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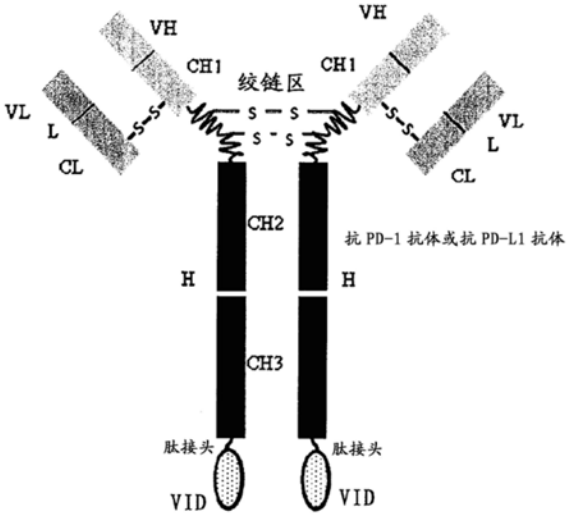
(54)发明名称

靶向PD-1或PD-L1且靶向VEGF家族的双靶向融合蛋白及其用途

(57)摘要

本发明提供了靶向PD-1或PD-L1且靶向VEGF家族这两者的双靶向融合蛋白,所述双靶向融合蛋白包含(i)抗PD-1抗体或者抗PD-L1抗体和(ii)在所述抗PD-1抗体或者抗PD-L1抗体的两条重链中的每一重链的C端有效连接的一个VID。本发明还提供了编码所述双靶向融合蛋白的多核苷酸、包含所述多核苷酸的载体、包含所述多核苷酸或载体的宿主细胞、以及所述双靶向融合蛋白在个体中治疗、预防和/或诊断与PD-1活性、PD-L1活性和VEGF家族活性相关的疾病中的用途。



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1.靶向PD-1且靶向VEGF家族的双靶向融合蛋白,所述双靶向融合蛋白抑制PD-1与其配体的结合、且抑制VEGF家族的信号传导途径,其包含

(i)抗PD-1抗体;和

(ii)在所述抗PD-1抗体的两条重链中的每一重链的C端有效连接的一个抑制VEGF家族的结构域,其中所述抑制VEGF家族的结构域也缩写为VID,所述VID是人VEGFR1的免疫球蛋白样结构域2和人VEGFR2的免疫球蛋白样结构域3,为SEQ ID NO:63所示的氨基酸序列;由此,两个相同的VID各自在它们的N端氨基酸处与所述抗PD-1抗体的重链之一的C端氨基酸通过肽接头有效连接,其中所述肽接头是选自SEQ ID NO:36－62的肽接头;

其中所述抗PD-1抗体包含SEQ ID NO:1/2的成对重链可变区序列/轻链可变区序列中所含的全部重链CDR与轻链CDR。

2.根据权利要求1所述的双靶向融合蛋白,其中所述抗PD-1抗体是IgG类抗体。

3.根据权利要求2所述的双靶向融合蛋白,其中所述抗PD-1抗体是IgG_1亚类、IgG_2亚类或IgG_4亚类抗体。

4.根据权利要求3所述的双靶向融合蛋白,其中所述抗PD-1抗体是IgG_4亚类抗体,且在Fc区中第S228位置处具有氨基酸置换。

5.根据权利要求4所述的双靶向融合蛋白,其中所述抗PD-1抗体是IgG_4亚类抗体,且在Fc区中第S228位置处具有氨基酸置换S228P。

6.根据权利要求1所述的双靶向融合蛋白,其中所述抗PD-1抗体的轻链型别为κ型或λ型。

7.根据权利要求1所述的双靶向融合蛋白,其中所述抗PD-1抗体包含SEQ ID NO:1/2的成对重链可变区序列/轻链可变区序列。

8.根据权利要求7所述的双靶向融合蛋白,其中所述抗PD-1抗体是纳武单抗。

9.根据权利要求1所述的双靶向融合蛋白,其是

由SEQ ID NO: 73的抗PD-1抗体轻链亚基和SEQ ID NO: 75的抗PD-1抗体重链-VID融合亚基组成的双靶向融合蛋白。

10.多核苷酸,其编码权利要求1－9中任一项所述的双靶向融合蛋白。

11.载体,所述载体包含权利要求10所述的多核苷酸。

12.根据权利要求11所述的载体,其是表达载体。

13.根据权利要求11所述的载体,其是具有双表达盒的谷氨酰胺合成酶表达载体。

14.宿主细胞,其包含权利要求10所述的多核苷酸或权利要求11－13中任一项所述的载体。

15.用于产生权利要求1－9中任一项所述的双靶向融合蛋白的方法,所述方法包括步骤(i)在适于表达所述双靶向融合蛋白的条件下培养权利要求14所述的宿主细胞,和(ii)回收所述双靶向融合蛋白。

16.药物组合物,其包含权利要求1－9中任一项所述的双靶向融合蛋白和可药用载体。

17.权利要求1－9中任一项所述的双靶向融合蛋白和权利要求16所述的药物组合物用于制备在个体中治疗或预防与PD-1活性和VEGF家族活性相关的癌性疾病的药物中的用途,其中所述癌性疾病是黑素瘤、乳腺癌、结肠癌、食管癌、胃肠道间质肿瘤、肾癌、肝癌、非小细胞肺癌、卵巢癌、胰腺癌、前列腺癌、头颈部肿瘤、胃癌、血液学恶性病,所述个体是哺乳动

物。

18.权利要求17所述的用途,其中所述个体是人。

19.权利要求18所述的用途,其中所述肾癌是肾细胞癌,所述血液学恶性病是淋巴瘤。

20.诊断试剂盒,其包含权利要求1－9中任一项所述的融合蛋白和任选地标记物或用于偶联的试剂。

21.根据权利要求20所述的诊断试剂盒,其包含用正电子发射断层摄影术可检测的标记物标记的权利要求1－9中任一项所述的融合蛋白。

22.根据权利要求21所述的诊断试剂盒,其中所述标记物是^{18}F-氟脱氧葡萄糖。

23.权利要求20－22中任一项所述的诊断试剂盒用于制备在个体中诊断与PD-1活性相关的癌性疾病的产品中的用途,其中所述癌性疾病是黑素瘤、乳腺癌、结肠癌、食管癌、胃肠道间质肿瘤、肾癌、肝癌、非小细胞肺癌、卵巢癌、胰腺癌、前列腺癌、头颈部肿瘤、胃癌、血液学恶性病,所述个体是哺乳动物。

24.权利要求23所述的用途,其中所述个体是人。

25.权利要求24所述的用途,其中所述肾癌是肾细胞癌,所述血液学恶性病是淋巴瘤。

靶向PD-1或PD-L1且靶向VEGF家族的双靶向融合蛋白及其用途

技术领域

[0001] 本发明总体上涉及医药生物技术领域。具体地，本发明涉及靶向程序性死亡蛋白-1(programmed death-1(PD-1))或程序性死亡蛋白配体1(programmed death-1ligand(PD-L1))、且靶向血管内皮细胞生长因子(Vascular Endothelial Cell Growth Factor(VEGF))家族这两者的双靶向融合蛋白、编码所述双靶向融合蛋白的多核苷酸、包含所述多核苷酸的载体、包含所述多核苷酸或载体的宿主细胞、以及所述双靶向融合蛋白在个体中治疗、预防和/或诊断与PD-1或PD-L1活性和VEGF家族活性相关的疾病中的用途。

背景技术

[0002] 免疫检查点(immune checkpoint)是免疫系统中存在的一类抑制性信号分子，通过调节外周组织中免疫反应的持续性和强度避免组织损伤，并参与维持对于自身抗原的耐受(Pardoll DM.,The blockade of immune checkpoints in cancer immunotherapy.Nat Rev Cancer,2012,12(4):252-264)。研究发现，肿瘤细胞能够逃避体内免疫系统而失控增殖的原因之一是利用了免疫检查点的抑制性信号通路，由此抑制了T淋巴细胞活性，使得T淋巴细胞不能有效发挥对肿瘤的杀伤效应(Yao S,Zhu Y和Chen L.,Advances in targeting cell surface signaling molecules for immune modulation.Nat Rev Drug Discov,2013,12(2):130-146)。

[0003] 程序性死亡蛋白-1(PD-1)是一种重要的免疫检查点蛋白，目前也是肿瘤免疫治疗的一个重要靶标。PD-1在1992年首次被发现，对其基因的克隆和表达表明PD-1活化后能够诱导T细胞程序性死亡。在活化的T细胞、B细胞和髓样细胞上均发现存在PD-1蛋白。PD-1还诱导性地表达于巨噬细胞、树突状细胞以及单核细胞。在静息的淋巴细胞表面无PD-1表达。

[0004] PD-1是一种55kDa I型跨膜蛋白，其胞浆区含有一个免疫受体酪氨酸抑制基序，与CD28和CTLA-4具有同源性。已鉴定到PD-1的两种细胞表面糖蛋白配体，分别为程序性死亡蛋白配体1(PD-L1)和程序性死亡蛋白配体2(PD-L2)。已经在许多癌细胞上发现了PD-1的配体表达，包括人肺癌、卵巢癌、结肠癌和多种骨髓瘤。另外，在各类上皮癌、血液癌和其他恶性肿瘤细胞表面上高表达PD-1的配体。在肿瘤患者中，PD-1的配体如PD-L1的表达经常与癌的预后不良相关(Iwai Y等人,Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade,PNAS,2002,99(19):12293-7)。

[0005] PD-1与PD-1的配体的结合对于调节T淋巴细胞活性和维持外周免疫耐受发挥重要作用。PD-1与PD-1的配体结合后可导致T细胞凋亡、免疫无应答、T细胞“耗竭”和分泌IL-10等。因此，PD-1发挥限制T细胞活化、抑制T细胞增殖和提高对抗原的耐受性的功能。活化的淋巴细胞表面PD-1的表达上调能够导致对获得性或者固有的免疫反应的抑制，由此导致了(包括T淋巴细胞在内的)肿瘤浸润性淋巴细胞虽然具有肿瘤抗原特异性，但由于肿瘤细胞上PD-1的配体与肿瘤浸润性淋巴细胞上的PD-1结合产生了抑制肿瘤浸润性淋巴细胞活化

的信号,从而肿瘤细胞能够逃避免疫系统对肿瘤细胞的杀伤。

[0006] 研究表明,这些表达PD-1的肿瘤浸润性淋巴细胞是功能障碍型淋巴细胞,所述淋巴细胞的生物学功能可以通过阻断PD-1与PD-1的配体结合的抗体恢复。目前,抑制PD-1与PD-1的配体结合的抗体主要包括抗PD-1单克隆抗体和抗PD-L1单克隆抗体,但也有针对PD-L2的产品。

[0007] 当前,研究比较成熟的抗PD-1抗体有百时美施贵宝(BMS)公司的纳武单抗(Nivolumab)和默克(Merck)公司的派姆单抗(Pembrolizumab)。纳武单抗(商品名OPDIVO®)为完全人源化的IgG4抗体分子,派姆单抗(商品名KEYTRUDA®)为人源化IgG4抗体分子。所述抗PD-1单克隆抗体与T淋巴细胞上的PD-1结合后能够抑制PD-1与其配体PD-L1和PD-L2的结合,由此促进T淋巴细胞活化、增殖和产生免疫活化型细胞因子如IL-2,并解除PD-1对具有抗肿瘤活性的T淋巴细胞免疫监视的抑制。美国食品药品监督管理局目前批准的纳武单抗适应症包括:黑素瘤、非小细胞肺癌、肾癌、头颈部肿瘤等;派姆单抗的适应症包括:头颈部肿瘤、非小细胞肺癌、黑素瘤等。关于抗PD-L1抗体,罗氏(Roche)研发的atezolizumab、德国默克(Merck KGaA)和美国辉瑞(Pfizer)合作开发的avelumab、阿斯利康研发的durvalumab也显示了对肿瘤的治疗效果。

[0008] 虽然抗PD-1抗体、抗PD-L1抗体对肿瘤具有治疗效果,但它们平均的治疗有效率仅为20%左右,肺癌的五年生存率仅16%。仍有相当一部分的肿瘤患者对使用抗PD-1抗体、抗PD-L1抗体的治疗无应答。因此,如何提高肿瘤治疗的有效性仍是目前肿瘤治疗领域迫切需要解决的一个难题。

[0009] 另一方面,肿瘤血管形成(angiogenesis)也是肿瘤快速生长的一个重要原因(Ferrara N和Alitalo K,Clinical applications of angiogenic growth factors and their inhibitors,Nat Med.,1999;5(12):1359-64)。在肿瘤的表面和深处,到处都可以见到粗细不等的血管,生命的营养物质和氧气通过这些血管被运送至肿瘤组织。肿瘤血管形成是一个相当复杂的过程,受多种因子的正负调控。在这多种因子中,血管内皮细胞生长因子家族是一类作用最强的正性调控因子,发挥着刺激新生血管形成的功能。正常组织内血管内皮细胞生长因子和血管内皮细胞生长抑制因子同时存在,且保持相对平衡,这种平衡使得人体血管可以正常地生成和分化。但是,在肿瘤生长过程中,VEGF家族分子数量激增,与血管生成抑制因子之间的调节失衡,由此,极大地促进了血管内皮细胞的分裂增殖和迁移、提高了血管通透性、抑制肿瘤细胞凋亡,为肿瘤的生长和转移提供了良好的微环境。

[0010] VEGF家族包含六种密切相关的多肽,分别是高度保守的同源二聚体糖蛋白,有六个亚型:VEGF-A、-B、-C、-D、-E、和胎盘生长因子(placental growth factor(PLGF)),分子量从35至44kDa不等。VEGF-A(包括其剪接物如$VEGF_{165}$)的表达与一些实体瘤的微血管密度具有相关性,并且组织中VEGF-A的浓度与乳腺癌、肺癌、前列腺癌和结肠癌等实体瘤的预后有关。每个VEGF家族成员的生物学活性通过细胞表面VEGF受体(VEGFR)家族中的一种或多种介导,所述VEGFR家族包括VEGFR1(也称为Flt-1)、VEGFR2(也称为KDR、Flk-1)、VEGFR3(也称为Flt-4)等,其中VEGFR1、VEGFR2与血管的生成关系密切,VEGF-C/D/VEGFR3则与淋巴管生成密切相关。VEGF家族的主要生物学功能包括:(1)选择性促进血管内皮细胞有丝分裂,刺激内皮细胞增殖并促进血管形成;(2)提高血管尤其是微小血管的通透性,使血浆大分子外渗沉积在血管外的基质中,为肿瘤细胞的生长和新生毛细血管网的建立提供营养;(3)促

进肿瘤的增殖和转移,所述肿瘤的增殖和转移依赖VEGF家族使血管内皮细胞分泌胶原酶和纤溶酶原,借以降解血管基底膜,同时,肿瘤组织内部新形成的微血管基膜不完善,这种性质使肿瘤易于进入血循环;(4)其他作用:VEGF家族可诱导上皮细胞出现间隙及开窗现象,可活化上皮细胞的胞质小泡及细胞器;VEGF家族直接刺激内皮细胞释放蛋白水解酶,降解基质,释放更多的VEGF家族分子,加速肿瘤的发展,细胞外蛋白酶又可激活细胞外基质的结合性和VEGF家族的释放;VEGF家族通过增加血管通透性使血浆蛋白(包括纤维蛋白原)释放,形成纤维素网络,为肿瘤生长、发展和转移提供了良好的基质;(5)VEGF家族抑制机体的免疫反应,促进恶性肿瘤的浸润与转移(Lapeyre-Prost A等人,Immunomodulatory Activity of VEGF in Cancer,Int Rev Cell Mol Biol.2017;330:295-342)。

[0011] 在VEGF家族中,胎盘生长因子(PLGF)的40％氨基酸序列和VEGF-A同源,参与病理状态下的新生血管和侧支血管的形成。PLGF的生物学功能是通过特异结合其受体VEGFR1/Flt-1来激活的。VEGFR1/Flt-1具有很强的生物学活性,结合其配体后可介导内皮细胞与基质细胞的作用,也影响内皮细胞的分化成熟。PLGF能促进早孕时滋养细胞增殖与分化,可诱导内皮细胞增殖、迁移,抗内皮细胞凋亡,并能增加血管的通透性,能增强低浓度VEGF的生物学活性,是参与多种肿瘤血管生成的重要的促血管生长因子。过度的PLGF表达导致肿瘤生长的增加和血管的存活。在原发肿瘤中观察到PLGF在所有血管丰富的肿瘤中表达,而血管少的肿瘤只部分表达PLGF。因此,PLGF可用来解释脑部肿瘤血管新生的机制,而通过抑制PLGF的生物学活性可以达到抑制肿瘤生长的目的。

