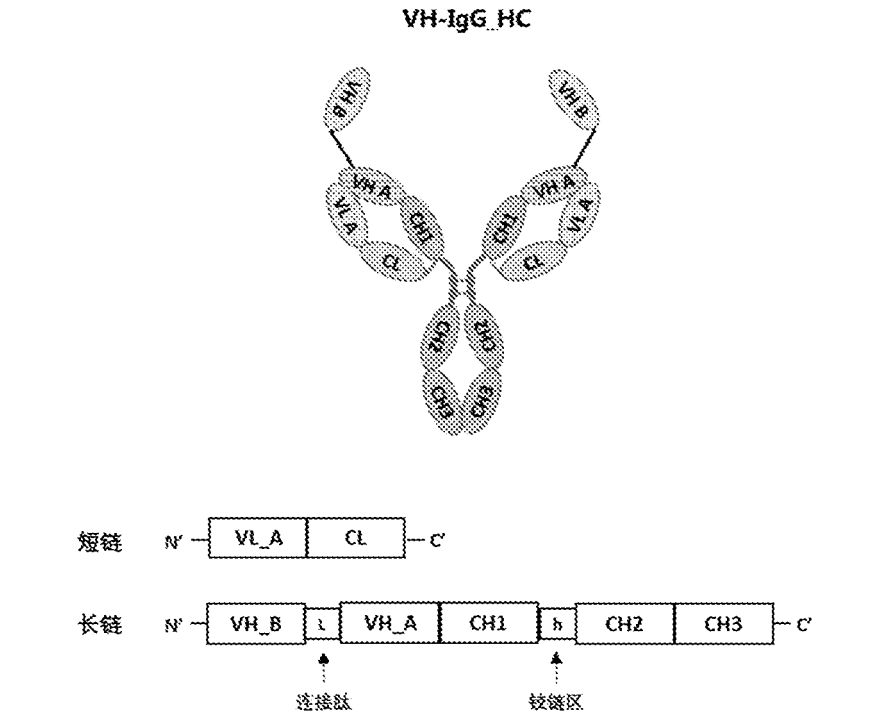
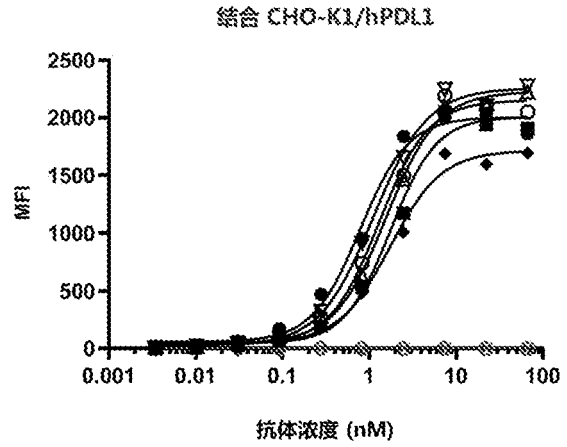
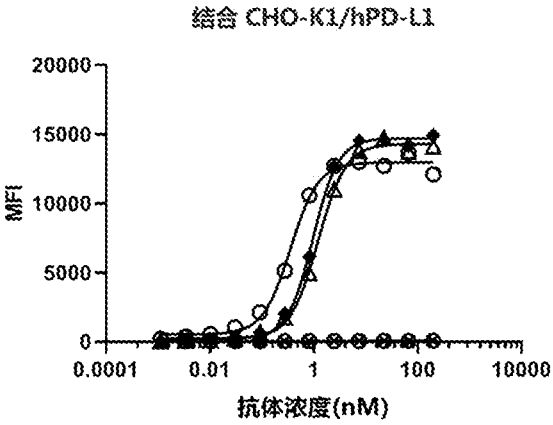

VH-IgG_HC
VH_B
VH_A
VL_A
CH1
CL
CH2
CH3
短链
N'
VL_A
CL
C'
长链
N'
VH_B
L
VH_A
CH1
h
CH2
CH3
C'
连接肽
铰链区

图23E



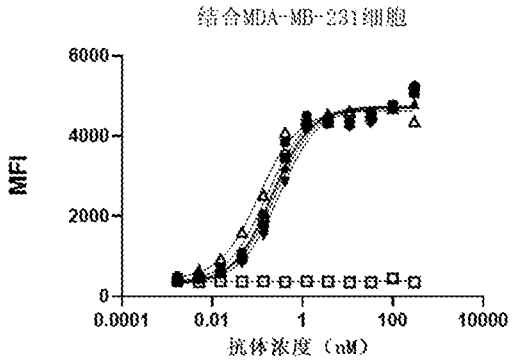
抗体	EC50 (nM)	MFI 最大值
PR003052	1.750	2006
PR000701	1.723	1714
PR003549	1.558	2224
PR003550	1.111	2254
PR003551	1.294	2149
PR000265	0.7807	2004

图24A



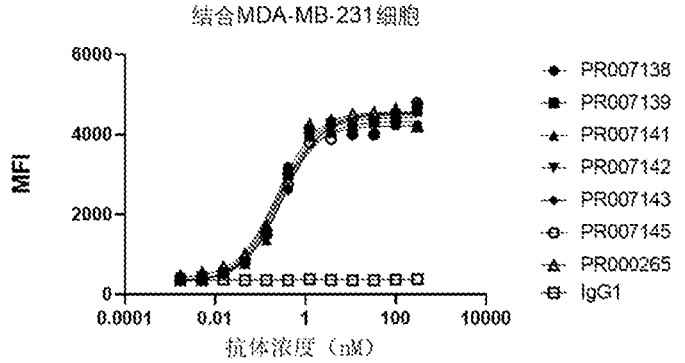
抗体	EC50 (nM)	MFI 最大值
PR004268	1.202	14313
PR004270	0.963	14716
PR000265	0.356	12960

图24B



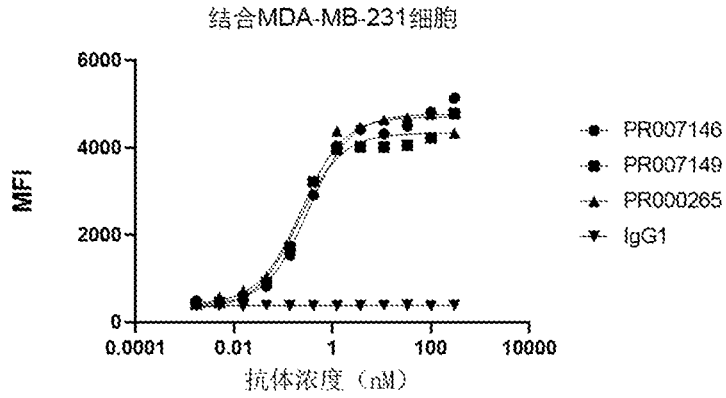
抗体	EC50(nM)	荧光最大值
PR007130	0.1608	4597
PR007132	0.2196	5080
PR007133	0.2162	4805
PR007135	0.2986	5029
PR007136	0.2531	5274
PR007137	0.2032	5218
PR000265	0.1095	4698

图24C



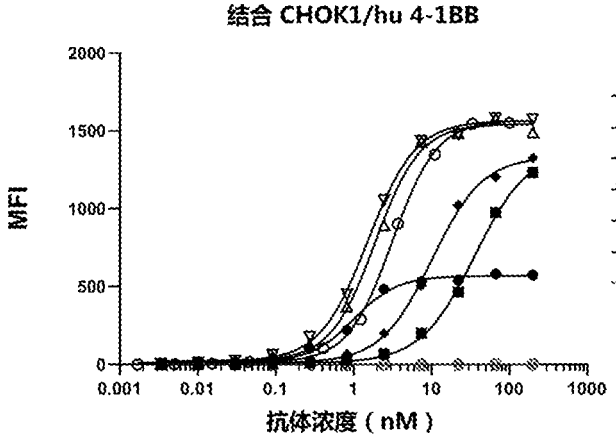
抗体	EC50(nM)	荧光最大值
PR007138	0.2016	4237
PR007139	0.257	4585
PR007141	0.3314	4801
PR007142	0.2634	4708
PR007143	0.3147	4663
PR007145	0.2859	4795
PR000265	0.2327	4637

图24D



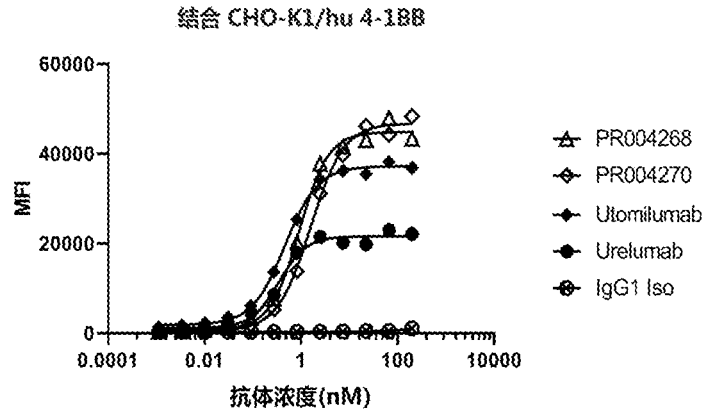
抗体	EC50(nM)	荧光最大值
PR007146	0.3266	5139
PR007149	0.2056	4788
PR000265	0.2326	4776

图24E



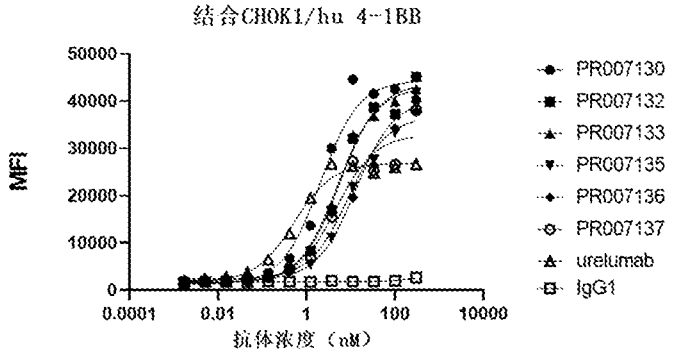
抗体	EC50 (nM)	MFI 最大值
PR003052	36	1390
PR000701	10.15	1338
PR003549	1.898	1546
PR003550	1.523	1567
PR003551	3.148	1570
Urelumab	1.014	570

图25A



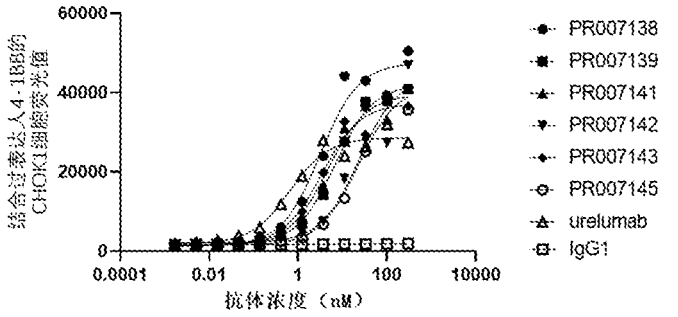
抗体	EC50 (nM)	MFI 最大值
PR004268	0.9162	44886
PR004270	1.576	46812
Urelumab	0.3469	21640
Utomilumab	0.4635	37245

图25B



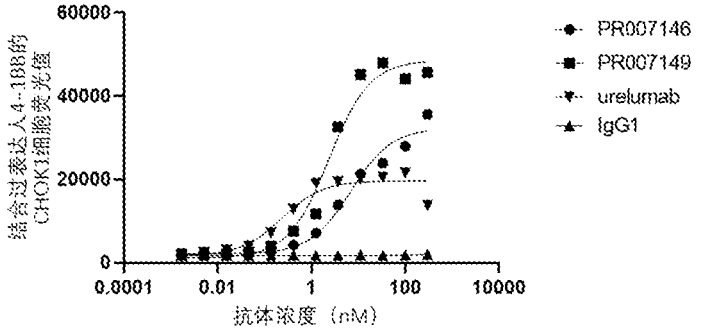
抗体	EC50(nM)	荧光最大值
PR007130	2.062	42609
PR007132	5.578	45164
PR007133	5.057	42561
PR007135	12.88	41819
PR007136	8.738	37764
PR007137	4.649	38094
urelumab	0.5189	26668