[0012] 临床研究显示利用单克隆抗体或可溶性VEGFR能够阻断VEGF家族与其受体的结合,阻碍VEGF家族信号通路的传导也是目前治疗肿瘤的方法之一。基因泰克(Genentech)公司研发的贝伐单抗(Bevacizumab,商品名Avastin)是一种重组的人鼠嵌合抗VEGF抗体,可通过阻断VEGF-A与VEGFR的结合,使VEGFR无法活化,由此发挥抗血管生成的作用。贝伐单抗目前用于一线治疗转移性结直肠癌,将来有可能用于转移性肺癌、乳癌、胰脏癌、肾脏癌等疾病的治疗。贝伐单抗也是开发较为成功的抗体药物之一。Sanofi-aventis公司和Regeneron公司研制的阿柏西普(aflibercept)是一种VEGF-Trap,其是将VEGFR1胞外第2个结构域和VEGFR2胞外第3个结构域与人IgG1恒定区融合获得的一种融合蛋白,能通过抑制血管生成而对一部分肿瘤患者发挥抗肿瘤作用。

[0013] 仍有大部分的肿瘤患者对目前可用的抗PD-1抗体、抗PD-L1抗体、抗VEGF抗体或VEGF-Trap的单独治疗无反应。

[0014] 鉴于免疫检查点蛋白PD-1、PD-L1在调节免疫应答中的重要性,以及VEGF家族在肿瘤微环境中抑制抗肿瘤免疫和促进肿瘤血管形成的作用,本领域仍需要治疗肿瘤的备选疗法。优选地,这类备选疗法能够既靶向免疫抑制性蛋白PD-1或PD-L1,又靶向具有免疫抑制作用和促血管生成作用的VEGF家族分子,从而导致免疫系统的激活和肿瘤血管的消退,从而对靶向PD-1或PD-L1的单一治疗无反应或者靶向VEGF家族的单一治疗无反应的患者显示功效。这类备选疗法的一个方案是共施用靶向PD-1或PD-L1和靶向VEGF家族分子的两种不同的生物制品。共施用需要注射两个独立的产品或单次注射两种不同蛋白的联合制剂。尽管两次注射允许给药量和给药时间的灵活性,但是它造成了患者不便依从和疼痛。另外,尽管联合制剂可能提供在给药量方面的某种灵活性,但它通常难以找到在溶液中允许两种蛋白的化学和物理稳定性的配制条件,原因在于两种蛋白的分子特征不同。另外,共施用和联

合制剂两种不同药物的疗法可能增加患者和/或付款人的额外花费。因此，仍需要治疗肿瘤的备选疗法，并且优选地这类备选疗法包含靶向PD-1或PD-L1且靶向VEGF家族的双靶向融合蛋白。

[0015] 本发明提供了靶向PD-1或PD-L1且靶向VEGF家族的双靶向新型融合蛋白，其能够抑制对PD-1途径或对PD-L1途径和对VEGF家族信号传导途径的激活，并用于在个体中治疗、预防和/或诊断与PD-1、PD-L1活性和VEGF家族活性相关的疾病。

[0016] 发明概述

[0017] 本发明公开了一种新型的靶向PD-1或PD-L1且靶向VEGF家族的双靶向融合蛋白、编码所述双靶向融合蛋白的多核苷酸、包含所述多核苷酸的载体、包含所述多核苷酸或载体的宿主细胞、以及所述双靶向融合蛋白在个体中治疗、预防和/或诊断与PD-1、PD-L1活性和VEGF家族活性相关的疾病中的用途。

[0018] 因此，在一个方面，本发明提供了靶向PD-1或PD-L1且靶向VEGF家族的双靶向融合蛋白，所述双靶向融合蛋白抑制PD-1与其配体的结合或抑制PD-L1与其受体的结合、且抑制VEGF家族的信号传导途径，其包含(i)抗PD-1抗体或者抗PD-L1抗体；和(ii)与所述抗PD-1抗体或者抗PD-L1抗体有效连接的至少两个抑制VEGF家族的结构域(VEGFs familiy inhibiting domain，下文中缩写为VID)。

[0019] 在一个实施方案中，本发明的双靶向融合蛋白包含(i)抗PD-1抗体或者抗PD-L1抗体；和(ii)在所述抗PD-1抗体或者抗PD-L1抗体的两条重链中的每一重链的C端有效连接的一个VID，任选地，所述(i)和所述(ii)通过肽接头有效连接，由此，两个相同或者不同的VID各自在它们的N端氨基酸处与所述抗PD-1抗体或者抗PD-L1抗体的重链之一的C端氨基酸融合，任选地通过肽接头融合，优选地，所述VID包含VEGF家族的受体的胞外结构域的一部分。

[0020] 所述双靶向融合蛋白中包含的抗PD-1抗体可以是任何抗PD-1抗体，只要是能够抑制或减少PD-1与其配体结合的抗体即可，包括现有技术中已知的抗PD-1抗体和将来研发出的抗PD-1抗体。在一个实施方案中，所述抗PD-1抗体包含选自SEQ ID NO:1/2、3/4、5/6、7/8、9/10、11/12、13/14、15/16、17/18、19/20、21/22、23/24、和120/121的成对重链可变区序列/轻链可变区序列中所含的全部重链CDR与轻链CDR，优选地，所述抗PD-1抗体包含选自SEQ ID NO:1/2、3/4、5/6、7/8、9/10、11/12、13/14、15/16、17/18、19/20、21/22、23/24、和120/121的成对重链可变区序列/轻链可变区序列，或与所述成对重链可变区序列/轻链可变区序列具有至少90％、91％、92％、93％、94％、95％、96％、97％、98％、99％或更多序列同一性的序列；更优选地，所述抗PD-1抗体包含选自纳武单抗、pidilizumab和派姆单抗的抗PD-1抗体的重链可变区和轻链可变区，特别地，所述抗PD-1抗体选自纳武单抗、pidilizumab和派姆单抗。

[0021] 所述双靶向融合蛋白中包含的抗PD-L1抗体可以是任何抗PD-L1抗体，只要是能够抑制或减少PD-L1与其受体结合(例如与PD-1或CD80(B7-1)或与这两者结合)的抗体即可，包括现有技术中已知的抗PD-L1抗体和将来研发出的抗PD-L1抗体。在一个实施方案中，本发明融合蛋白中的抗PD-L1抗体包含选自SEQ ID NO:25/26、27/28和29/30的成对重链可变区序列/轻链可变区序列中所含的全部重链CDR与轻链CDR。优选地，所述抗PD-L1抗体包含选自SEQID NO:25/26、27/28和29/30的成对重链可变区序列/轻链可变区序列，或与所述成对重链可变区序列/轻链可变区序列具有至少90％、91％、92％、93％、94％、95％、96％、

97％、98％、99％或更多序列同一性的序列；更优选地，所述抗PD-L1抗体选自atezolizumab、avelumab和durvalumab。

[0022] 在一个实施方案中，所述抗PD-1抗体或抗PD-L1抗体是IgG类抗体，特别地是IgG_1亚类、IgG_2亚类、IgG_4亚类抗体。在一个优选的实施方案中，包含于本发明融合蛋白中的所述抗PD-1抗体或抗PD-L1抗体是IgG_4亚类抗体，特别地是人IgG_4亚类抗体。在一个实施方案中，所述IgG_4亚类抗体在Fc区中第S228位置(EU编号)处包含氨基酸置换，特别是氨基酸置换S228P。SEQ ID NO:33中显示了示例性IgG_1亚类抗PD-1抗体的重链恒定区氨基酸序列。SEQ ID NO:34中显示了示例性IgG_2亚类抗PD-1抗体的重链恒定区氨基酸序列。SEQ ID NO:35中显示了示例性IgG_4亚类抗PD-1抗体的重链恒定区氨基酸序列。

[0023] 在一个实施方案中，所述抗PD-1抗体或抗PD-L1抗体包含完全抗体的可变区和恒定区。本发明的双靶向融合蛋白中的抗体轻链恒定区型别可以是κ型或λ型，优选地是κ型。SEQ ID NO:31中显示了示例性抗PD-1抗体的κ型轻链恒定区氨基酸序列。SEQ ID NO:32中显示了示例性抗PD-1抗体的λ型轻链恒定区氨基酸序列。

[0024] 所述双靶向融合蛋白中包含的VID包含VEGF家族的受体的胞外结构域的一部分。在一个实施方案中，所述VID包含VEGFR1的免疫球蛋白(Ig)样结构域2(Domain 2，缩写为D2)和VEGFR2的Ig样结构域3(Domain 3，缩写为D3)。在一个具体实施方案中，所述VEGFR1-D2/VEGFR2-D3具有SEQ ID NO:63所示的氨基酸序列，或与SEQ ID NO:63的氨基酸序列具有至少90％、91％、92％、93％、94％、95％、96％、97％、98％、99％或更多同一性的氨基酸序列。在一个实施方案中，所述VID包含VEGFR1-D2以及VEGFR2-D3和VEGFR2的Ig样结构域4(Domain 4，缩写为D4)。在一个具体实施方案中，所述VEGFR1-D2/VEGFR2-D3-D4具有SEQ ID NO:64所示的氨基酸序列，或与SEQ ID NO:64的氨基酸序列具有至少90％、91％、92％、93％、94％、95％、96％、97％、98％、99％或更多同一性的氨基酸序列。在一个实施方案中，所述VID包含VEGFR1-D2。在一个具体实施方案中，所述VEGFR1-D2具有SEQ ID NO:65所示的氨基酸序列，或与SEQ ID NO:65的氨基酸序列具有至少90％、91％、92％、93％、94％、95％、96％、97％、98％、99％或更多同一性的氨基酸序列。

[0025] 在一个实施方案中，在所述抗PD-1抗体或抗PD-L1抗体的重链的C端连接所述VID的肽接头包含一个或多个氨基酸，优选地包含选自SEQ ID NO:36-62的肽接头。

[0026] 在一个具体实施方案中，所述融合蛋白包含SEQ ID NO:73的抗PD-1抗体轻链亚基和SEQ ID NO:75的抗PD-1抗体重链-VID融合亚基，下文中称为融合蛋白BY24.3。在一个具体实施方案中，所述融合蛋白包含SEQ ID NO:77的抗PD-1抗体轻链亚基和SEQ ID NO:79的抗PD-1抗体重链-VID融合亚基，下文中称为融合蛋白BY24.7。在一个具体实施方案中，所述融合蛋白包含SEQ ID NO:81的抗PD-1抗体轻链亚基和SEQ ID NO:83的抗PD-1抗体重链-VID融合亚基，下文中称为融合蛋白BY24.4。在一个具体实施方案中，所述融合蛋白包含SEQID NO:85的抗PD-1抗体轻链亚基和SEQ ID NO:87的抗PD-1抗体重链-VID融合亚基，下文中称为融合蛋白BY24.5。在一个具体实施方案中，所述融合蛋白包含SEQ ID NO:89的抗PD-1抗体轻链亚基和SEQ ID NO:91的抗PD-1抗体重链-VID融合亚基，下文中称为融合蛋白BY24.6。在一个具体实施方案中，所述融合蛋白包含SEQ ID NO:93的抗PD-1抗体轻链亚基和SEQ ID NO:95的抗PD-1抗体重链-VID融合亚基，下文中称为融合蛋白BY24.8。在一个具体实施方案中，所述融合蛋白包含SEQ ID NO:97的抗PD-1抗体轻链亚基和SEQ IDNO:99的

抗PD-1抗体重链-VID融合亚基，下文中称为融合蛋白BY24.9。在一个具体实施方案中，所述融合蛋白包含SEQ ID NO:101的抗PD-1抗体轻链亚基和SEQ ID NO:103的抗PD-1抗体重链-VID融合亚基，下文中称为融合蛋白BY24.10。在一个具体实施方案中，所述融合蛋白包含SEQ ID NO:105的抗PD-1抗体轻链亚基和SEQ ID NO:107的抗PD-1抗体重链-VID融合亚基，下文中称为融合蛋白BY24.11。在一个具体实施方案中，所述融合蛋白包含SEQ ID NO:109的抗PD-1抗体轻链亚基和SEQ ID NO:111的抗PD-1抗体重链-VID融合亚基，下文中称为融合蛋白BY24.12。在一个具体实施方案中，所述融合蛋白包含SEQ ID NO:113的抗PD-1抗体轻链亚基和SEQ ID NO:115的抗PD-1抗体重链-VID融合亚基，下文中称为融合蛋白BY24.13。在一个具体实施方案中，所述融合蛋白包含SEQ ID NO:117的抗PD-1抗体轻链亚基和SEQ ID NO:119的抗PD-1抗体重链-VID融合亚基，下文中称为融合蛋白BY24.14。

[0027] 在一个具体实施方案中，所述融合蛋白包含(i)一个选自atezolizumab、avelumab和durvalumab的抗PD-L1抗体和(ii)在所述抗PD-L1抗体的两条重链中的每一重链的C端有效连接的一个VID分子。

[0028] 在一个实施方案中，所述融合蛋白特异性地靶向PD-1或PD-L1和VEGF家族分子，抑制由PD-1或PD-L1和VEGF家族分子介导的信号传导。本发明的融合蛋白不仅在N端能高亲和性结合PD-1或PD-L1，而且在C端也能高亲和性地结合多种VEGF因子。本发明所设计的融合蛋白的结构充分保证了该融合蛋白与两类靶标结合的合适物理空间距离，这种结构的融合蛋白与PD-1或PD-L1和VEGF家族分子中的一种分子特异性结合后不影响该融合蛋白与PD-1或PD-L1和VEGF家族分子中另一种分子的特异性结合。

[0029] 本发明还提供了编码本发明融合蛋白的多核苷酸、包含编码本发明融合蛋白的多核苷酸的载体，优选地表达载体，最优选地具有双表达盒的谷氨酰胺合成酶表达载体。在另一个方面，本发明提供了包含本发明多核苷酸或载体的宿主细胞。本发明也提供了一种用于产生本发明融合蛋白的方法，包括步骤(i)在适于表达本发明融合蛋白的条件下培养本发明的宿主细胞，和(ii)回收本发明的融合蛋白。

[0030] 在一个方面，本发明提供了一种包含本发明融合蛋白的诊断试剂盒和药物组合物。进一步地，还提供了本发明的融合蛋白、诊断试剂盒或药物组合物的用途，用于治疗、预防和/或诊断与PD-1或PD-L1活性和VEGF家族活性相关的疾病，特别地用于治疗、预防和/或诊断癌性疾病(例如，实体瘤和软组织瘤)，最特别地用于治疗、预防和/或诊断黑素瘤、乳腺癌、结肠癌、食管癌、胃肠道间质肿瘤(GIST)、肾癌(例如，肾细胞癌)、肝癌、非小细胞肺癌(NSCLC)、卵巢癌、胰腺癌、前列腺癌、头颈部肿瘤、胃癌、血液学恶性病(例如，淋巴瘤)。

[0031] 除非另外限定，否则本文中所用的全部技术与科学术语具有如本发明所属领域的普通技术人员通常理解的相同含义。本文所提及的全部出版物、专利申请、专利和其他参考文献通过引用的方式完整地并入。此外，本文中所述的材料、方法和例子仅是说明性的并且不意在是限制性的。本发明的其他特征、目的和优点将从本说明书及附图并且从后附的权利要求书中显而易见。

[0032] 附图简述

[0033] 结合以下附图一起阅读时，将更好地理解以下详细描述的本发明的优选实施方案。出于说明本发明的目的，图中显示了目前优选的实施方案。然而，应当理解本发明不限于图中所示实施方案的精确安排和手段。

[0034] 图1:例示了本发明的靶向PD-1或PD-L1且靶向VEGF家族的双靶向融合蛋白的结构示意图。

[0035] 图2:显示了实施例2中制备并纯化的本发明融合蛋白在还原剂(5mM 1,4-二硫苏糖醇)存在下通过SDS-PAGE并用考马斯蓝染色后的结果。图2A中的泳道1:蛋白分子量标准标志物;泳道2:融合蛋白BY24.3;泳道3:融合蛋白BY24.4;泳道4:融合蛋白BY24.5;泳道5:融合蛋白BY24.6;泳道6:融合蛋白BY24.8;泳道7:融合蛋白BY24.9;泳道8:融合蛋白BY24.10;泳道9:融合蛋白BY24.11;图2B中的泳道1:蛋白分子量标准标志物;泳道2:融合蛋白BY24.12;泳道3:融合蛋白BY24.13;泳道4:融合蛋白BY24.14;泳道5:抗体BY18.1;泳道6:蛋白301-8;泳道7:融合蛋白BY24.7。

[0036] 图3:显示了本发明的融合蛋白BY24.3、抗体BY18.1和蛋白301-8对实验动物体重的影响。

[0037] 图4:显示了将本发明的融合蛋白BY24.3与抗体BY18.1和蛋白301-8的体内抗肿瘤作用进行比较的示意图。

[0038] 发明详述

[0039] 本发明提供了阻断免疫检查点PD-1途径或PD-L1途径和VEGF家族信号传导途径的融合蛋白和药物组合物。本发明还提供了用于产生该融合蛋白的方法,以及该融合蛋白在个体中治疗、预防和/或诊断与PD-1或PD-L1活性和VEGF家族活性相关的疾病中的用途。