图25C



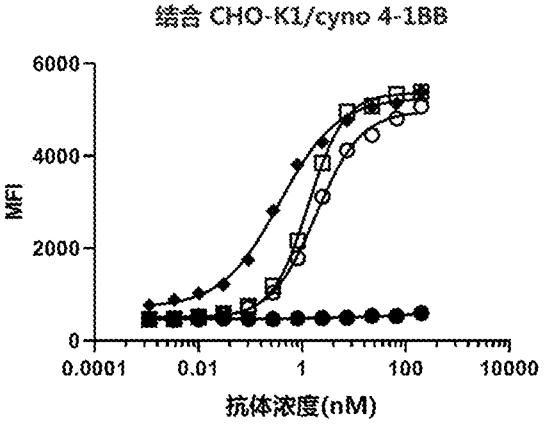
抗体	EC50(nM)	荧光最大值
PR007138	3.149	50503
PR007139	6.837	40908
PR007141	4.62	40992
PR007142	23.83	46865
PR007143	3.404	38102
PR007145	22.42	38848
urelumab	0.6534	31963

图25D



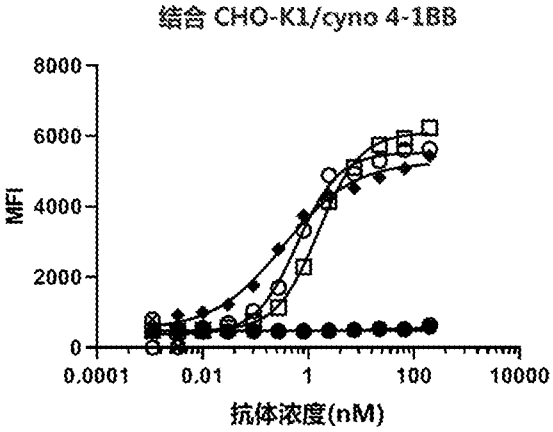
抗体	EC50(nM)	荧光最大值
PR007146	6.951	35639
PR007149	2.368	47971
Urelumab	0.2347	21623

图25E



抗体	EC50 (nM)	MFI 最大值
PR003549	1.859	4977
PR003550	1.321	5365
Utomilumab	0.3469	21640
Urelumab	不结合	

图26A



抗体	EC50 (nM)	MFI 最大值
PR004268	0.6208	5537
PR004270	1.554	6103
Utomilumab	0.3368	5271
Urelumab	不结合	

图26B

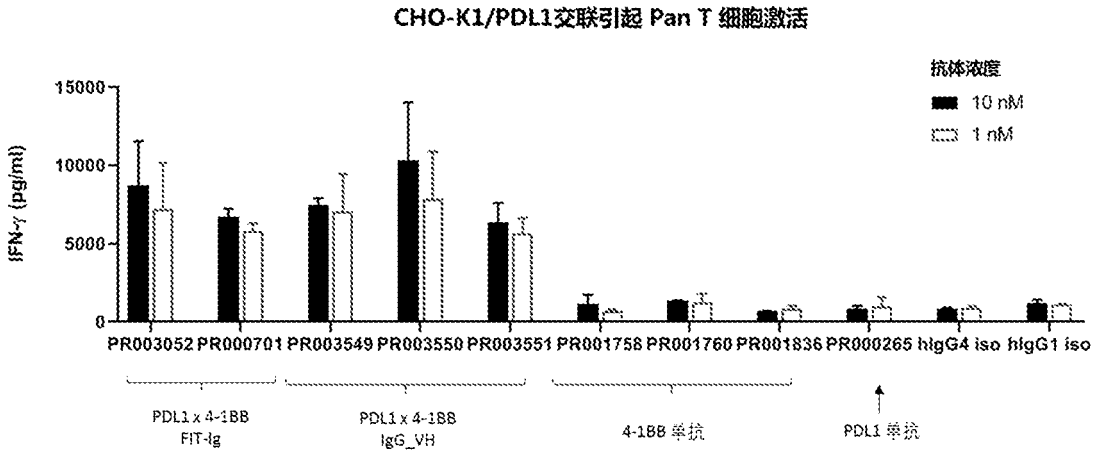


图27A

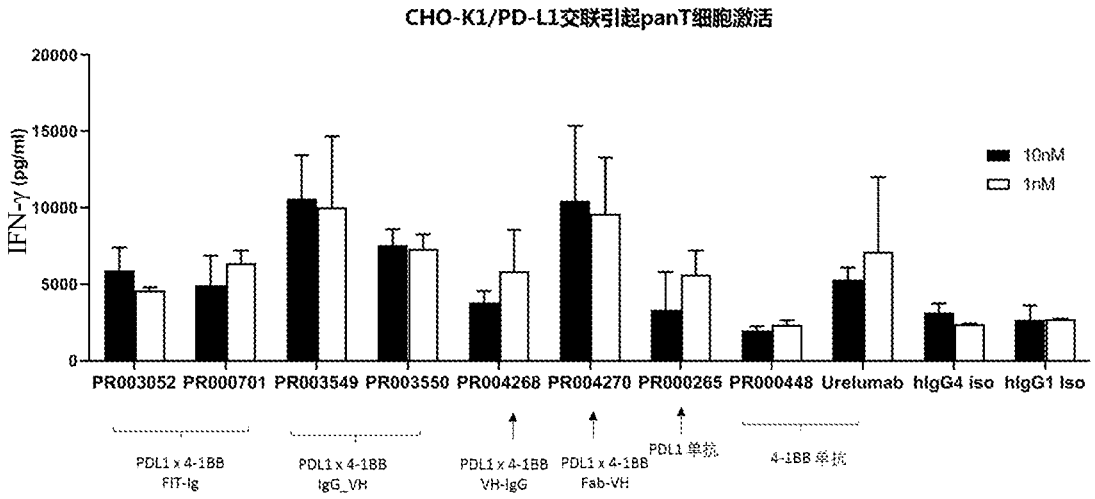


图27B

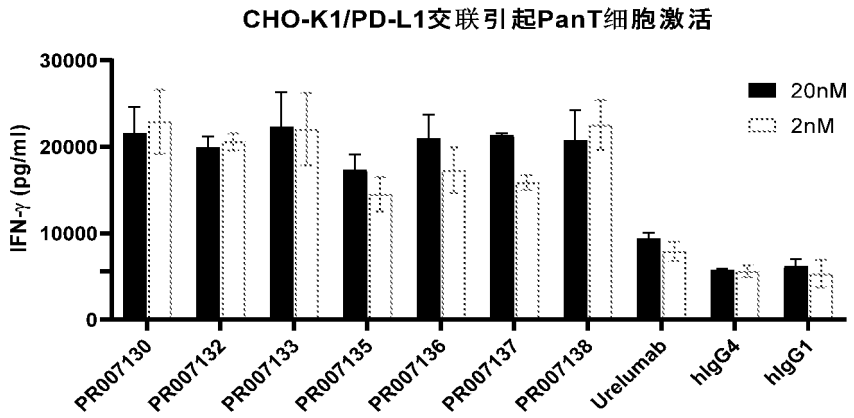


图27C

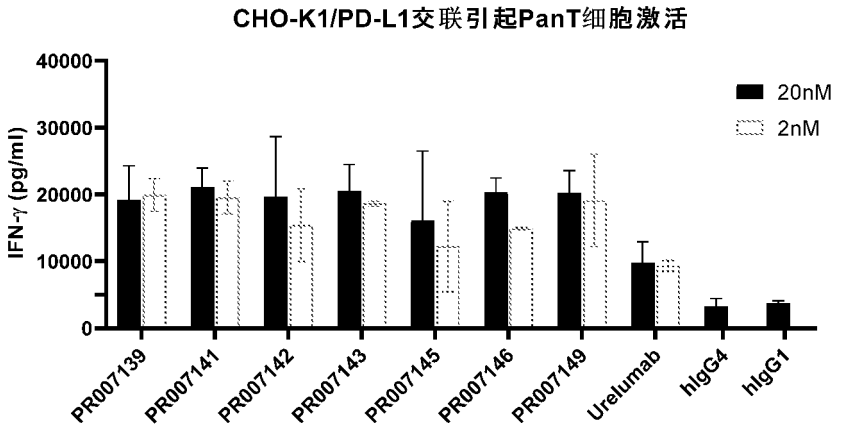

CHO-K1/PD-L1交联引起PanT细胞激活
IFN-γ (pg/ml)
40000
30000
20000
10000
0
20nM
2nM
PR007139
PR007141
PR007142
PR007143
PR007145
PR007146
PR007149
Urelumab
hIgG4
hIgG1

图27D

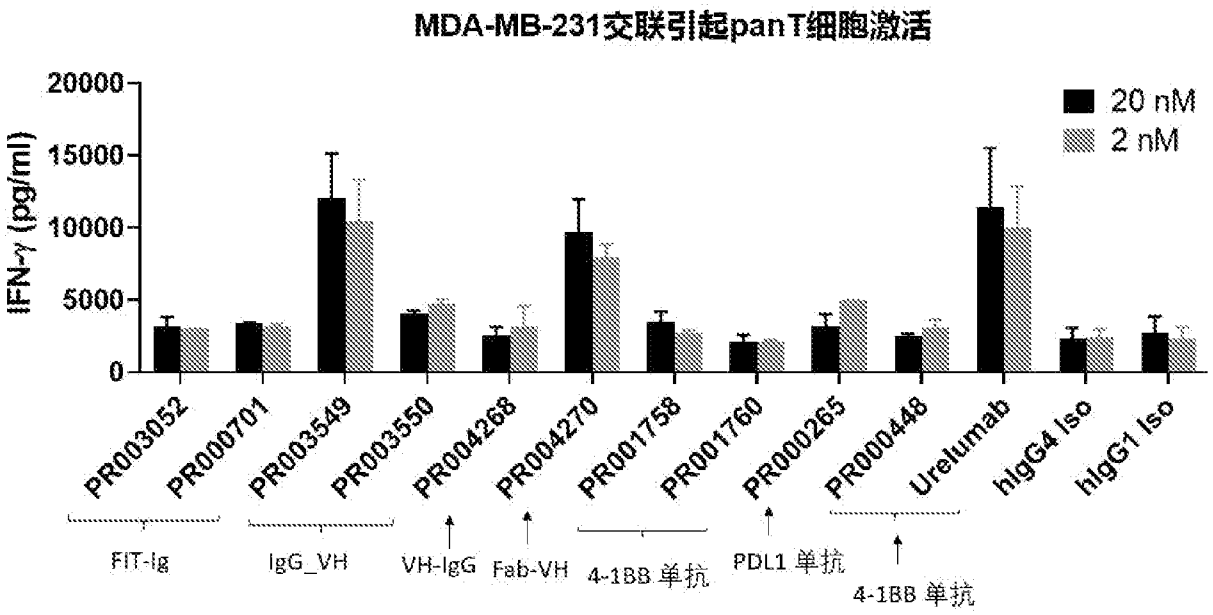
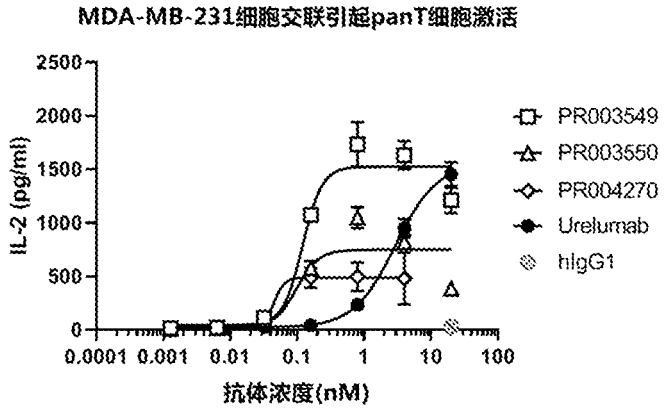
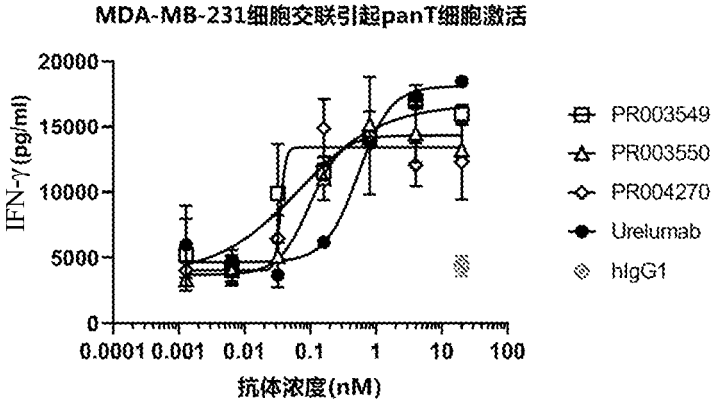