[0040] 除非下文中另外定义,否则本说明书中的术语如本领域通常所用那样使用。

[0041] I.定义

[0042] 术语“约”在与数字数值联合使用时意为涵盖具有比指定数字数值小5%的下限和比指定数字数值大5%的上限的范围内的数字数值。

[0043] 如本文中所用,术语“包含”或“包括”意指包括所述的要素、整数或步骤,但是不排除任意其他要素、整数或步骤。

[0044] “PD-1途径”是指任何通过与PD-1结合而引发的细胞内信号传导途径,包括但不限于PD-1与PD-L1结合而引发的细胞内信号传导途径、或PD-1与PD-L2结合而引发的细胞内信号传导途径、或者PD-1与PD-L1和PD-L2这两者结合而引发的细胞内信号传导途径。

[0045] “PD-L1途径”是指任何通过与PD-L1结合而引发的细胞内信号传导途径,包括但不限于PD-L1与PD-1结合而引发的细胞内信号传导途径、或PD-L1与CD80(B7-1)结合而引发的细胞内信号传导途径、或者PD-L1与PD-1和CD80(B7-1)这两者结合而引发的细胞内信号传导途径。

[0046] 如本文所用,术语“特异性结合”意指对抗原或目的分子的结合具有选择性并且可以与不想要的或非特异的相互作用区别。所述特异性结合可以通过酶联免疫吸附测定(ELISA)或本领域技术人员熟悉的其他技术,例如表面等离子体共振(SPR)技术(在BIAcore仪上分析)(Liljeblad等人,Analysis of agalacto-IgG in rheumatoid arthritis using surface plasmon resonance,Glyco J.,2000,17,323-329)测量。

[0047] “亲和力”或“结合亲和力”指反映结合对子的成员之间相互作用的固有结合亲和力。分子X对其配偶物Y的亲和力可以通常由解离常数(K_D)代表,解离常数是解离速率常数和缔合速率常数(分别是k_{off}和k_{on})的比例。亲和力可以由本领域已知的常见方法测量。用于测量亲和力的一个具体方法是表面等离子体共振法(SPR)。

[0048] 术语“抗体”在本文中以最广意义使用并且包括但不限于单克隆抗体、多克隆抗体、多特异性抗体(例如,双特异性抗体)、只要它们显示出所需的抗原结合活性即可。抗体可以是完整抗体分子,也可以是完整抗体分子的功能性片段,包括但不限于例如Fab、F(ab')$_2$。抗体的恒定区可以经改变(例如经突变)以修饰抗体特性(例如,以增加或减少以下一个或多个特性:抗体糖基化、半胱氨酸残基数目、效应细胞功能或补体功能)。

[0049] 术语“全抗体”、“全长抗体”、“完全抗体”和“完整抗体”在本文中可互换地用来指这样的抗体,所述抗体具有基本上与天然抗体结构相似的结构。

[0050] 术语“抗体重链”指在抗体分子中存在的两种类型多肽链中的较大者,其在正常情况下决定抗体所属的类别。

[0051] 术语“抗体轻链”指在抗体分子中存在的两种类型多肽链中的较小者。κ轻链和λ轻链指两个主要的抗体轻链同种型。

[0052] 氨基酸序列的“同一性百分数(%)”是指将候选序列与本说明书中所示的具体氨基酸序列进行比对并且如有必要的话为达到最大序列同一性百分数而引入空位后,并且不考虑任何保守置换作为序列同一性的一部分时,候选序列中与本说明书中所示的具体氨基酸序列的氨基酸残基相同的氨基酸残基百分数。

[0053] 术语“有效连接”意指指定的各组分处于一种允许它们以预期的方式起作用的关系。

[0054] “信号序列”是连接至蛋白质的N-端部分的氨基酸的序列,其促进蛋白质分泌至细胞外。细胞外蛋白质的成熟形式没有信号序列,其在分泌过程期间被切除。

[0055] 术语“N端”指N端的最末氨基酸,术语“C端”指C端的最末氨基酸。

[0056] 术语“融合”指将两个或多个组分由肽键直接连接或借助一个或多个肽接头有效连接。

[0057] 如本文所用,术语“融合蛋白”指包含抗体轻链亚基和抗体重链-VID融合亚基的融合多肽分子,其中抗体轻链亚基是融合蛋白中存在的多肽链中的较小者,抗体重链-VID融合亚基是融合蛋白中存在的多肽链中的较大者。

[0058] 术语“宿主细胞”指已经向其中引入外源多核苷酸的细胞,包括这类细胞的子代。宿主细胞包括“转化体”和“转化的细胞”,这包括原代转化的细胞和从其衍生的子代。宿主细胞是可以用来产生本发明融合蛋白的任何类型的细胞系统。宿主细胞包括培养的细胞,也包括转基因动物、转基因植物或培养的植物组织或动物组织内部的细胞。

[0059] 术语“个体”或“受试者”可互换地使用,是指哺乳动物。哺乳动物包括但不限于驯化动物(例如,奶牛、绵羊、猫、犬和马)、灵长类(例如,人和非人灵长类如猴)、兔和啮齿类(例如,小鼠和大鼠)。特别地,个体是人。

[0060] 术语“治疗”指意欲改变正在接受治疗的个体中疾病之天然过程的临床介入。想要的治疗效果包括但不限于防止疾病出现或复发、减轻症状、减小疾病的任何直接或间接病理学后果、防止转移、降低病情进展速率、改善或缓和疾病状态,以及缓解或改善预后。在一些实施方案中,本发明的融合蛋白用来延缓疾病发展或用来减慢疾病的进展。

[0061] 术语“抗肿瘤作用”指可以通过多种手段展示的生物学效果,包括但不限于例如,肿瘤体积减少、肿瘤细胞数目减少、肿瘤细胞增殖减少或肿瘤细胞存活减少。术语“肿瘤”和“癌症”在本文中互换地使用,涵盖实体瘤和液体肿瘤。

[0062] II.融合蛋白

[0063] 本发明提供了靶向PD-1或PD-L1且靶向VEGF家族的双靶向融合蛋白，其包含(i)抗PD-1抗体或者抗PD-L1抗体；和(ii)与所述抗PD-1抗体或者抗PD-L1抗体有效连接的至少两个VID，其中融合蛋白的这两种组分彼此通过肽键直接或经肽接头连接。另外，融合蛋白中的组分(i)抗PD-1抗体或抗PD-L1抗体的各条肽链可以例如通过二硫键连接。

[0064] 在一些实施方案中，本发明的融合蛋白是由二硫键键合的两条抗体轻链亚基和两条抗体重链-VID融合亚基组成的异四聚体糖蛋白。从N端至C端，每条抗体重链-VID融合亚基具有一个抗体重链，随后是一个VID，其中抗体重链和VID由肽键直接连接或借助一个或多个肽接头连接。

[0065] 本发明的融合蛋白阻断免疫检查点PD-1途径或PD-L1途径且抑制VEGF家族信号传导途径。该融合蛋白阻断的免疫检查点PD-1途径是PD-1与其配体结合所介导的信号传导途径。该融合蛋白阻断的PD-L1途径是PD-L1与其受体结合所介导的信号传导途径。该融合蛋白抑制的VEGF家族信号传导途径是由VEGF-A、-B、-C、-D、-E和PLGF与VEGF家族的受体(例如VEGFR1、VEGFR2和VEGFR3)结合所介导的信号传导途径。

[0066] 在一些实施方案中，本发明的融合蛋白以10^{-8}M或更小、例如以10^{-9}M至10^{-12}M的解离常数(K_D)与PD-1或PD-L1结合；且以10^{-8}M或更小、例如以10^{-9}M至10^{-12}M的解离常数(K_D)与VEGF家族特异性结合。

[0067] 一抗PD-1抗体或抗PD-L1抗体

[0068] 本发明融合蛋白中包含的抗PD-1抗体或抗PD-L1抗体是由二硫键键合的两条轻链和两条重链组成的异四聚体糖蛋白。

[0069] 在一个实施方案中，从N端至C端，每条抗PD-1抗体或抗PD-L1抗体的重链具有一个可变区(VH)，也称作可变重链域或重链可变结构域，随后是三个恒定结构域(CH1、CH2和CH3)，也称作重链恒定区。类似地，从N端至C端，每条抗PD-1抗体或抗PD-L1抗体的轻链具有一个可变区(VL)，也称作可变轻链域或轻链可变结构域，随后一个恒定轻链(CL)结构域，也称作轻链恒定区。抗PD-1抗体或抗PD-L1抗体基本上由借助抗PD-1抗体或抗PD-L1抗体的铰链区连接的两个Fab分子和一个Fc结构域组成。

[0070] 本发明融合蛋白中包含的抗PD-1抗体或抗PD-L1抗体能够以高的亲和力，例如以10^{-8}M或更小、优选地以10^{-9}M至10^{-12}M的K_D，分别与PD-1或PD-L1特异性结合，并由此阻断PD-1与配体PD-L1/PD-L2结合所介导的信号传导途径或阻断PD-L1与受体PD-1/CD80(B7-1)结合所介导的信号传导途径。

[0071] 本文在下表1A中提供了本发明融合蛋白中包含的抗PD-1抗体的成对重链可变区(VH)和轻链可变区(VL)的例子。另外，本文在下表1B中提供了本发明融合蛋白中包含的抗PD-L1抗体的成对重链可变区(VH)和轻链可变区(VL)的例子。在一些实施方案中，本发明融合蛋白中的抗PD-1抗体或抗PD-L1抗体分别包含与表1A或表1B中所示的氨基酸序列基本上同一的序列，例如，与表1A或表1B所示的成对重链可变区序列/轻链可变区序列具有至少90％、91％、92％、93％、94％、95％、96％、97％、98％、99％或更多序列同一性的序列。

[0072] 表1A.融合蛋白中的抗PD-1抗体的重链可变区和轻链可变区序列的例子

[0073]

可变区	氨基酸序列	序列编号(SEQ ID NO:)
VH	QVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVAVIWYDGSKRY YADSVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCATNDDYWGQG	1
VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFS GSGSGTDFTLTISSLEPEDFAVYYCQQSSNWPRTFGQG	2
VH	QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGT NFNEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQG	3
VL	EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQAPRLLIYLASYLESGVP ARFSGSGSGTDFTLTISSLEPEDFAVYYCQHSRDLPLTFGGG	4
VH	QVQLVQSGSELKKPGASVKISCKASGYTFTNYGMNWVRQAPGQGLQWMGWINTDSGEST YAEEFKGRFVFSLDTSVNTAYLQITSLTAEDTGMYFCVRVGYDALDYWGQG	5
VL	EIVLTQSPSSLSASVGDRVTITCSARSSVSYMHWFQQKPGKAPKLWIYRTSNLASGVPSRFSG SGSGTSYCLTINSLQPEDFATYYCQQRSSFPLTFGGG	6
VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYMMSWVRQAPGKGLEWVATISGGGANTYY PDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARQLYYFDYWGQG	7
VL	DIQMTQSPSSLSASVGDRVTITCLASQTIGTWLTWYQQKPGKAPKLLIYTATSLADGVPS RFSGSGSGTDFTLTISSLQPEDFATYYCQQVYSIPWTFGGG	8
VH	QVTLKESGPALVKPTQTLTLTCTFSGFSLSTSGTCVSWIRQPPGKALEWLATICWEDSKGYN PSLKSRLTISKDTSKNQAVLTMTNMDPVDTATYYCARREDSGYFWFPYWGQG	9
VL	NIQMTQSPSSLSASVGDRVTITCKAGQNVNNYLAWYQQKPGKAPKVLIFNANSLQTGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQYNSWTTFGGG	10
VH	QVQLQESGPGLVKPSETLSLTCTVSGFSLTSYGVHWIRQPPGKGLEWLGVIWAGGSTNYNP SLKSRLTISKDNSKSQVSLKMSSVTAADTAVYYCARAYGNYWYIDVWGQG	11
VL	DIVMTQSPDSLAVSLGERATINCKASQSVSNDVAWYQQKPGQPPKLLINYAFHRFTGVPDR FSGSGYGTDFTLTISSLQAEDVAVYYCHQAYSSPYTFGGG	12
VH	VQLVESGGGVVQPGRSLRLDCKASGITFSNYGMHWVRQAPGKGLEWVAVIWYDSSRKYY ADSVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCATNNDYWGQG	13
VL	DIQMTQSPSSLSASVGDRVTITCRASQSVSNYLDWYQQKPGKAPKLLIYDASTRATGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQNMQLPLTFGQG	14
VH	DLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMGWISAYNGNTNYA QKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARGRGYSYGIDAFDIWGQG	15
VL	LSYVLTQPPSVSVSPGQTARITCSGDALPKQYAYWYQQKPGQAPVLVIYKDSERPSGIPERFS GSSSGTTVTLTISGVQAEDEADYYCQSADSSGTYVVFGGG	16
VH	QGQLVQSGAEVKKPGASVKVSCKASGYTFTDYEMHWVRQAPGQGLEWMGVIESETGGTA YNQKFQGRVTLTADKSSSTAYMELSSLRSEDTAVYYCTREGITTVATTYYWYFDVWGQG	17
VL	DVVMTQSPLSLPVTLGQPASISCRSSQSIVHSNGNTYLEWYLQKPGQSPQLLIYKVSNRFSGV PDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVPLTFGQG	18
VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGKGLEWVATISGGGSDTYY ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARQLNYAWFAYWGQG	19
VL	DIVLTQSPASLAVSPGQRATITCRASESVDNYGISFMNWYQQKPGQPPKLLIYTSSNKDTGV PARFSGSGSGTDFTLTINPMEAEDTAVYYCQQSKEVPWTFGGG	20
VH	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGLIIPMFDTAGY AQKFQGRVAITVDESTSTAYMELSSLRSEDTAVYYCARAEHSSTGTFDYWGQG	21
VL	DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLISAASSLQSGVPSRFS GSGSGTDFTLTISSLQPEDFATYYCQQANHLPFTFGGG	22

[0074]

[0075]

VH	QLQLQESGPGLVKPSETLTLTCTVSADSISSTTYYWVWIRQPPGKGLEWIGSISYSGSTYYNP SLKSRVTVSVDTSKNQFSLKLNSVAATDTALYYCARHLGYNGRYLPFDYWGQG	23
VL	QSALTQPASVSGSPGQSITISCTGTSSDVGFYNYVSWYQQHPGKAPELMIYDVSNRPSGVSD RFSGSKSGNTASLTISGLQAEDEADYYCSSYTNISTWVFGGG	24
VH	QVQLVESGGGVVQPGRSLRLTCKASGLTFSSSGMHWVRQAPGKGLEWVAVIWYDGSKRY YADSVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCATNNDYWGQG	120
VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYTASNRATGIPARFS GSGSGTDFTLTISSLEPEDFAVYYCQQYSNWPRTFGQG	121

[0076] 表1B.融合蛋白中的抗PD-L1抗体的重链可变区和轻链可变区序列的例子

[0077]

可变区	氨基酸序列	序列编号(SEQ ID NO:)
VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWVAWISPYGGSTYY ADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQG	25
VL	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQYLYHPATFGQG	26
VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSRYWMSWVRQAPGKGLEWVANIKQDGSEKY YVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGGWFGELAFDYWGQG	27
VL	EIVLTQSPGTLSLSPGERATLSCRASQRVSSSYLAWYQQKPGQAPRLLIYDASSRATGIPDRF SGSGSGTDFTLTISRLEPEDFAVYYCQQYGSLPWTFGQG	28
VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYIMMWVRQAPGKGLEWVSSIYPSGGITFYAD TVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARIKLGTVTTVDYWGQG	29
VL	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSNRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTRVFGTG	30

[0078] 在一个实施方案中,本发明融合蛋白中的抗PD-1抗体包含选自SEQ ID NO:1/2、3/4、5/6、7/8、9/10、11/12、13/14、15/16、17/18、19/20、21/22、23/24、和120/121的成对重链可变区序列/轻链可变区序列中所含的全部重链CDR与轻链CDR。在一个实施方案中,本发明融合蛋白中的抗PD-L1抗体包含选自SEQ ID NO:25/26、27/28和29/30的成对重链可变区序列/轻链可变区序列中所含的全部重链CDR与轻链CDR。用于鉴定重链可变区与轻链可变区的氨基酸序列中的CDR的方法及技术为本领域中已知的,且可用于鉴定本文公开的特定重链可变区及/或轻链可变区的氨基酸序列中的CDR。可用于鉴定CDR边界的示例性公知技术包括例如Kabat界定法、Chothia界定法以及AbM界定法。参见,例如Kabat,Sequences of Proteins of Immunological Interest,National Institutes of Health,Bethesda,Md.(1991);Al-Lazikani等人,Standard conformations for the canonical structures of immunoglobulins.,J.Mol.Biol.273:927-948(1997);以及Martin AC等人,Modeling antibody hypervariable loops:a combined algorithm,Proc.Natl.Acad.Sci.USA 86:9268-9272(1989)。

[0079] 本发明融合蛋白中的抗PD-1抗体或抗PD-L1抗体可以基于其轻链恒定区的氨基酸序列而划分为κ型或λ型,优选为κ型。

[0080] 本文在下表2中提供了本发明融合蛋白中的抗PD-1抗体轻链恒定区的氨基酸序列的例子。

[0081] 表2.融合蛋白中的抗PD1抗体轻链恒定区序列的例子

[0082]