MDA-MB-231交联引起panT细胞激活
IFN-γ (pg/ml)
20000
15000
10000
5000
0
20 nM
2 nM
PR003052
PR000701
PR003549
PR003550
PR004268
PR004270
PR001758
PR001760
PR000265
PR000448
Urelumab
hIgG4 Iso
hIgG1 Iso
FIT-Ig
IgG_VH
VH-IgG
Fab-VH
4-1BB 单抗
PDL1 单抗
4-1BB 单抗

图27E



抗体	EC50 (nM)	IL-2释放最大值
PR003549	0.1203	1526
PR003550	0.0981	748.6
PR004270	0.04461	488.6
Urelumab	2.944	1554

图27F



抗体	EC50 (nM)	IFN释放最大值
PR003549	0.06951	16735
PR003550	0.0975	14320
PR004270	~ 0.03524	13401
Urelumab	0.536	18131

图27G

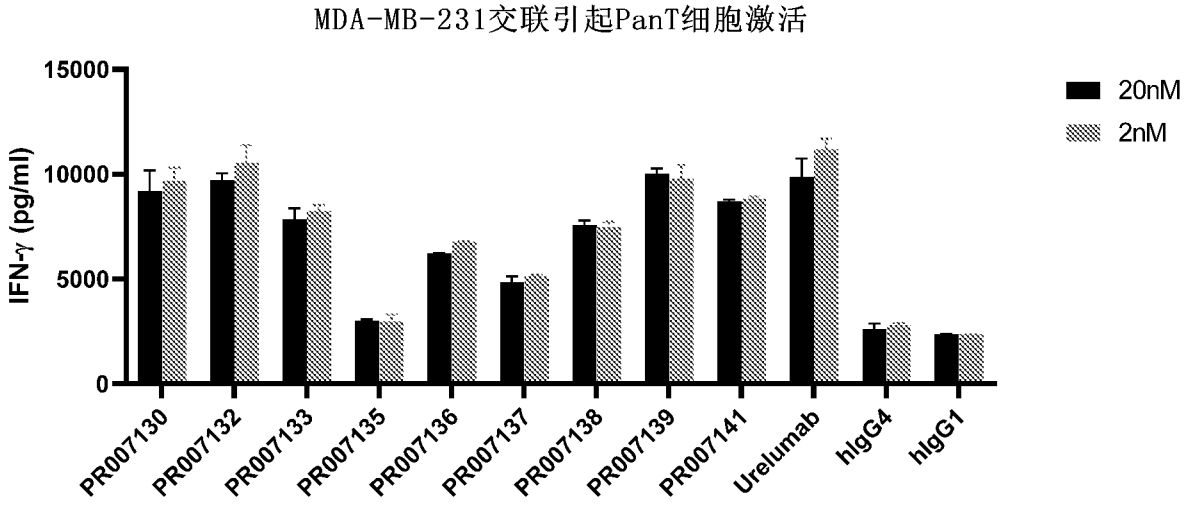


图27H

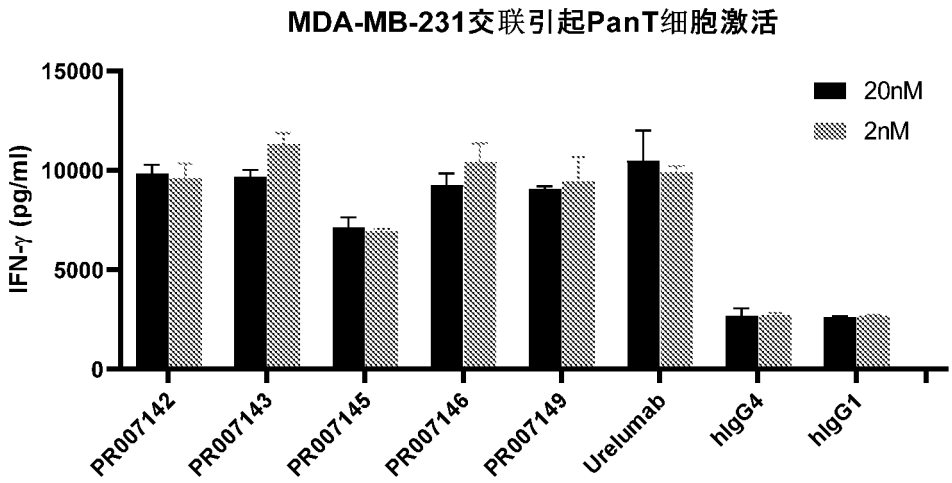


图27I

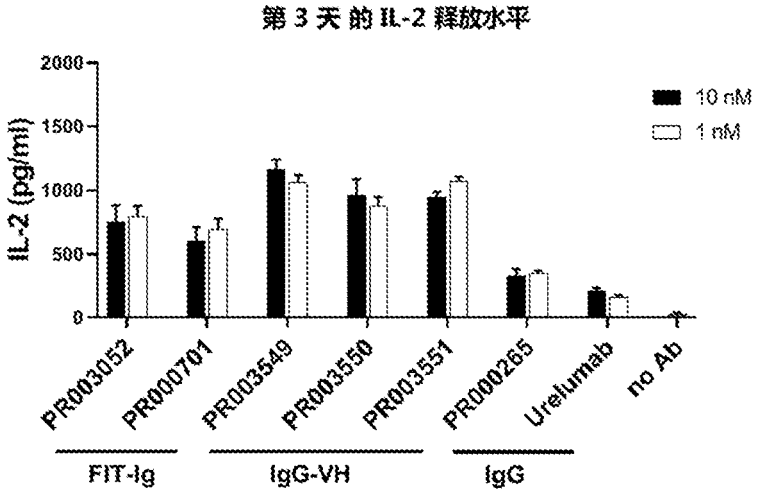


图28A

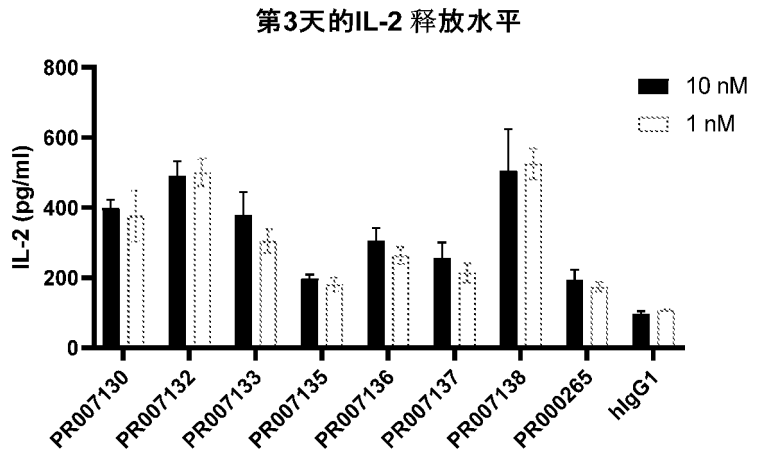


图28B

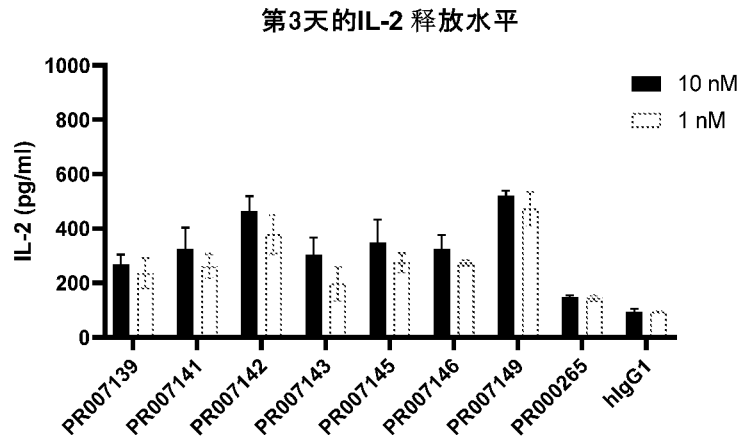


图28C

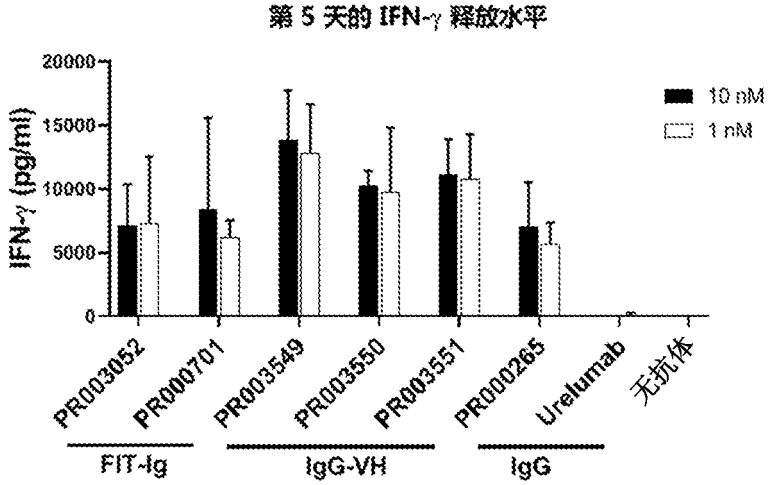


图28D

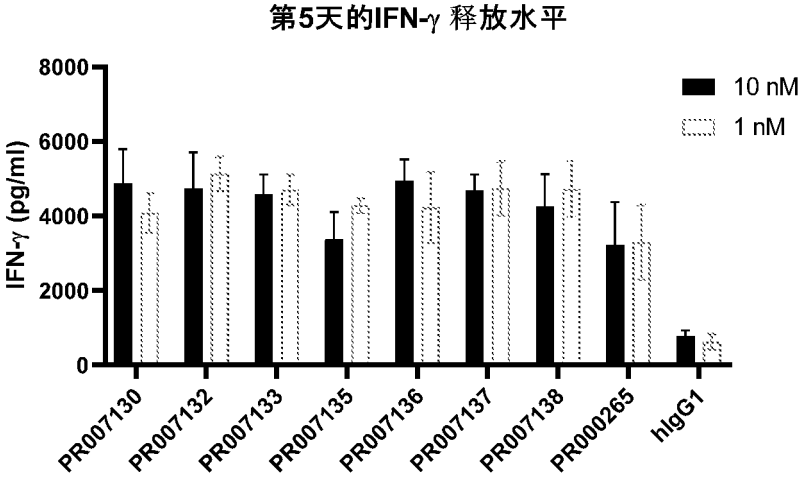


图28E

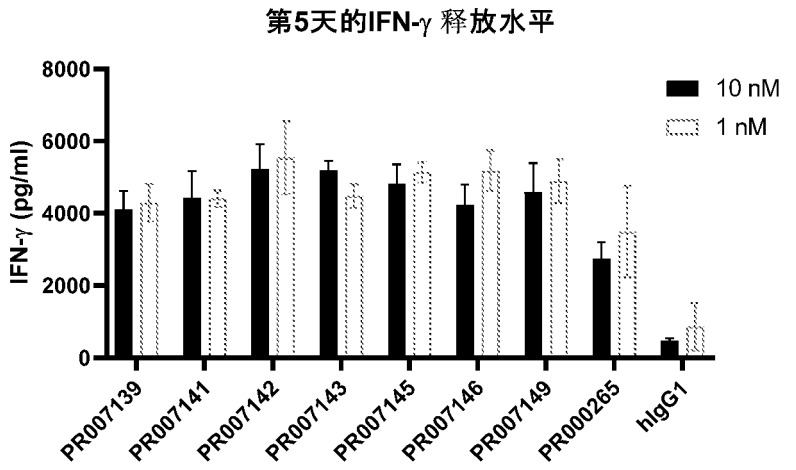

第5天的IFN-γ 释放水平
IFN-γ (pg/ml)
8000
6000
4000
2000
0
10 nM
1 nM
PR007139
PR007141