轻链区型别	氨基酸序列
κ型	TKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC （SEQ ID NO: 31）
λ型	TKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNK YAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS （SEQ ID NO: 32）

[0083] 本发明融合蛋白中的抗PD-1抗体或抗PD-L1抗体基于其重链恒定区的氨基酸序列优选地是IgG类抗体，特别地是IgG_1亚类、IgG_2亚类、IgG_4亚类抗体，更特别地是IgG_4亚类抗体。优选地，所述IgG_4亚类抗PD-1抗体或抗PD-L1抗体在Fc区中第S228位置处包含防止发生臂交换(arm-exchange)的氨基酸置换，特别地是氨基酸置换S228P。

[0084] 本文在下表3中提供了本发明融合蛋白中的抗PD-1抗体重链恒定区的氨基酸序列的例子。

[0085] 表3.融合蛋白中的抗PD1抗体重链恒定区序列的例子

[0086]

重链类别	氨基酸序列
IgG1	TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK（SEQ ID NO: 33）
IgG2	TTVTVSTASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNK GLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPML

[0087]

	DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK（SEQ ID NO: 34）
IgG4	TLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK（SEQ ID NO: 35）

[0088] —抑制VEGF家族的结构域(VID)

[0089] 本发明融合蛋白中的“抑制VEGF家族的结构域(VID)”包含VEGFR的胞外结构域的一部分。VEGFR受体是位于细胞表面的一种酪氨酸激酶受体，其胞外区由7个免疫球蛋白(Ig)样结构域组成。例如，人VEGFR1包含编号为1、2、3、4、5、6和7的七个Ig样结构域，Ig样结构域1在胞外结构域的N端，Ig样结构域7在胞外结构域的C端。除非本文另外指出，否则Ig样结构域从VEGFR蛋白的N端至C端顺序编号。在一些实施方案中，VID包含选自VEGFR1、VEGFR2和VEGFR3的一种或多种VEGFR的至少一个Ig样结构域。在一些方面，VID包含VEGFR的至少1、2、3、4、5、6个但不超过7个Ig样结构域。在另一方面，VID包含VEGFR的1至7、1至6、1至5、1至4、1至3或1至2个Ig样结构域。

[0090] 本文还考虑了包含两种或多种VEGFR的至少一个Ig样结构域的VID。在一些实施方

案中,VID包含来自两种或多种选自VEGFR1、VEGFR2和VEGFR3的VEGFR的至少一个Ig样结构域。本文考虑了包含每种VEGFR的七个Ig样结构域的任意组合的VID。例如,VID可以包含VEGFR1(例如人VEGFR1)的Ig样结构域2和VEGFR2(例如人VEGFR2)的Ig样结构域3。在另一实施方案中,VID可以包含VEGFR1(例如人VEGFR1)的Ig样结构域1-3、VEGFR1(例如人VEGFR1)的Ig样结构域2-3、VEGFR2(例如人VEGFR2)的Ig样结构域1-3、VEGFR1(例如人VEGFR1)的Ig样结构域2和VEGFR2(例如人VEGFR2)的Ig样结构域3-4,或VEGFR1(例如人VEGFR1)的Ig样结构域2和VEGFR3(例如人VEGFR3)的Ig样结构域3。这些Ig样结构域和其他可以用作VID的部分的Ig样结构域的更详细描述见美国专利号7531173;Yu DC等,Soluble vascular endothelial growth factor decoy receptor FP3 exerts potent antiangiogenic effects,Mol.Ther.,2012,20(3):938-947和Holash,J.等,VEGF-Trap:a VEGF blocker with potent antitumor effects,PNAS,2002,99(17):11393-11398,全部文献在此以其整体引入作为参考。在一些实施方案中,VID具有任一选自表4中SEQ ID NO:63－65所示的氨基酸序列或与SEQ ID NO:63－65所示的氨基酸序列具有至少90%、91%、92%、93%、94%、95%、96%、97%、98%、99%或更多同一性的氨基酸序列。

[0091] 表4融合蛋白中的VID氨基酸序列的例子

[0092]

VID	氨基酸序列
VEGFR1-D2/VEGFR2-D3	SDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLKKFPLDTLIPDGKRIIWDSRKGFIISN ATYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGIELSVGEKLVLNCTARTELNVG IDFNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKN STFVRVHEK （SEQ ID NO: 63）
VEGFR1-D2/VEGFR2-D3-D4	SDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLKKFPLDTLIPDGKRIIWDSRKGFIISN ATYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGIELSVGEKLVLNCTARTELNVG IDFNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKN STFVRVHEKPFVAFGSGMESLVEATVGERVRIPAKYLGYPPPEIKWYKNGIPLESNHTIKAGHVL TIMEVSERDTGNYTVILTNPISKEKQSHVVSLVVYVPPGPGD （SEQ ID NO: 64）
VEGFR1-D2	SDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLKKFPLDTLIPDGKRIIWDSRKGFIISN ATYKEIGLLTCEATVNGHLYKTNYLTHRQTNT （SEQ ID NO: 65）

[0093] 本发明融合蛋白中包含的VID能够以高的亲和力,例如以10^{-8}M或更小、优选地以10^{-9}M至10^{-12}M的K_D,与VEGF家族特异性结合,并由此抑制VEGF家族与细胞表面VEGFR的结合和随后的信号传导。

[0094] 一肽接头

[0095] 本发明融合蛋白中在抗PD-1抗体或抗PD-L1抗体的重链C端和VID N端任选包含的“肽接头”是一个或多个氨基酸、一般约2－20个氨基酸的肽。本领域已知或本文中描述了肽接头。

[0096] 在一些实施方案中,所述肽接头包含至少5个氨基酸,优选地包含选自AKTTPKLEEGEFSEAR(SEQ ID NO:36);AKTTPKLEEGEFSEARV(SEQ ID NO:37);AKTTPKLGG(SEQ ID NO:38);SAKTTPKLGG(SEQ ID NO:39);SAKTTP(SEQ ID NO:40);RADAAP(SEQ ID NO:41);RADAAPTVS(SEQ ID NO:42);RADAAAAGGPGS(SEQ ID NO:43);RADAAAA(SEQ ID NO:44);SAKTTPKLEEGEFSEARV(SEQ ID NO:45);ADAAP(SEQ ID NO:46);DAAPTVSIFPP(SEQ ID NO:

47);TVAAP(SEQ ID NO:48);TVAAPSVFIFPP(SEQ ID NO:49);QPKAAP(SEQ ID NO:50);QPKAAPSVTLFPP(SEQ ID NO:51);AKTTPP(SEQ ID NO:52);AKTTPPSVTPLAP(SEQ ID NO:53);AKTTAP(SEQ ID NO:54);AKTTAPSVYPLAP(SEQ ID NO:55);ASTKGP(SEQ ID NO:56);ASTKGPSVFPLAP(SEQ ID NO:57);GGGGSGGGGSGGGGS(SEQ ID NO:58);GENKVEYAPALMALS(SEQ ID NO:59);GPAKELTPLKEAKVS(SEQ ID NO:60);GHEAAAVMQVQYPAS(SEQ ID NO:61);和GGGGSGGGGSGGGGSA(SEQ ID NO:62)的肽接头。

[0097] III.本发明的双靶向融合蛋白的生产和纯化

[0098] 本发明的双靶向融合蛋白可以例如通过固态肽合成(例如Merrifield固相合成)或重组生产获得。为了重组生产,将编码所述双靶向融合蛋白的抗体轻链亚基的多核苷酸和/或编码所述双靶向融合蛋白的抗体重链-VID融合亚基的多核苷酸分离并插入一个或多个载体中以便进一步在宿主细胞中克隆和/或表达。使用常规方法,可以轻易地分离所述多核苷酸并将其测序。在一个实施方案中,提供了包含本发明的一种或多种多核苷酸的载体,优选地表达载体。

[0099] 可以使用本领域技术人员熟知的方法来构建表达载体。表达载体包括但不限于病毒、质粒、粘粒、λ噬菌体或酵母人工染色体(YAC)。在一个优选的实施方案中,使用了具有双表达盒的谷氨酰胺合成酶高效表达载体。

[0100] 一旦已经制备了用于表达的包含本发明的一种或多种多核苷酸的表达载体,则可以将表达载体转染或引入适宜的宿主细胞中。多种技术可以用来实现这个目的,例如,原生质体融合、磷酸钙沉淀、电穿孔、逆转录病毒的转导、病毒转染、基因枪、基于脂质体的转染或其他常规技术。

[0101] 在一个实施方案中,提供了包含一种或多种本发明多核苷酸的宿主细胞。在一些实施方案中,提供了包含本发明表达载体的宿主细胞。如本文所用,术语“宿主细胞”指可以工程化以产生本发明的双靶向融合蛋白的任何种类的细胞系统。适于复制和支持本发明的双靶向融合蛋白表达的宿主细胞是本领域熟知的。根据需要,这类细胞可以用特定表达载体转染或转导,并且可以培育大量含有载体的细胞用于接种大规模发酵器以获得足够量的本发明双靶向融合蛋白用于临床应用。合适的宿主细胞包括原核微生物,如大肠杆菌,真核微生物如丝状真菌或酵母,或各种真核细胞,如中国仓鼠卵巢细胞(CHO)、昆虫细胞等。可以使用适于悬浮培养的哺乳动物细胞系。有用的哺乳动物宿主细胞系的例子包括SV40转化的猴肾CV1系(COS-7);人胚肾系(293或293F细胞)、幼仓鼠肾细胞(BHK)、猴肾细胞(CV1)、非洲绿猴肾细胞(VERO-76)、人宫颈癌细胞(HELA)、犬肾细胞(MDCK)、布法罗大鼠肝脏细胞(BRL 3A)、人肺细胞(W138)、人肝脏细胞(Hep G2)、CHO细胞、骨髓瘤细胞系如YO、NS0、P3X63和Sp2/0等。适于产生蛋白质的哺乳动物宿主细胞系的综述参见例如Yazaki和Wu,Methods in Molecular Biology,第248卷(B.K.C.Lo编著,Humana Press,Totowa,NJ),第255-268页(2003)。

[0102] 本领域已知在这些宿主细胞系统中表达外源基因的标准技术。在一个实施方案中,提供了产生本发明的双靶向融合蛋白的方法,其中所述方法包括在适于表达所述双靶向融合蛋白的条件下培养如本文中提供的宿主细胞,所述宿主细胞包含编码所述双靶向融合蛋白的多核苷酸,并且从宿主细胞(或宿主细胞培养基)回收所述双靶向融合蛋白。

[0103] 如本文所述制备的双靶向融合蛋白可以通过已知的现有技术如高效液相色谱、离

子交换层析、凝胶电泳、亲和层析、大小排阻层析等纯化。用来纯化特定蛋白质的实际条件还取决于如净电荷、疏水性、亲水性等因素，并且这些对本领域技术人员是显而易见的。

[0104] 可以通过多种熟知分析方法中的任一种方法确定本发明的双靶向融合蛋白的纯度，所述熟知分析方法包括凝胶电泳、高效液相色谱等。可以通过本领域已知的多种测定法，鉴定、筛选或表征本文提供的双靶向融合蛋白的物理/化学特性和/或生物学活性。

[0105] IV.药物组合物和试剂盒

[0106] 在另一个方面，本发明提供了组合物，例如，药物组合物，所述组合物包含与可药用载体配制在一起的本文所述的双靶向融合蛋白。如本文所用，“可药用载体”包括生理上相容的任何和全部溶剂、分散介质、等渗剂和吸收延迟剂等。本发明的药物组合物适于静脉内、肌内、皮下、肠胃外、直肠、脊髓或表皮施用(例如，通过注射或输注)。

[0107] 本发明的组合物可以处于多种形式。这些形式例如包括液体、半固体和固体剂型，如液态溶液剂(例如，可注射用溶液剂和可输注溶液剂)、分散体剂或混悬剂、脂质体剂和栓剂。优选的形式取决于预期的施用模式和治疗用途。常见的优选组合物处于可注射用溶液剂或可输注溶液剂形式。优选的施用模式是肠胃外(例如，静脉内、皮下、腹腔(i.p.)、肌内)注射。在一个优选实施方案中，通过静脉内输注或注射施用双靶向融合蛋白。在另一个优选实施方案中，通过肌内、腹腔或皮下注射施用双靶向融合蛋白。

[0108] 如本文所用的短语“肠胃外施用“和“肠胃外方式施用”意指除了肠施用和局部施用之外的施用模式，通常通过注射施用，并且包括但不限于静脉内、肌内、动脉内、皮内、腹腔、经气管、皮下注射和输注。

[0109] 治疗性组合物一般应当是无菌的并且在制造和储存条件下稳定。可以将组合物配制为溶液、微乳液、分散体、脂质体或冻干形式。可以通过将活性化合物(即双靶向融合蛋白)以要求的量加入适宜的溶剂中，随后过滤消毒，制备无菌可注射溶液剂。通常，通过将所述活性化合物并入无菌溶媒中来制备分散体，所述无菌溶媒含有基础分散介质和其他成分。可以使用包衣剂如卵磷脂等。在分散体的情况下，可以通过使用表面活性剂来维持溶液剂的适宜流动性。可以通过在组合物中包含延迟吸收的物质例如单硬脂酸盐和明胶而引起可注射组合物的延长吸收。

[0110] 在某些实施方案中，可以口服施用本发明的双靶向融合蛋白，例如随惰性稀释剂或可食用载体一起经口施用。本发明的双靶向融合蛋白也可以封闭在硬壳或软壳明胶胶囊中、压缩成片剂或直接掺入受试者的膳食中。对于口服治疗施用，所述化合物可以随赋形剂一起掺入并且以可摄取的片剂、颊用片剂、锭剂(troche)、胶囊剂、酏剂、混悬剂、糖浆剂、糯米纸囊剂(wafer)等形式使用。为了通过非肠胃外施用方法施用本发明的双靶向融合蛋白，可能需要将所述双靶向融合蛋白与防止其失活的材料包衣或随这种材料共施用。还可以用本领域已知的医疗装置施用治疗组合物。

[0111] 本发明的药物组合物可以包含“治疗有效量”或“预防有效量”的本发明所述双靶向融合蛋白。“治疗有效量”指以需要的剂量并持续需要的时间段，有效实现所需治疗结果的量。可以根据多种因素如疾病状态、个体的年龄、性别和重量等变动治疗有效量。治疗有效量是任何有毒或有害作用不及治疗有益作用的量。相对于未治疗的受试者，“治疗有效量”优选地抑制可度量参数(例如肿瘤生长率)至少约20％、更优选地至少约40％、甚至更优选地至少约60％和仍更优选地至少约80％。可以在预示人肿瘤中的功效的动物模型系统中

评价本发明的双靶向融合蛋白抑制可度量参数(例如,肿瘤体积)的能力。

[0112] “预防有效量”指以需要的剂量并持续需要的时间段,有效实现所需预防结果的量。通常,由于预防性剂量在受试者中在疾病较早阶段之前或在疾病较早阶段使用,故预防有效量小于治疗有效量。

[0113] 包含本文所述双靶向融合蛋白的试剂盒也处于本发明的范围内。试剂盒可以包含一个或多个其他要素,例如包括:使用说明书;其他试剂,例如标记物或用于偶联的试剂;可药用载体;和用于施用至受试者的装置或其他材料。

[0114] V.双靶向融合蛋白的用途

[0115] 本文公开的双靶向融合蛋白具有体外和体内诊断用途以及治疗性和预防性用途。例如,可以将这些分子施用至体外或离体的培养细胞或施用至受试者,例如,人类受试者,以治疗、预防和/或诊断多种与PD-1活性、PD-L1活性和VEGF家族活性相关的疾病,例如癌症。

[0116] 在一个方面,本发明提供了体外或体内检测生物样品,例如血清、精液或尿或组织活检样品(例如,来自过度增生性或癌性病灶)中存在PD-1或PD-L1和VEGF家族分子的诊断方法。该诊断方法包括:(i)在允许相互作用发生的条件下使样品(和任选地,对照样品)与如本文所述的双靶向融合蛋白接触或向受试者施用所述双靶向融合蛋白和(ii)检测所述双靶向融合蛋白和样品(和任选地,对照样品)之间复合物的形成。复合物的形成表示存在PD-1或PD-L1和VEGF家族分子,并且可以显示本文所述治疗和/或预防的适用性或需求。

[0117] 在一些实施方案中,在治疗之前,例如,在起始治疗之前或在治疗间隔后的某次治疗之前检测PD-1或PD-L1和VEGF家族分子。可以使用的检测方法包括免疫组织化学、免疫细胞化学、FACS、ELISA测定、PCR-技术(例如,RT-PCR)或体内成像技术。一般地,体内和体外检测方法中所用的双靶向融合蛋白直接或间接地用可检测物质标记以促进检测结合的或未结合的结合物。合适的可检测物质包括多种生物学活性酶、辅基、荧光物质、发光物质、顺磁(例如,核磁共振活性)物质和放射性物质。

[0118] 在一些实施方案中,体内确定PD-1或PD-L1和VEGF家族分子的水平和/或分布,例如,以非侵入方式确定(例如,通过使用合适的成像技术(例如,正电子发射断层摄影术(PET)扫描)检测可检测物标记的本发明双靶向融合蛋白。在一个实施方案中,例如,通过检测用PET试剂(例如,^{18}F-氟脱氧葡萄糖(FDG))以可检测方式标记的本发明双靶向融合蛋白,体内测定PD-1或PD-L1和VEGF家族分子的水平和/或分布。

[0119] 在一个实施方案中,本发明提供了包含本文所述双靶向融合蛋白和使用说明书的诊断试剂盒。

[0120] 在另一个方面,本发明涉及使用双靶向融合蛋白体内用来治疗或预防需要在受试者中增强免疫应答并减少血管形成的疾病,从而抑制或减少相关疾病如癌性肿瘤的生长或出现、转移或复发。可以单独使用双靶向融合蛋白以抑制癌性肿瘤的生长或者预防其出现。备选地,双靶向融合蛋白可以与其他癌症治疗剂/预防剂组合施用。当本发明的双靶向融合蛋白与一种或多种其他药物组合施用时,这种组合可以按任何顺序施用或者同时施用。

[0121] 因此,在一个实施方案中,本发明提供一种抑制受试者中肿瘤细胞生长的方法,所述方法包括向受试者施用治疗有效量的本文所述的双靶向融合蛋白。在另一个实施方案中,本发明提供一种防止受试者中肿瘤细胞出现或者转移或者复发的方法,所述方法包括

向受试者施用预防有效量的本文所述的双靶向融合蛋白。

[0122] 在一些实施方案中，用双靶向融合蛋白治疗和/或预防的癌包括但不限于实体瘤、血液学癌(例如，白血病、淋巴瘤、骨髓瘤，例如，多发性骨髓瘤)及转移性病灶。在一个实施方案中，癌是实体瘤。实体瘤的例子包括恶性肿瘤，例如，多个器官系统的肉瘤和癌，如侵袭肺、乳房、卵巢、淋巴样、胃肠道的(例如，结肠)、肛门、生殖器和生殖泌尿道(例如，肾、膀胱上皮、膀胱细胞、前列腺)、咽、CNS(例如，脑、神经的或神经胶质细胞)、头和颈、皮肤(例如，黑素瘤)、鼻咽(例如，分化或未分化的转移性或局部复发性鼻咽癌)和胰的那些癌、以及腺癌，包括恶性肿瘤，如结肠癌、直肠癌、肾细胞癌、肝癌、非小细胞肺癌、小肠癌和食道癌。癌症可以处于早期、中期或晚期或是转移性癌。

[0123] 在一些实施方案中，癌选自黑素瘤、乳腺癌、结肠癌、食管癌、胃肠道间质肿瘤(GIST)、肾癌(例如，肾细胞癌)、肝癌、非小细胞肺癌(NSCLC)、卵巢癌、胰腺癌、前列腺癌、头颈部肿瘤、胃癌、血液学恶性病(例如，淋巴瘤)。

[0124] 描述以下实施例以辅助对本发明的理解。不意在且不应当以任何方式将实施例解释成限制本发明的保护范围。

实施例

[0125] 实施例1、包含目的基因的谷氨酰胺合成酶高效表达载体的构建

[0126] (1)作为对照的抗PD1抗体BY18.1的编码核苷酸的合成及表达载体的构建

[0127] 根据International Nonproprietary Name(INN)数据库中编号为9623的纳武单抗的氨基酸序列数据，优化为适合在中国仓鼠卵巢癌细胞(CHO)中表达的下述核苷酸序列，并委托上海捷瑞生物工程有限公司合成该核苷酸序列。所述核苷酸序列表达后产生的抗PD1抗体在本文中表示为抗体BY18.1。

[0128] 抗PD1抗体BY18.1的轻链(BY18.1L)核苷酸序列(SEQ ID NO:66)：

[0129] CTCGAGGCCACCATGGAGACCGACACACTCCTCCTGTGGGTGCTGCTGCTGTGGGTGCCTGGCTCCACT
GGCGAGATTGTGCTGACACAGTCCCCCGCTACTCTGAGCCTGAGCCCTGGCGAGAGGGCTACACTGTCTTGCAGAGC
TTCTCAGTCCGTGTCTTCTTACCTCGCTTGGTATCAGCAGAAGCCCGGCCAGGCTCCAAGACTGCTGATCTATGACG
CTTCTAACCGCGCTACAGGCATTCCTGCTAGGTTCAGCGGCAGCGGCTCTGGCACCGACTTCACACTCACAATTAGC
TCTCTTGAACCTGAGGACTTCGCCGTGTACTACTGCCAGCAGTCTAGCAACTGGCCTAGAACATTCGGCCAGGGCAC
TAAGGTGGAGATTAAGAGAACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCTCCCAGCGACGAGCAGCTGAAGTCTG
GCACCGCCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCC
CTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACTCCAAGGACAGCACCTACAGCCTGAGCAGCACCCT
GACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGACTGTCTAGCCCCG
TGACCAAGAGCTTCAACCGGGGCGAGTGCTAAGAATTC

[0130] 抗PD1抗体BY18.1的轻链(BY18.1L)氨基酸序列(SEQ ID NO:67)：

[0131] METDTLLLWVLLLWVPGSTGEIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIY
DASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQSSNWPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLK
SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS
PVTKSFNRGEC

[0132] 抗PD1抗体BY18.1的重链(BY18.1H)核苷酸序列(SEQ ID NO:68)：

[0133] TCTAGAGCCACCATGGAGACCGACACCCTGCTGCTGTGGGTGCTGCTCCTGTGGGTGCCTGGCTCCAC
AGGCCAGGTGCAGCTCGTGGAGTCCGGCGGCGGCGTGGTGCAGCCCGGCAGATCCCTCAGACTGGACTGCAAGGCA
TCCGGCATTACATTCTCTAACTCTGGAATGCACTGGGTGAGACAGGCTCCTGGCAAGGGCCTGGAATGGGTGGCCG
TGATTTGGTACGACGGCTCTAAGAGATACTACGCTGACTCCGTGAAGGGCCGGTTCACAATTAGCAGAGACAACTC
CAAGAACACTCTGTTCCTCCAGATGAACAGCCTGAGAGCCGAGGACACCGCTGTGTACTACTGCGCCACCAACGAC
GACTACTGGGGCCAGGGCACCCTCGTGACAGTGTCTTCCGCCTCCACCAAGGGCCCTTCCGTGTTCCCTCTGGCCC
CTTGCTCCCGCTCCACCTCCGAGTCCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCTGAGCCTGTGAC
CGTGTCCTGGAACTCCGGCGCCCTGACCTCCGGCGTGCACACCTTCCCTGCCGTGCTGCAGTCCTCCGGCCTGTAC
TCCCTGTCCTCCGTGGTGACCGTGCCTTCCTCCTCCCTGGGCACCAAGACCTACACCTGCAACGTGGACCACAAGC
CTTCCAACACCAAGGTGGACAAGCGCGTGGAGTCCAAGTACGGCCCTCCTTGCCCTCCTTGCCCTGCCCCTGAGTT
CCTGGGCGGCCCTTCCGTGTTCCTGTTCCCTCCTAAGCCTAAGGACACCCTGATGATCTCCCGCACCCCTGAGGTG
ACCTGCGTGGTGGTGGACGTGTCCCAGGAGGACCCTGAGGTGCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGC
ACAACGCCAAGACCAAGCCTCGCGAGGAGCAGTTCAACTCCACCTACCGCGTGGTGTCCGTGCTGACCGTGCTGCA
CCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGTCCAACAAGGGCCTGCCTTCCTCCATCGAGAAGACC
ATCTCCAAGGCCAAGGGCCAGCCTCGCGAGCCTCAGGTGTACACCCTGCCTCCTTCCCAGGAGGAGATGACCAAGA
ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCTTCCGACATCGCCGTGGAGTGGGAGTCCAACGGCCA
GCCTGAGAACAACTACAAGACCACCCCTCCTGTGCTGGACTCCGACGGCTCCTTCTTCCTGTACTCCCGCCTGACC
GTGGACAAGTCCCGCTGGCAGGAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACA
CCCAGAAGTCCCTGTCCCTGTCCCTGGGCAAGTAA GTCGAC

[0134] 抗PD1抗体BY18.1的重链(BY18.1H)氨基酸序列(SEQ ID NO:69):

[0135] METDTLLLWVLLLWVPGSTGQVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVA
VIWYDGSKRYYADSVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSSASTKGPSVFPLAP
CSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS
NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA
KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL
SLSLGK

[0136] 其中带下划线部分“METDTLLLWVLLLWVPGSTG”为信号肽序列。

[0137] 上海捷瑞生物工程有限公司合成了上述BY18.1L编码核苷酸序列和BY18.1H编码核苷酸序列。分别将BY18.1L编码核苷酸用XhoI-EcoRI双酶切,将具有双表达盒的谷氨酰胺合成酶高效表达载体(专利授权号:CN104195173B,获自北京比洋生物技术有限公司)用XhoI-EcoRI双酶切,再通过连接酶将经XhoI-EcoRI双酶切的BY18.1L编码核苷酸连接入经XhoI-EcoRI双酶切的具有双表达盒的谷氨酰胺合成酶高效表达载体,获得已导入了BY18.1L编码核苷酸的具有双表达盒的谷氨酰胺合成酶高效表达载体;然后,分别将BY18.1H编码核苷酸用XbaI-SalI双酶切,将已导入了BY18.1L编码核苷酸的具有双表达盒的谷氨酰胺合成酶高效表达载体用XbaI-SalI双酶切,再通过连接酶将经XbaI-SalI双酶切的BY18.1H编码核苷酸连接入经XbaI-SalI双酶切的已导入了BY18.1L编码核苷酸的具有双表达盒的谷氨酰胺合成酶高效表达载体,由此获得了已导入BY18.1L编码核苷酸和BY18.1H编码核苷酸的具有双表达盒的谷氨酰胺合成酶高效表达载体,经测序验证正确后表达,获

得抗PD1抗体BY18.1。

[0138] 备选地，也可以将BY18.1L编码核苷酸连接入已导入了BY18.1H编码核苷酸的具有双表达盒的谷氨酰胺合成酶高效表达载体，表达并获得抗体BY18.1。

[0139] (2)作为对照的蛋白301-8编码核苷酸的合成及表达载体构建

[0140] 根据International Nonproprietary Name(INN)数据库中编号为8739的阿柏西普(aflibercept)的氨基酸序列数据，优化为适合在中国仓鼠卵巢癌细胞(CHO)中表达的下述核苷酸序列，并委托上海捷瑞生物工程有限公司合成该核苷酸序列。所述核苷酸序列表达后产生的蛋白产物在本文中表示为蛋白301-8。

[0141] 蛋白301-8的编码核苷酸序列(SEQ ID NO:70)：

[0142] AAGCTTGCCACCATGGAGACCGACACCCTGCTGCTCTGGGTGCTGCTGCTCTGGGTGCCCGGCTCCACC
GGATCCGACACCGGCCGCCCTTTCGTGGAGATGTACTCCGAGATCCCTGAGATCATCCACATGACCGAGGGCCGCGA
GCTGGTGATCCCTTGCCGCGTGACCTCCCCTAACATCACCGTGACCCTGAAGAAGTTCCCTCTGGACACCCTGATCC
CTGACGGCAAGCGCATCATCTGGGACTCCCGCAAGGGCTTCATCATCTCCAACGCCACCTACAAGGAGATCGGCCTG
CTGACCTGCGAGGCCACCGTGAACGGCCACCTGTACAAGACCAACTACCTGACCCACCGCCAGACCAACACCATCAT
CGACGTGGTGCTGTCCCCTTCCCACGGCATCGAGCTGTCCGTGGGCGAGAAGCTGGTGCTGAACTGCACCGCCCGCA
CCGAGCTGAACGTGGGCATCGACTTCAACTGGGAGTACCCTTCCTCCAAGCACCAGCACAAGAAGCTGGTGAACCGC
GACCTGAAGACCCAGTCCGGCTCCGAGATGAAGAAGTTCCTGTCCACCCTGACCATCGACGGCGTGACCCGCTCCGA
CCAGGGCCTGTACACCTGCGCCGCCTCCTCCGGCCTGATGACCAAGAAGAACTCCACCTTCGTGCGCGTGCACGAGA
AGGATAAGACCCATACATGTCCCCCATGCCCCGCTCCAGAACTGCTGGGCGGACCTTCCGTGTTTCTGTTCCCACCC
AAACCAAAGGACACACTGATGATCAGCAGAACCCCTGAGGTGACTTGCGTGGTCGTGGACGTGAGCCATGAGGACCC
CGAGGTGAAGTTCAACTGGTATGTGGATGGCGTGGAAGTGCATAATGCCAAGACAAAACCTAGGGAAGAGCAGTACA
ACAGCACCTACAGGGTGGTGAGCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAGGAATACAAGTGCAAG
GTGTCCAATAAGGCTCTGCCTGCACCTATCGAGAAGACCATCAGCAAAGCCAAGGGCCAACCCAGAGAGCCTCAAGT
CTACACCCTGCCCCCAAGCAGGGATGAGCTGACCAAAAATCAAGTGAGCCTGACATGCCTGGTCAAAGGCTTCTACC
CTAGCGACATCGCCGTGGAGTGGGAGAGCAATGGCCAGCCTGAGAACAACTACAAGACCACTCCCCCCGTCCTGGAT
AGCGACGGCAGCTTCTTCCTGTACTCCAAACTGACAGTCGATAAAAGCAGGTGGCAGCAAGGCAATGTCTTTAGCTG
TAGCGTGATGCACGAGGCCCTGCATAACCACTACACTCAAAAGTCCCTGTCCCTGAGCCCCGGA

[0143] 蛋白301-8的氨基酸序列(SEQ ID NO:71)：

[0144] METDTLLLWVLLLWVPGSTGSDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLKKFPLDTL
IPDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGIELSVGEKLVLNCTA
RTELNVGIDFNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVH
EKDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ
YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF
YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0145] 分别将蛋白301-8的编码核苷酸序列用XhoI-EcoRI双酶切，将具有双表达盒的谷氨酰胺合成酶高效表达载体(专利授权号：CN104195173B，获自北京比洋生物技术有限公司)用XhoI-EcoRI双酶切，再通过连接酶将经XhoI-EcoRI双酶切的蛋白301-8编码核苷酸连接入经XhoI-EcoRI双酶切的具有双表达盒的谷氨酰胺合成酶高效表达载体，获得已导入了蛋白301-8的编码核苷酸序列的具有双表达盒的谷氨酰胺合成酶高效表达载体。经测序验

证正确后用于表达，所表达的蛋白命名为蛋白301-8。蛋白301-8的氨基酸序列与现有技术中公开的阿柏西普的氨基酸序列相同。

[0146] (3)PD-1和VEGF家族的双靶向融合蛋白编码核苷酸的合成及表达载体的构建

[0147] 根据表1A中抗PD-1抗体的重链可变区和轻链可变区序列、表2中抗体的轻链恒定区序列、表3中抗体的重链恒定区序列、表4中的VID序列、以及SEQ ID NO:36－62的肽接头序列，优化为适合在中国仓鼠卵巢癌细胞(CHO)中表达的核苷酸序列，并委托上海捷瑞生物工程有限公司合成如下SEQ ID NO:72－118中偶数编号所示的多核苷酸序列。

[0148] 融合蛋白BY24.3(κ,IgG4)的轻链亚基(BY24.3L)核苷酸序列(SEQ ID NO:72)：

[0149] CTCGAGGCCACCATGGAGACCGACACACTCCTCCTGTGGGTGCTGCTGCTGTGGGTGCCTGGCTCCACT
GGCGAGATTGTGCTGACACAGTCCCCCGCTACTCTGAGCCTGAGCCCTGGCGAGAGGGCTACACTGTCTTGCAGAGC
TTCTCAGTCCGTGTCTTCTTACCTCGCTTGGTATCAGCAGAAGCCCGGCCAGGCTCCAAGACTGCTGATCTATGACG
CTTCTAACCGCGCTACAGGCATTCCTGCTAGGTTCAGCGGCAGCGGCTCTGGCACCGACTTCACACTCACAATTAGC
TCTCTTGAACCTGAGGACTTCGCCGTGTACTACTGCCAGCAGTCTAGCAACTGGCCTAGAACATTCGGCCAGGGCAC
TAAGGTGGAGATTAAGAGAACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCTCCCAGCGACGAGCAGCTGAAGTCTG
GCACCGCCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCC
CTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACTCCAAGGACAGCACCTACAGCCTGAGCAGCACCCT
GACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGACTGTCTAGCCCCG
TGACCAAGAGCTTCAACCGGGGCGAGTGCTAAGAATTC

[0150] 融合蛋白BY24.3(κ,IgG4)的轻链亚基(BY24.3L)氨基酸序列(SEQ ID NO:73)：ME
TDTLLLWVLLLWVPGSTGEIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIP
ARFSGSGSGTDFTLTISSLEPEDFAVYYCQQSSNWPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL
NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE
C