PR007142
PR007143
PR007145
PR007146
PR007149
PR000265
hIgG1

图28F

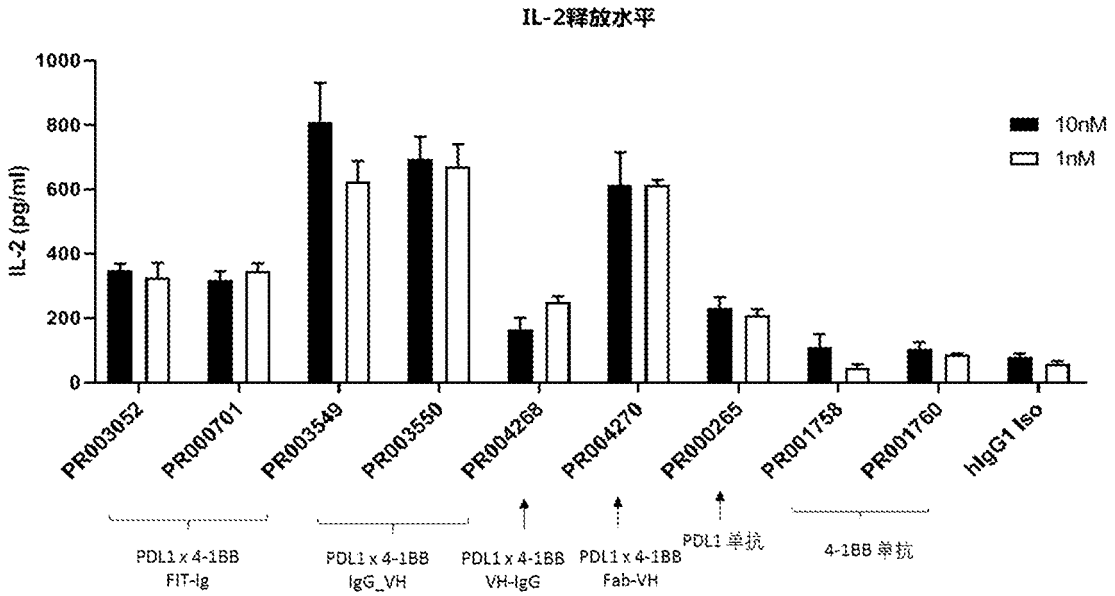

IL-2释放水平
IL-2 (pg/ml)
1000
800
600
400
200
0
10nM
1nM
PR003052
PR000701
PR003549
PR003550
PR004268
PR004270
PR000265
PR001758
PR001760
hIgG1 Iso
PDL1 x 4-1BB FIT-Ig
PDL1 x 4-1BB IgG_VH
PDL1 x 4-1BB VH-IgG
PDL1 x 4-1BB Fab-VH
PDL1 单抗
4-1BB 单抗

图28G

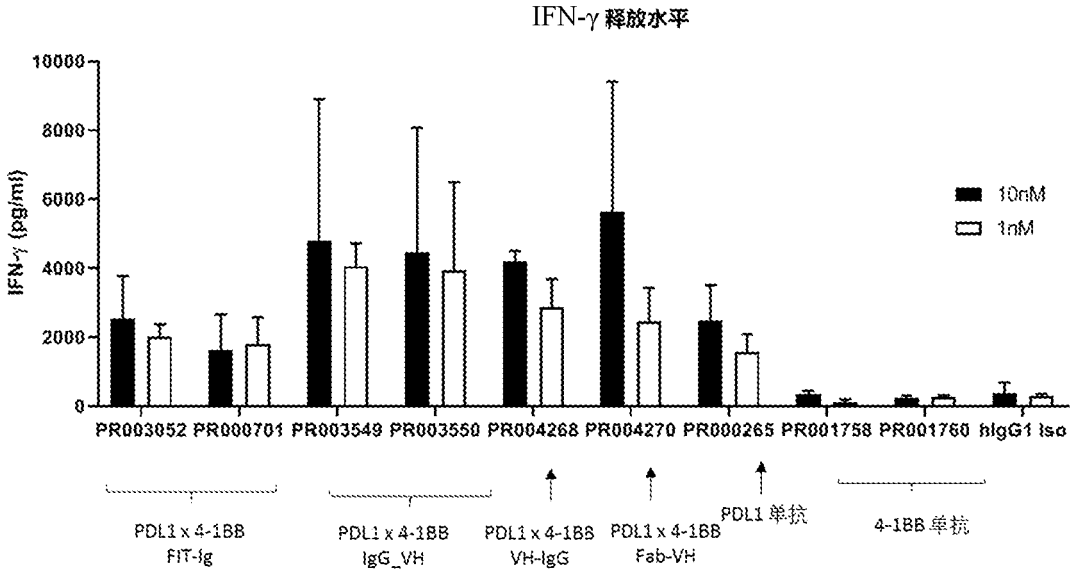
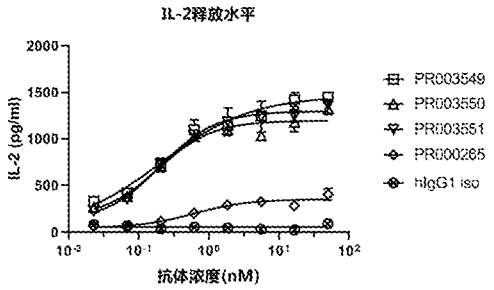
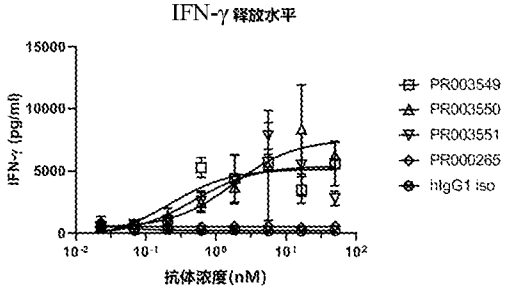