[0151] 融合蛋白BY24.3(κ,IgG4)的重链-VID融合亚基(BY24.3H)核苷酸序列(SEQ ID NO:74)：

[0152] TCTAGAGCCACCATGGAGACCGACACCCTGCTGCTGTGGGTGCTGCTCCTGTGGGTGCCTGGCTCCACA
GGCCAGGTGCAGCTCGTGGAGTCCGGCGGCGGCGTGGTGCAGCCCGGCAGATCCCTCAGACTGGACTGCAAGGCATC
CGGCATTACATTCTCTAACTCTGGAATGCACTGGGTGAGACAGGCTCCTGGCAAGGGCCTGGAATGGGTGGCCGTGA
TTTGGTACGACGGCTCTAAGAGATACTACGCTGACTCCGTGAAGGGCCGGTTCACAATTAGCAGAGACAACTCCAAG
AACACTCTGTTCCTCCAGATGAACAGCCTGAGAGCCGAGGACACCGCTGTGTACTACTGCGCCACCAACGACGACTA
CTGGGGCCAGGGCACCCTCGTGACAGTGTCTTCCGCCTCCACCAAGGGCCCTTCCGTGTTCCCTCTGGCCCCTTGCT
CCCGCTCCACCTCCGAGTCCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCTGAGCCTGTGACCGTGTCC
TGGAACTCCGGCGCCCTGACCTCCGGCGTGCACACCTTCCCTGCCGTGCTGCAGTCCTCCGGCCTGTACTCCCTGTC
CTCCGTGGTGACCGTGCCTTCCTCCTCCCTGGGCACCAAGACCTACACCTGCAACGTGGACCACAAGCCTTCCAACA
CCAAGGTGGACAAGCGCGTGGAGTCCAAGTACGGCCCTCCTTGCCCTCCTTGCCCTGCCCCTGAGTTCCTGGGCGGC
CCTTCCGTGTTCCTGTTCCCTCCTAAGCCTAAGGACACCCTGATGATCTCCCGCACCCCTGAGGTGACCTGCGTGGT
GGTGGACGTGTCCCAGGAGGACCCTGAGGTGCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGA
CCAAGCCTCGCGAGGAGCAGTTCAACTCCACCTACCGCGTGGTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTG
AACGGCAAGGAGTACAAGTGCAAGGTGTCCAACAAGGGCCTGCCTTCCTCCATCGAGAAGACCATCTCCAAGGCCAA

GGGCCAGCCTCGCGAGCCTCAGGTGTACACCCTGCCTCCTTCCCAGGAGGAGATGACCAAGAACCAGGTGTCCCTGA
CCTGCCTGGTGAAGGGCTTCTACCCTTCCGACATCGCCGTGGAGTGGGAGTCCAACGGCCAGCCTGAGAACAACTAC
AAGACCACCCCTCCTGTGCTGGACTCCGACGGCTCCTTCTTCCTGTACTCCCGCCTGACCGTGGACAAGTCCCGCTG
GCAGGAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCC
TGTCCCTGGGCGGCGGAGGATCTGGCGGCGGAGGCAGTGGAGGCGGCGGAAGCGCTTCCGACACCGGCCGCCCTTTC
GTGGAGATGTACTCCGAGATCCCTGAGATCATCCACATGACCGAGGGCCGCGAGCTGGTGATCCCTTGCCGCGTGAC
CTCCCCTAACATCACCGTGACCCTGAAGAAGTTCCCTCTGGACACCCTGATCCCTGACGGCAAGCGCATCATCTGGG
ACTCCCGCAAGGGCTTCATCATCTCCAACGCCACCTACAAGGAGATCGGCCTGCTGACCTGCGAGGCCACCGTGAAC
GGCCACCTGTACAAGACCAACTACCTGACCCACCGCCAGACCAACACCATCATCGACGTGGTGCTGTCCCCTTCCCA
CGGCATCGAGCTGTCCGTGGGCGAGAAGCTGGTGCTGAACTGCACCGCCCGCACCGAGCTGAACGTGGGCATCGACT
TCAACTGGGAGTACCCTTCCTCCAAGCACCAGCACAAGAAGCTGGTGAACCGCGACCTGAAGACCCAGTCCGGCTCC
GAGATGAAGAAGTTCCTGTCCACCCTGACCATCGACGGCGTGACCCGCTCCGACCAGGGCCTGTACACCTGCGCCGC
CTCCTCCGGCCTGATGACCAAGAAGAACTCCACCTTCGTGCGCGTGCACGAGAAGTAAGTCGAC

[0153] 融合蛋白BY24.3(κ,IgG4)的重链-VID融合亚基(BY24.3H)氨基酸序列(SEQ ID NO:75)：

[0154] METDTLLLWVLLLWVPGSTGQVQLVESGGGVVQPGRSLRLDCKASGITFSNSGMHWVRQAPGKGLEWVA
VIWYDGSKRYYADSVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCATNDDYWGQGTLVTVSSASTKGPSVFPLAP
CSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPS
NTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA
KTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL
SLSLGGGGSGGGGSGGGGSASDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLKKFPLDTLIPDGKRII
WDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGIELSVGEKLVLNCTARTELNVGI
DFNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEK

[0155] 融合蛋白BY24.7(κ,IgG2)的轻链亚基(BY24.7L)核苷酸序列(SEQ ID NO:76)：

[0156] CTCGAGGCCACCATGGAGACCGACACACTCCTCCTGTGGGTGCTGCTGCTGTGGGTGCCTGGCTCCACT
GGCGAGATCAAGCGGACCGTGGCCGCCCCATCCGTGTTCATTTTCCCACCTTCCGAGATTGTGCTGACACAGTCCCC
CGCTACTCTGAGCCTGAGCCCTGGCGAGAGGGCTACACTGTCTTGCAGAGCTTCCAAGGGCGTGAGCACATCCGGCT
ACTCCTACCTCCACTGGTATCAGCAGAAGCCAGGCCAGGCCCCAAGACTGCTGATATACCTCGCTTCTTACTTAGAG
TCTGGCGTGCCCGCTCGGTTCAGCGGCTCCGGCTCTGGCACCGACTTCACCCTGACAATTTCTAGCCTGGAGCCCGA
GGACTTCGCCGTGTACTACTGCCAGCACTCTAGGGACCTGCCTCTCACATTCGGCGGCGGCACTAAGGTGGAGATTA
AGAGAACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCTCCCAGCGACGAGCAGCTGAAGTCTGGCACCGCCAGCGTG
GTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGCGGCAA
CAGCCAGGAGAGCGTGACCGAGCAGGACTCCAAGGACAGCACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGG
CCGACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGACTGTCTAGCCCCGTGACCAAGAGCTTC
AACCGGGGCGAGTGCTAAGAATTC

[0157] 融合蛋白BY24.7(κ,IgG2)的轻链亚基(BY24.7L)氨基酸序列(SEQ ID NO:77)：

[0158] METDTLLLWVLLLWVPGSTGEIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQAPR
LLIYLASYLESGVPARFSGSGSGTDFTLTISSLEPEDFAVYYCQHSRDLPLTFGGGTKVEIKRTVAAPSVFIFPPSD

EQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[0159] 融合蛋白BY24.7(κ,IgG2)的重链-VID融合亚基(BY24.7H)核苷酸序列(SEQ ID NO:78)：

[0160] TCTAGAGCCACCATGGAGACCGACACCCTGCTGCTGTGGGTGCTGCTCCTGTGGGTGCCTGGCTCCACAGGCCAGGTGCAGCTCGTGCAGTCTGGCGTGGAGGTGAAGAAGCCTGGCGCCTCTGTGAAGGTGTCTTGCAAGGCTTCCGGCTACACTTTCACTAACTACTACATGTACTGGGTGAGACAGGCTCCCGGCCAGGGCCTAGAGTGGATGGGCGGCATTAACCCTAGCAACGGCGGCACAAACTTCAACGAGAAGTTCAAGAACCGCGTGACCCTGACCACAGACTCTAGCACAACAACTGCTTACATGGAGCTGAAGTCTCTCCAGTTCGACGACACCGCTGTGTACTACTGCGCTCGGAGGGACTACAGATTCGACATGGGCTTCGACTACTGGGGCCAGGGCACCACTGTGACAGTGTCTACAGCCTCCACCAAGGGCCCTTCCGTGTTCCCTCTGGCCCCTTGCTCCCGCTCCACCTCCGAGTCCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCTGAGCCTGTGACCGTGTCCTGGAACTCCGGCGCCCTGACCTCCGGCGTGCACACCTTCCCTGCCGTGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTGGTGACCGTGCCTTCCTCCAACTTCGGCACCCAGACATACACATGCAACGTGGACCACAAGCCTTCTAACACAAAGGTGGACAAGACCGTGGAGCGGAAGTGCTGCGTGGAGTGCCCACCTTGCCCCGCTCCTCCTGTGGCCGGCCCTTCTGTGTTCCTGTTCCCACCTAAGCCAAAGGACACACTCATGATCAGCAGAACCCCTGAGGTGACCTGCGTGGTGGTGGACGTGAGCCACGAGGACCCCGAGGTGCAGTTCAACTGGTATGTGGACGGCGTGGAGGTGCACAACGCTAAGACCAAGCCTAGAGAAGAACAGTTCAACAGCACATTCAGAGTGGTGTCCGTGCTCACCGTGGTGCACCAGGACTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGGCCTGCCAGCCCCTATCGAAAAAACAATCAGCAAGACCAAGGGCCAGCCTAGAGAGCCTCAGGTGTACACACTGCCTCCATCTCGGGAAGAAATGACAAAGAACCAGGTGTCCCTCACATGCCTCGTGAAGGGCTTCTACCCATCCGACATCGCTGTGGAGTGGGAGTCTAACGGCCAGCCCGAGAACAACTACAAGACCACCCCTCCTATGCTCGACTCCGACGGCTCTTTCTTCCTGTACTCTAAGCTGACCGTGGACAAGTCCAGATGGCAGCAGGGCAACGTGTTCTCTTGCAGCGTGATGCACGAGGCTCTCCACAACCACTACACCCAGAAGTCCCTGAGCCTGTCTCCAGGCGGCGGAGGATCTGGCGGCGGAGGCAGTGGAGGCGGCGGAAGCGCTTCCGACACCGGCCGCCCTTTCGTGGAGATGTACTCCGAGATCCCTGAGATCATCCACATGACCGAGGGCCGCGAGCTGGTGATCCCTTGCCGCGTGACCTCCCCTAACATCACCGTGACCCTGAAGAAGTTCCCTCTGGACACCCTGATCCCTGACGGCAAGCGCATCATCTGGGACTCCCGCAAGGGCTTCATCATCTCCAACGCCACCTACAAGGAGATCGGCCTGCTGACCTGCGAGGCCACCGTGAACGGCCACCTGTACAAGACCAACTACCTGACCCACCGCCAGACCAACACCTAAGTCGAC

[0161] 融合蛋白BY24.7(κ,IgG2)的重链-VID融合亚基(BY24.7H)氨基酸序列(SEQ ID NO:79)：

[0162] METDTLLLWVLLLWVPGSTGQVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGGINPSNGGTNFNEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRDYRFDMGFDYWGQGTTVTVSTASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGGGSGGGGSGGGGSASDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLKKFPLDTLIPDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLTHRQTNT

[0163] 融合蛋白BY24.4(κ,IgG4)的轻链亚基(BY24.4L)核苷酸序列(SEQ ID NO:80)：

[0164] CTCGAGGCCACCATGGAGACCGACACACTCCTCCTGTGGGTGCTGCTGCTGTGGGTGCCTGGCTCCACT

GGCGAGATCGTGCTGACACAGAGTCCTAGTTCCCTGAGCGCATCCGTCGGCGATAGGGTGACTATCACTTGTAGCGC
ACGCAGTAGCGTGTCTTACATGCACTGGTTTCAGCAGAAGCCCGGCAAGGCACCCAAGCTGTGGATCTACCGGACCA
GTAACCTCGCCTCTGGAGTGCCATCCAGGTTTAGTGGCTCCGGAAGTGGAACTTCTTACTGCCTCACAATTAATAGT
CTCCAGCCCGAGGATTTTGCAACATACTACTGTCAGCAGCGGTCTAGCTTTCCCCTGACATTCGGCGGAGGCACTAA
GGTGGAGATTAAGAGAACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCTCCCAGCGACGAGCAGCTGAAGTCTGGCA
CCGCCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTG
CAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACTCCAAGGACAGCACCTACAGCCTGAGCAGCACCCTGAC
CCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGACTGTCTAGCCCCGTGA
CCAAGAGCTTCAACCGGGGCGAGTGCTAAGAATTC

[0165] 融合蛋白BY24.4(κ,IgG4)的轻链亚基(BY24.4L)氨基酸序列(SEQ ID NO:81):ME
TDTLLLWVLLLWVPGSTGEIVLTQSPSSLSASVGDRVTITCSARSSVSYMHWFQQKPGKAPKLWIYRTSNLASGVPS
RFSGSGSGTSYCLTINSLQPEDFATYYCQQRSSFPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN
NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[0166] 融合蛋白BY24.4(κ,IgG4)的重链-VID融合亚基(BY24.4H)核苷酸序列(SEQ ID NO:82):

[0167] TCTAGAGCCACCATGGAGACCGACACCCTGCTGCTGTGGGTGCTGCTCCTGTGGGTGCCTGGCTCCACA
GGCCAGGTGCAGCTGGTCCAGAGCGGAAGCGAGCTTAAGAAGCCTGGAGCATCTGTCAAGATTAGTTGTAAGGCAAG
TGGCTACACATTTACCAACTACGGAATGAATTGGGTGCGCCAGGCACCCGGACAGGGCCTCCAGTGGATGGGATGGA
TCAATACCGATAGCGGCGAGTCTACATACGCTGAGGAGTTTAAGGGCCGGTTCGTGTTCAGTCTCGATACAAGCGTG
AACACAGCTTACCTCCAAATCACTTCTCTGACTGCTGAGGACACCGGCATGTACTTTTGCGTCCGCGTCGGCTACGA
CGCACTCGATTACTGGGGACAGGGCACCCTCGTGACAGTGTCTTCCGCCTCCACCAAGGGCCCTTCCGTGTTCCCTC
TGGCCCCTTGCTCCCGCTCCACCTCCGAGTCCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCTGAGCCT
GTGACCGTGTCCTGGAACTCCGGCGCCCTGACCTCCGGCGTGCACACCTTCCCTGCCGTGCTGCAGTCCTCCGGCCT
GTACTCCCTGTCCTCCGTGGTGACCGTGCCTTCCTCCTCCCTGGGCACCAAGACCTACACCTGCAACGTGGACCACA
AGCCTTCCAACACCAAGGTGGACAAGCGCGTGGAGTCCAAGTACGGCCCTCCTTGCCCTCCTTGCCCTGCCCCTGAG
TTCCTGGGCGGCCCTTCCGTGTTCCTGTTCCCTCCTAAGCCTAAGGACACCCTGATGATCTCCCGCACCCCTGAGGT
GACCTGCGTGGTGGTGGACGTGTCCCAGGAGGACCCTGAGGTGCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGC
ACAACGCCAAGACCAAGCCTCGCGAGGAGCAGTTCAACTCCACCTACCGCGTGGTGTCCGTGCTGACCGTGCTGCAC
CAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGTCCAACAAGGGCCTGCCTTCCTCCATCGAGAAGACCAT
CTCCAAGGCCAAGGGCCAGCCTCGCGAGCCTCAGGTGTACACCCTGCCTCCTTCCCAGGAGGAGATGACCAAGAACC
AGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCTTCCGACATCGCCGTGGAGTGGGAGTCCAACGGCCAGCCT
GAGAACAACTACAAGACCACCCCTCCTGTGCTGGACTCCGACGGCTCCTTCTTCCTGTACTCCCGCCTGACCGTGGA
CAAGTCCCGCTGGCAGGAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGA
AGTCCCTGTCCCTGTCCCTGGGCGGCGGAGGATCTGGCGGCGGAGGCAGTGGAGGCGGCGGAAGCGCTTCCGACACC
GGCCGCCCTTTCGTGGAGATGTACTCCGAGATCCCTGAGATCATCCACATGACCGAGGGCCGCGAGCTGGTGATCCC
TTGCCGCGTGACCTCCCCTAACATCACCGTGACCCTGAAGAAGTTCCCTCTGGACACCCTGATCCCTGACGGCAAGC
GCATCATCTGGGACTCCCGCAAGGGCTTCATCATCTCCAACGCCACCTACAAGGAGATCGGCCTGCTGACCTGCGAG
GCCACCGTGAACGGCCACCTGTACAAGACCAACTACCTGACCCACCGCCAGACCAACACCATCATCGACGTGGTGCT
GTCCCCTTCCCACGGCATCGAGCTGTCCGTGGGCGAGAAGCTGGTGCTGAACTGCACCGCCCGCACCGAGCTGAACG