图28H

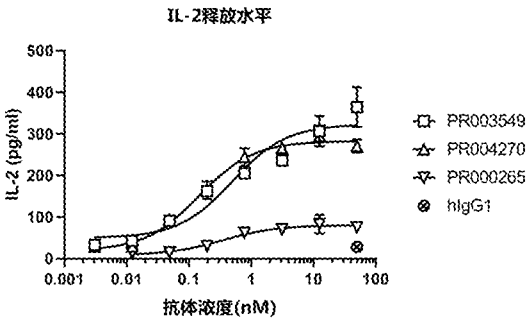


抗体	EC50(nM)	最大值
PR003549	0.2113	1461
PR003550	0.1863	1195
PR003551	0.2026	1296
PR000265	0.6133	353

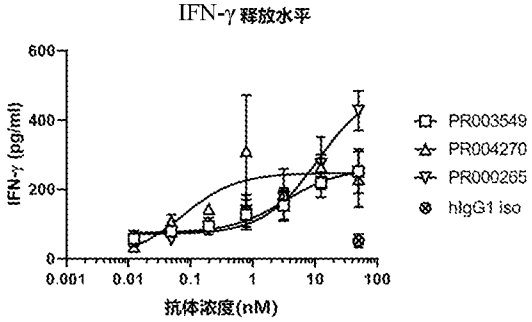


抗体	EC50(nM)	最大值
PR003549	0.2219	5162
PR003550	1.801	7518
PR003551	0.4881	5410
PR000265		~ 577.4

图28I

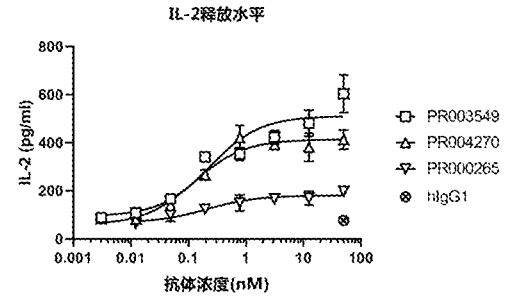


抗体	EC50(nM)	最大值	最小值
PR003549	0.5007	323.5	49.81
PR004270	0.1452	283.2	18.93
PR000265	0.3523	80.99	6.589

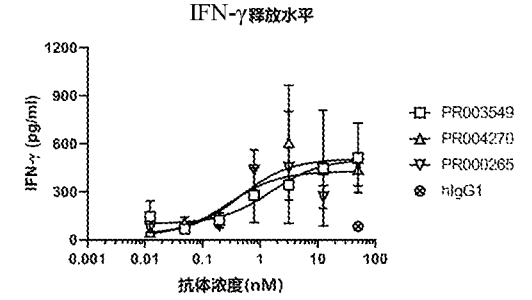


抗体	EC50(nM)	最大值	最小值
PR003549	3.276	260.1	74.87
PR004270	0.07387	248	0.6324
PR000265	10.87	494.4	71.05

图28J



抗体	EC50(nM)	最大值	最小值
PR003549	0.2392	511.7	94.4
PR004270	0.1245	414.7	58.62
PR000265	0.2085	181.4	67.12



抗体	EC50(nM)	最大值	最小值
PR003549	1.551	505.4	100.1
PR004270	0.4459	508.1	36
PR000265	0.2765	429.7	22.83

图28K

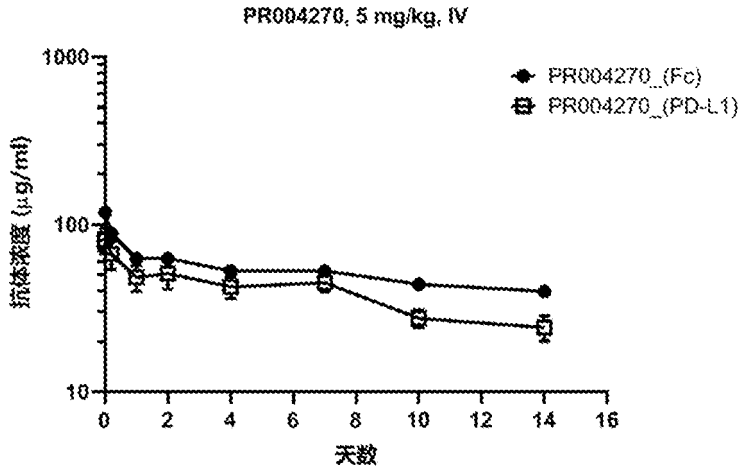


图29