TGGGCATCGACTTCAACTGGGAGTACCCTTCCTCCAAGCACCAGCACAAGAAGCTGGTGAACCGCGACCTGAAGACC
CAGTCCGGCTCCGAGATGAAGAAGTTCCTGTCCACCCTGACCATCGACGGCGTGACCCGCTCCGACCAGGGCCTGTA
CACCTGCGCCGCCTCCTCCGGCCTGATGACCAAGAAGAACTCCACCTTCGTGCGCGTGCACGAGAAGTAAGTCGAC

[0168] 融合蛋白BY24.4(κ,IgG4)的重链-VID融合亚基(BY24.4H)氨基酸序列(SEQ ID NO:83)：

[0169] METDTLLLWVLLLWVPGSTGQVQLVQSGSELKKPGASVKISCKASGYTFTNYGMNWVRQAPGQGLQWMG
WINTDSGESTYAEEFKGRFVFSLDTSVNTAYLQITSLTAEDTGMYFCVRVGYDALDYWGQGTLVTVSSASTKGPSVF
PLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVD
HKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVE
VHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYT
QKSLSLSLGGGGSGGGGSGGGGSASDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLKKFPLDTLIPDG
KRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGIELSVGEKLVLNCTARTEL
NVGIDFNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEK

[0170] 融合蛋白BY24.5(κ,IgG4)的轻链亚基(BY24.5L)核苷酸序列(SEQ ID NO:84)：

[0171] CTCGAGGCCACCATGGAGACCGACACACTCCTCCTGTGGGTGCTGCTGCTGTGGGTGCCTGGCTCCACT
GGCGACATTCAGATGACCCAGTCTCCAAGCTCTCTGAGCGCTTCCGTGGGCGACCGCGTGACAATTACATGCCTCGC
ATCTCAGACCATTGGCACCTGGCTGACATGGTATCAGCAGAAGCCTGGCAAGGCCCCTAAGCTGCTGATTTACACCG
CTACCTCCCTCGCCGACGGCGTGCCATCTAGGTTCTCTGGCTCCGGCTCCGGCACAGACTTCACACTCACTATTTCT
TCCCTCCAGCCCGAGGACTTCGCCACATACTACTGCCAGCAGGTGTACTCTATCCCTTGGACTTTCGGCGGCGGCAC
TAAGGTGGAGATTAAGAGAACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCTCCCAGCGACGAGCAGCTGAAGTCTG
GCACCGCCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCC
CTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACTCCAAGGACAGCACCTACAGCCTGAGCAGCACCCT
GACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGACTGTCTAGCCCCG
TGACCAAGAGCTTCAACCGGGGCGAGTGCTAAGAATTC

[0172] 融合蛋白BY24.5(κ,IgG4)的轻链亚基(BY24.5L)氨基酸序列(SEQ ID NO:85)：METDTLLLWVLLLWVPGSTGDIQMTQSPSSLSASVGDRVTITCLASQTIGTWLTWYQQKPGKAPKLLIYTATSLADGVP
SRFSGSGSGTDFTLTISSLQPEDFATYYCQQVYSIPWTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL
NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE
C

[0173] 融合蛋白BY24.5(κ,IgG4)的重链-VID融合亚基(BY24.5H)核苷酸序列(SEQ ID NO:86)：

[0174] TCTAGAGCCACCATGGAGACCGACACCCTGCTGCTGTGGGTGCTGCTCCTGTGGGTGCCTGGCTCCACA
GGCGAGGTCCAGCTCGTCGAGAGTGGAGGCGGCCTCGTGCAGCCCGGCGGAAGCCTCAGACTGTCTTGTGCTGCATC
TGGCTTCACTTTCTCTAGTTACATGATGAGTTGGGTGAGACAGGCACCAGGAAAGGGATTGGAGTGGGTCGCAACAA
TCAGTGGCGGAGGAGCAAACACATACTACCCCGATAGCGTCAAGGGACGGTTCACCATTAGTCGCGATAACGCTAAG
AACTCCCTGTACCTTCAGATGAATAGTCTCCGCGCTGAGGATACCGCCGTGTACTACTGCGCACGGCAGCTCTACTA
CTTCGATTACTGGGGCCAGGGCACCCTCGTGACAGTGTCTTCCGCCTCCACCAAGGGCCCTTCCGTGTTCCCTCTGG
CCCCTTGCTCCCGCTCCACCTCCGAGTCCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCTGAGCCTGTG

ACCGTGTCCTGGAACTCCGGCGCCCTGACCTCCGGCGTGCACACCTTCCCTGCCGTGCTGCAGTCCTCCGGCCTGTA
CTCCCTGTCCTCCGTGGTGACCGTGCCTTCCTCCTCCCTGGGCACCAAGACCTACACCTGCAACGTGGACCACAAGC
CTTCCAACACCAAGGTGGACAAGCGCGTGGAGTCCAAGTACGGCCCTCCTTGCCCTCCTTGCCCTGCCCCTGAGTTC
CTGGGCGGCCCTTCCGTGTTCCTGTTCCCTCCTAAGCCTAAGGACACCCTGATGATCTCCCGCACCCCTGAGGTGAC
CTGCGTGGTGGTGGACGTGTCCCAGGAGGACCCTGAGGTGCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACA
ACGCCAAGACCAAGCCTCGCGAGGAGCAGTTCAACTCCACCTACCGCGTGGTGTCCGTGCTGACCGTGCTGCACCAG
GACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGTCCAACAAGGGCCTGCCTTCCTCCATCGAGAAGACCATCTC
CAAGGCCAAGGGCCAGCCTCGCGAGCCTCAGGTGTACACCCTGCCTCCTTCCCAGGAGGAGATGACCAAGAACCAGG
TGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCTTCCGACATCGCCGTGGAGTGGGAGTCCAACGGCCAGCCTGAG
AACAACTACAAGACCACCCCTCCTGTGCTGGACTCCGACGGCTCCTTCTTCCTGTACTCCCGCCTGACCGTGGACAA
GTCCCGCTGGCAGGAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGT
CCCTGTCCCTGTCCCTGGGCGGCGGAGGATCTGGCGGCGGAGGCAGTGGAGGCGGCGGAAGCGCTTCCGACACCGGC
CGCCCTTTCGTGGAGATGTACTCCGAGATCCCTGAGATCATCCACATGACCGAGGGCCGCGAGCTGGTGATCCCTTG
CCGCGTGACCTCCCCTAACATCACCGTGACCCTGAAGAAGTTCCCTCTGGACACCCTGATCCCTGACGGCAAGCGCA
TCATCTGGGACTCCCGCAAGGGCTTCATCATCTCCAACGCCACCTACAAGGAGATCGGCCTGCTGACCTGCGAGGCC
ACCGTGAACGGCCACCTGTACAAGACCAACTACCTGACCCACCGCCAGACCAACACCATCATCGACGTGGTGCTGTC
CCCTTCCCACGGCATCGAGCTGTCCGTGGGCGAGAAGCTGGTGCTGAACTGCACCGCCCGCACCGAGCTGAACGTGG
GCATCGACTTCAACTGGGAGTACCCTTCCTCCAAGCACCAGCACAAGAAGCTGGTGAACCGCGACCTGAAGACCCAG
TCCGGCTCCGAGATGAAGAAGTTCCTGTCCACCCTGACCATCGACGGCGTGACCCGCTCCGACCAGGGCCTGTACAC
CTGCGCCGCCTCCTCCGGCCTGATGACCAAGAAGAACTCCACCTTCGTGCGCGTGCACGAGAAGTAAGTCGAC

[0175] 融合蛋白BY24.5(κ,IgG4)的重链-VID融合亚基(BY24.5H)氨基酸序列(SEQ ID NO:87)：

[0176] METDTLLLWVLLLWVPGSTGEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYMMSWVRQAPGKGLEWVA
TISGGGANTYYPDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARQLYYFDYWGQGTLVTVSSASTKGPSVFP
LAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDH
KPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEV
HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKN
QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGGGGSGGGGSGGGGSASDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLKKFPLDTLIPDGK
RIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGIELSVGEKLVLNCTARTELN
VGIDFNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEK

[0177] 融合蛋白BY24.6(κ,IgG2)的轻链亚基(BY24.6L)核苷酸序列(SEQ ID NO:88)：

[0178] CTCGAGGCCACCATGGAGACCGACACACTCCTCCTGTGGGTGCTGCTGCTGTGGGTGCCTGGCTCCACT
GGCAATATTCAGATGACCCAGAGTCCTAGTAGCCTGAGCGCATCCGTCGGCGACCGCGTGACCATTACATGTAAGGC
CGGACAGAACGTGAATAATTACCTCGCTTGGTATCAGCAGAAGCCAGGCAAGGCTCCAAAGGTGCTCATCTTCAATG
CTAACAGTCTCCAGACTGGCGTCCCTTCCCGGTTTAGTGGAAGTGGATCTGGCACCGATTTCACACTCACTATCAGT
TCTTTGCAACCCGAGGATTTTGCCACATACTACTGTCAGCAGTACAATAGCTGGACAACTTTCGGCGGAGGAACTAA
GGTGGAGATTAAGAGAACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCTCCCAGCGACGAGCAGCTGAAGTCTGGCA
CCGCCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTG

CAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACTCCAAGGACAGCACCTACAGCCTGAGCAGCACCCTGAC
CCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGACTGTCTAGCCCCGTGA
CCAAGAGCTTCAACCGGGGCGAGTGCTAAGAATTC

[0179] 融合蛋白BY24.6(κ,IgG2)的轻链亚基(BY24.6L)氨基酸序列(SEQ ID NO:89):ME
TDTLLLWVLLLWVPGSTGNIQMTQSPSSLSASVGDRVTITCKAGQNVNNYLAWYQQKPGKAPKVLIFNANSLQTGVP
SRFSGSGSGTDFTLTISSLQPEDFATYYCQQYNSWTTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN
NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[0180] 融合蛋白BY24.6(κ,IgG2)的重链-VID融合亚基(BY24.6H)核苷酸序列(SEQ ID
NO:90):

[0181] TCTAGAGCCACCATGGAGACCGACACCCTGCTGCTGTGGGTGCTGCTCCTGTGGGTGCCTGGCTCCACA
GGCCAGGTCACACTCAAGGAGTCCGGCCCAGCTCTCGTGAAGCCTACACAGACCCTCACTCTCACCTGTACATTCAG
CGGATTTAGCCTGAGCACTTCTGGAACATGCGTGTCTTGGATTCGGCAGCCACCCGGAAAGGCACTCGAATGGCTCG
CAACCATCTGTTGGGAGGACAGTAAGGGCTACAATCCATCTCTGAAGTCTAGGCTGACAATTAGTAAGGACACCTCC
AAGAATCAGGCCGTGCTGACTATGACTAATATGGACCCCGTCGATACCGCCACATACTACTGCGCTAGACGCGAGGA
TAGTGGCTACTTTTGGTTTCCTTACTGGGGCCAGGGAACCCTCGTGACAGTGTCTTCCGCCTCCACCAAGGGCCCTT
CCGTGTTCCCTCTGGCCCCTTGCTCCCGCTCCACCTCCGAGTCCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTAC
TTCCCTGAGCCTGTGACCGTGTCCTGGAACTCCGGCGCCCTGACCTCCGGCGTGCACACCTTCCCTGCCGTGCTGCA
GTCCTCCGGCCTGTACTCCCTGTCCTCCGTGGTGACCGTGCCTTCCTCCTCCCTGGGCACCAAGACCTACACCTGCA
ACGTGGACCACAAGCCTTCCAACACCAAGGTGGACAAGCGCGTGGAGTCCAAGTACGGCCCTCCTTGCCCTCCTTGC
CCTGCCCCTGAGTTCCTGGGCGGCCCTTCCGTGTTCCTGTTCCCTCCTAAGCCTAAGGACACCCTGATGATCTCCCG
CACCCCTGAGGTGACCTGCGTGGTGGTGGACGTGTCCCAGGAGGACCCTGAGGTGCAGTTCAACTGGTACGTGGACG
GCGTGGAGGTGCACAACGCCAAGACCAAGCCTCGCGAGGAGCAGTTCAACTCCACCTACCGCGTGGTGTCCGTGCTG
ACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGTCCAACAAGGGCCTGCCTTCCTCCAT
CGAGAAGACCATCTCCAAGGCCAAGGGCCAGCCTCGCGAGCCTCAGGTGTACACCCTGCCTCCTTCCCAGGAGGAGA
TGACCAAGAACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCTTCCGACATCGCCGTGGAGTGGGAGTCC
AACGGCCAGCCTGAGAACAACTACAAGACCACCCCTCCTGTGCTGGACTCCGACGGCTCCTTCTTCCTGTACTCCCG
CCTGACCGTGGACAAGTCCCGCTGGCAGGAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACC
ACTACACCCAGAAGTCCCTGTCCCTGTCCCTGGGCGGCGGAGGATCTGGCGGCGGAGGCAGTGGAGGCGGCGGAAGC
GCTTCCGACACCGGCCGCCCTTTCGTGGAGATGTACTCCGAGATCCCTGAGATCATCCACATGACCGAGGGCCGCGA
GCTGGTGATCCCTTGCCGCGTGACCTCCCCTAACATCACCGTGACCCTGAAGAAGTTCCCTCTGGACACCCTGATCC
CTGACGGCAAGCGCATCATCTGGGACTCCCGCAAGGGCTTCATCATCTCCAACGCCACCTACAAGGAGATCGGCCTG
CTGACCTGCGAGGCCACCGTGAACGGCCACCTGTACAAGACCAACTACCTGACCCACCGCCAGACCAACACCATCAT
CGACGTGGTGCTGTCCCCTTCCCACGGCATCGAGCTGTCCGTGGGCGAGAAGCTGGTGCTGAACTGCACCGCCCGCA
CCGAGCTGAACGTGGGCATCGACTTCAACTGGGAGTACCCTTCCTCCAAGCACCAGCACAAGAAGCTGGTGAACCGC
GACCTGAAGACCCAGTCCGGCTCCGAGATGAAGAAGTTCCTGTCCACCCTGACCATCGACGGCGTGACCCGCTCCGA
CCAGGGCCTGTACACCTGCGCCGCCTCCTCCGGCCTGATGACCAAGAAGAACTCCACCTTCGTGCGCGTGCACGAGA
AGTAAGTCGAC

[0182] 融合蛋白BY24.6(κ,IgG2)的重链-VID融合亚基(BY24.6H)氨基酸序列(SEQ ID
NO:91):

[0183] METDTLLLWVLLLWVPGSTGQVTLKESGPALVKPTQTLTLTCTFSGFSLSTSGTCVSWIRQPPGKALEW LATICWEDSKGYNPSLKSRLTISKDTSKNQAVLTMTNMDPVDTATYYCARREDSGYFWFPYWGQGTLVTVSSASTKG PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYT CNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALH NHYTQKSLSLSLGGGGSGGGGSGGGGSASDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLKKFPLDTL IPDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGIELSVGEKLVLNCTA RTELNVGIDFNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVH EK

[0184] 融合蛋白BY24.8(κ,IgG4)的轻链亚基(BY24.8L)核苷酸序列(SEQ ID NO:92)：

[0185] CTCGAGGCCACCATGGAGACCGACACACTCCTCCTGTGGGTGCTGCTGCTGTGGGTGCCTGGCTCCACT GGCGACATCGTGATGACCCAGAGTCCTGATAGTCTGGCCGTGTCCCTCGGCGAGCGCGCAACAATCAATTGCAAGGC ATCTCAGTCCGTTTCCAACGATGTCGCATGGTATCAGCAGAAGCCTGGACAGCCACCTAAGCTGCTCATTAACTACG CCTTCCACAGATTCACTGGCGTGCCCGATCGGTTTTCCGGAAGTGGATACGGAACCGACTTTACACTGACTATTAGT TCTCTACAAGCTGAGGACGTCGCTGTGTACTACTGTCACCAGGCTTACTCTAGCCCATACACATTTGGAGGCGGCAC TAAGGTGGAGATTAAGAGAACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCTCCCAGCGACGAGCAGCTGAAGTCTG GCACCGCCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCC CTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACTCCAAGGACAGCACCTACAGCCTGAGCAGCACCCT GACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGACTGTCTAGCCCCG TGACCAAGAGCTTCAACCGGGGCGAGTGCTAAGAATTC

[0186] 融合蛋白BY24.8(κ,IgG4)的轻链亚基(BY24.8L)氨基酸序列(SEQ ID NO:93)：

[0187] METDTLLLWVLLLWVPGSTGDIVMTQSPDSLAVSLGERATINCKASQSVSNDVAWYQQKPGQPPKLLIN YAFHRFTGVPDRFSGSGYGTDFTLTISSLQAEDVAVYYCHQAYSSPYTFGGGTKVEIKRTVAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGEC

[0188] 融合蛋白BY24.8(κ,IgG4)的重链-VID融合亚基(BY24.8H)核苷酸序列(SEQ ID NO:94)：

[0189] TCTAGAGCCACCATGGAGACCGACACCCTGCTGCTGTGGGTGCTGCTCCTGTGGGTGCCTGGCTCCACA GGCCAGGTCCAGCTCCAGGAGAGCGGACCTGGCCTCGTGAAGCCTAGCGAGACTCTGTCTCTGACATGTACAGTGTC CGGCTTTAGCCTCACTTCTTACGGCGTGCACTGGATTCGCCAGCCACCCGGAAAGGGATTGGAATGGCTCGGCGTCA TTTGGGCCGGAGGCAGCACTAACTACAACCCATCTCTCAAGTCTAGGCTCACAATCAGCAAGGATAATAGTAAGAGT CAGGTGTCCCTGAAGATGAGTTCCGTCACCGCTGCCGATACCGCTGTGTACTACTGCGCACGCGCATACGGCAATTA CTGGTACATCGACGTGTGGGGACAGGGCACCCTCGTGACAGTGTCTTCCGCCTCCACCAAGGGCCCTTCCGTGTTCC CTCTGGCCCCTTGCTCCCGCTCCACCTCCGAGTCCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCTGAG CCTGTGACCGTGTCCTGGAACTCCGGCGCCCTGACCTCCGGCGTGCACACCTTCCCTGCCGTGCTGCAGTCCTCCGG CCTGTACTCCCTGTCCTCCGTGGTGACCGTGCCTTCCTCCTCCCTGGGCACCAAGACCTACACCTGCAACGTGGACC ACAAGCCTTCCAACACCAAGGTGGACAAGCGCGTGGAGTCCAAGTACGGCCCTCCTTGCCCTCCTTGCCCTGCCCCT GAGTTCCTGGGCGGCCCTTCCGTGTTCCTGTTCCCTCCTAAGCCTAAGGACACCCTGATGATCTCCCGCACCCCTGA

GGTGACCTGCGTGGTGGTGGACGTGTCCCAGGAGGACCCTGAGGTGCAGTTCAACTGGTACGTGGACGGCGTGGAGG
TGCACAACGCCAAGACCAAGCCTCGCGAGGAGCAGTTCAACTCCACCTACCGCGTGGTGTCCGTGCTGACCGTGCTG
CACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGTCCAACAAGGGCCTGCCTTCCTCCATCGAGAAGAC
CATCTCCAAGGCCAAGGGCCAGCCTCGCGAGCCTCAGGTGTACACCCTGCCTCCTTCCCAGGAGGAGATGACCAAGA
ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCTTCCGACATCGCCGTGGAGTGGGAGTCCAACGGCCAG
CCTGAGAACAACTACAAGACCACCCCTCCTGTGCTGGACTCCGACGGCTCCTTCTTCCTGTACTCCCGCCTGACCGT
GGACAAGTCCCGCTGGCAGGAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCC
AGAAGTCCCTGTCCCTGTCCCTGGGCGGCGGAGGATCTGGCGGCGGAGGCAGTGGAGGCGGCGGAAGCGCTTCCGAC
ACCGGCCGCCCTTTCGTGGAGATGTACTCCGAGATCCCTGAGATCATCCACATGACCGAGGGCCGCGAGCTGGTGAT
CCCTTGCCGCGTGACCTCCCCTAACATCACCGTGACCCTGAAGAAGTTCCCTCTGGACACCCTGATCCCTGACGGCA
AGCGCATCATCTGGGACTCCCGCAAGGGCTTCATCATCTCCAACGCCACCTACAAGGAGATCGGCCTGCTGACCTGC
GAGGCCACCGTGAACGGCCACCTGTACAAGACCAACTACCTGACCCACCGCCAGACCAACACCATCATCGACGTGGT
GCTGTCCCCTTCCCACGGCATCGAGCTGTCCGTGGGCGAGAAGCTGGTGCTGAACTGCACCGCCCGCACCGAGCTGA
ACGTGGGCATCGACTTCAACTGGGAGTACCCTTCCTCCAAGCACCAGCACAAGAAGCTGGTGAACCGCGACCTGAAG
ACCCAGTCCGGCTCCGAGATGAAGAAGTTCCTGTCCACCCTGACCATCGACGGCGTGACCCGCTCCGACCAGGGCCT
GTACACCTGCGCCGCCTCCTCCGGCCTGATGACCAAGAAGAACTCCACCTTCGTGCGCGTGCACGAGAAGTAAGTCG
AC

[0190] 融合蛋白BY24.8(κ,IgG4)的重链-VID融合亚基(BY24.8H)氨基酸序列(SEQ ID NO:95)：

[0191] METDTLLLWVLLLWVPGSTGQVQLQESGPGLVKPSETLSLTCTVSGFSLTSYGVHWIRQPPGKGLEWLG
VIWAGGSTNYNPSLKSRLTISKDNSKSQVSLKMSSVTAADTAVYYCARAYGNYWYIDVWGQGTLVTVSSASTKGPSV
FPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV
DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGV
EVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHY
TQKSLSLSLGGGGSGGGGSGGGGSASDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLKKFPLDTLIPD
GKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGIELSVGEKLVLNCTARTE
LNVGIDFNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEK

[0192] 融合蛋白BY24.9(κ,IgG4)的轻链亚基(BY24.9L)核苷酸序列(SEQ ID NO:96)：

[0193] CTCGAGGCCACCATGGAGACCGACACACTCCTCCTGTGGGTGCTGCTGCTGTGGGTGCCTGGCTCCACT
GGCGATATTCAGATGACACAGTCCCCAAGTTCCCTGAGCGCCTCCGTCGGAGACCGGGTCACCATTACTTGTCGCGC
TTCTCAGAGCGTGAGTAATTACCTCGATTGGTATCAGCAGAAGCCAGGAAAGGCTCCTAAGCTGCTCATCTACGACG
CATCCACCCGCGCAACAGGCGTGCCTAGCCGGTTTAGCGGATCTGGAAGTGGCACTGATTTCACACTCACAATCTCT
AGTCTGCAACCCGAGGACTTTGCTACATACTACTGTCAGCAGAACATGCAGCTGCCACTGACATTCGGCCAGGGAAC
TAAGGTGGAGATTAAGAGAACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCTCCCAGCGACGAGCAGCTGAAGTCTG
GCACCGCCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCC
CTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACTCCAAGGACAGCACCTACAGCCTGAGCAGCACCCT
GACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGACTGTCTAGCCCCG
TGACCAAGAGCTTCAACCGGGGCGAGTGCTAAGAATTC

[0194] 融合蛋白BY24.9(κ,IgG4)的轻链亚基(BY24.9L)氨基酸序列(SEQ ID NO:97)：

[0195] METDTLLLWVLLLWVPGSTGDIQMTQSPSSLSASVGDRVTITCRASQSVSNYLDWYQQKPGKAPKLLIY DASTRATGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQNMQLPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGEC

[0196] 融合蛋白BY24.9(κ,IgG4)的重链-VID融合亚基(BY24.9H)核苷酸序列(SEQ ID NO:98)：

[0197] TCTAGAGCCACCATGGAGACCGACACCCTGCTGCTGTGGGTGCTGCTCCTGTGGGTGCCTGGCTCCACA GGCGTGCAGCTCGTCGAGTCCGGCGGAGGCGTGGTCCAGCCAGGACGCAGTCTGCGCCTGGATTGTAAGGCAAGCGG CATCACCTTTAGTAACTACGGTATGCACTGGGTGAGACAGGCTCCCGGAAAGGGCCTAGAATGGGTGGCCGTCATTT GGTACGACTCTTCTAGGAAGTACTACGCCGATAGTGTCAAGGGACGGTTCACAATCTCTCGCGATAATAGCAAGAAT ACACTGTTTTTGCAAATGAACTCCCTCAGAGCTGAGGATACCGCTGTGTACTACTGCGCAACCAACAATGATTACTG GGGACAGGGCACCCTCGTGACAGTGTCTTCCGCCTCCACCAAGGGCCCTTCCGTGTTCCCTCTGGCCCCTTGCTCCC GCTCCACCTCCGAGTCCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCTGAGCCTGTGACCGTGTCCTGG AACTCCGGCGCCCTGACCTCCGGCGTGCACACCTTCCCTGCCGTGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCTC CGTGGTGACCGTGCCTTCCTCCTCCCTGGGCACCAAGACCTACACCTGCAACGTGGACCACAAGCCTTCCAACACCA AGGTGGACAAGCGCGTGGAGTCCAAGTACGGCCCTCCTTGCCCTCCTTGCCCTGCCCCTGAGTTCCTGGGCGGCCCT TCCGTGTTCCTGTTCCCTCCTAAGCCTAAGGACACCCTGATGATCTCCCGCACCCCTGAGGTGACCTGCGTGGTGGT GGACGTGTCCCAGGAGGACCCTGAGGTGCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCA AGCCTCGCGAGGAGCAGTTCAACTCCACCTACCGCGTGGTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAAC GGCAAGGAGTACAAGTGCAAGGTGTCCAACAAGGGCCTGCCTTCCTCCATCGAGAAGACCATCTCCAAGGCCAAGGG CCAGCCTCGCGAGCCTCAGGTGTACACCCTGCCTCCTTCCCAGGAGGAGATGACCAAGAACCAGGTGTCCCTGACCT GCCTGGTGAAGGGCTTCTACCCTTCCGACATCGCCGTGGAGTGGGAGTCCAACGGCCAGCCTGAGAACAACTACAAG ACCACCCCTCCTGTGCTGGACTCCGACGGCTCCTTCTTCCTGTACTCCCGCCTGACCGTGGACAAGTCCCGCTGGCA GGAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCTGT CCCTGGGCGGCGGAGGATCTGGCGGCGGAGGCAGTGGAGGCGGCGGAAGCGCTTCCGACACCGGCCGCCCTTTCGTG GAGATGTACTCCGAGATCCCTGAGATCATCCACATGACCGAGGGCCGCGAGCTGGTGATCCCTTGCCGCGTGACCTC CCCTAACATCACCGTGACCCTGAAGAAGTTCCCTCTGGACACCCTGATCCCTGACGGCAAGCGCATCATCTGGGACT CCCGCAAGGGCTTCATCATCTCCAACGCCACCTACAAGGAGATCGGCCTGCTGACCTGCGAGGCCACCGTGAACGGC CACCTGTACAAGACCAACTACCTGACCCACCGCCAGACCAACACCATCATCGACGTGGTGCTGTCCCCTTCCCACGG CATCGAGCTGTCCGTGGGCGAGAAGCTGGTGCTGAACTGCACCGCCCGCACCGAGCTGAACGTGGGCATCGACTTCA ACTGGGAGTACCCTTCCTCCAAGCACCAGCACAAGAAGCTGGTGAACCGCGACCTGAAGACCCAGTCCGGCTCCGAG ATGAAGAAGTTCCTGTCCACCCTGACCATCGACGGCGTGACCCGCTCCGACCAGGGCCTGTACACCTGCGCCGCCTC CTCCGGCCTGATGACCAAGAAGAACTCCACCTTCGTGCGCGTGCACGAGAAGTAAGTCGAC

[0198] 融合蛋白BY24.9(κ,IgG4)的重链-VID融合亚基(BY24.9H)氨基酸序列(SEQ ID NO:99)：

[0199] METDTLLLWVLLLWVPGSTGVQLVESGGGVVQPGRSLRLDCKASGITFSNYGMHWVRQAPGKGLEWVAV IWYDSSRKYYADSVKGRFTISRDNSKNTLFLQMNSLRAEDTAVYYCATNNDYWGQGTLVTVSSASTKGPSVFPLAPC SRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSN

TKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAK
TKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLS
LSLGGGGSGGGGSGGGGSASDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLKKFPLDTLIPDGKRIIW
DSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGIELSVGEKLVLNCTARTELNVGID
FNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEK

[0200] 融合蛋白BY24.10(κ,IgG4)的轻链亚基(BY24.10L)核苷酸序列(SEQ ID NO:100)：

[0201] CTCGAGGCCACCATGGAGACCGACACACTCCTCCTGTGGGTGCTGCTGCTGTGGGTGCCTGGCTCCACT
GGCCTCAGTTACGTCCTCACACAGCCTCCATCCGTGTCTGTGAGTCCCGGACAGACCGCAAGAATCACATGTAGCGG
CGACGCACTGCCTAAGCAGTACGCTTACTGGTATCAGCAGAAGCCAGGACAGGCACCTGTGCTGGTGATCTACAAGG
ATAGCGAGCGCCCAAGTGGCATTCCCGAGAGATTTAGTGGCTCTTCTAGTGGAACAACCGTCACCCTGACTATTTCC
GGCGTGCAGGCCGAGGATGAGGCCGATTACTACTGTCAGTCTGCTGACTCTAGCGGAACATACGTCGTGTTTGGAGG
CGGAACTAAGGTGGAGATTAAGAGAACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCTCCCAGCGACGAGCAGCTGA
AGTCTGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGAC
AACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACTCCAAGGACAGCACCTACAGCCTGAGCAG
CACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGACTGTCTA
GCCCCGTGACCAAGAGCTTCAACCGGGGCGAGTGCTAAGAATTC

[0202] 融合蛋白BY24.10(κ,IgG4)的轻链亚基(BY24.10L)氨基酸序列(SEQ ID NO:101)：

METDTLLLWVLLLWVPGSTGLSYVLTQPPSVSVSPGQTARITCSGDALPKQYAYWYQQKPGQAPVLVIYKDSERPSG
IPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADSSGTYVVFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV
VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF
NRGEC

[0203] 融合蛋白BY24.10(κ,IgG4)的重链-VID融合亚基(BY24.10H)核苷酸序列(SEQ ID NO:102)：

[0204] TCTAGAGCCACCATGGAGACCGACACCCTGCTGCTGTGGGTGCTGCTCCTGTGGGTGCCTGGCTCCACA
GGCGACCTCGTGCAGTCCGGCGCCGAGGTGAAGAAGCCCGGCGCATCCGTCAAGGTGTCTTGCAAGGCAAGTGGCTA
CACTTTCACCAGTTACGGAATCAGTTGGGTCAGACAGGCACCTGGCCAGGGCCTGGAGTGGATGGGCTGGATTAGCG
CTTACAACGGAAACACCAATTACGCTCAGAAGCTCCAGGGTCGGGTGACTATGACAACCGACACATCTACCAGCACC
GCATACATGGAGCTGCGTAGTCTGAGATCCGACGATACCGCCGTGTACTACTGTGCTCGCGGCAGAGGATACTCCTA
CGGAATTGATGCATTCGATATTTGGGGACAGGGAACCCTCGTGACAGTGTCTTCCGCCTCCACCAAGGGCCCTTCCG
TGTTCCCTCTGGCCCCTTGCTCCCGCTCCACCTCCGAGTCCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTC
CCTGAGCCTGTGACCGTGTCCTGGAACTCCGGCGCCCTGACCTCCGGCGTGCACACCTTCCCTGCCGTGCTGCAGTC
CTCCGGCCTGTACTCCCTGTCCTCCGTGGTGACCGTGCCTTCCTCCTCCCTGGGCACCAAGACCTACACCTGCAACG
TGGACCACAAGCCTTCCAACACCAAGGTGGACAAGCGCGTGGAGTCCAAGTACGGCCCTCCTTGCCCTCCTTGCCCT
GCCCCTGAGTTCCTGGGCGGCCCTTCCGTGTTCCTGTTCCCTCCTAAGCCTAAGGACACCCTGATGATCTCCCGCAC
CCCTGAGGTGACCTGCGTGGTGGTGGACGTGTCCCAGGAGGACCCTGAGGTGCAGTTCAACTGGTACGTGGACGGCG
TGGAGGTGCACAACGCCAAGACCAAGCCTCGCGAGGAGCAGTTCAACTCCACCTACCGCGTGGTGTCCGTGCTGACC
GTGCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGTCCAACAAGGGCCTGCCTTCCTCCATCGA
GAAGACCATCTCCAAGGCCAAGGGCCAGCCTCGCGAGCCTCAGGTGTACACCCTGCCTCCTTCCCAGGAGGAGATGA

CCAAGAACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCTTCCGACATCGCCGTGGAGTGGGAGTCCAAC
GGCCAGCCTGAGAACAACTACAAGACCACCCCTCCTGTGCTGGACTCCGACGGCTCCTTCTTCCTGTACTCCCGCCT
GACCGTGGACAAGTCCCGCTGGCAGGAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCACT
ACACCCAGAAGTCCCTGTCCCTGTCCCTGGGCGGCGGAGGATCTGGCGGCGGAGGCAGTGGAGGCGGCGGAAGCGCT
TCCGACACCGGCCGCCCTTTCGTGGAGATGTACTCCGAGATCCCTGAGATCATCCACATGACCGAGGGCCGCGAGCT
GGTGATCCCTTGCCGCGTGACCTCCCCTAACATCACCGTGACCCTGAAGAAGTTCCCTCTGGACACCCTGATCCCTG
ACGGCAAGCGCATCATCTGGGACTCCCGCAAGGGCTTCATCATCTCCAACGCCACCTACAAGGAGATCGGCCTGCTG
ACCTGCGAGGCCACCGTGAACGGCCACCTGTACAAGACCAACTACCTGACCCACCGCCAGACCAACACCATCATCGA
CGTGGTGCTGTCCCCTTCCCACGGCATCGAGCTGTCCGTGGGCGAGAAGCTGGTGCTGAACTGCACCGCCCGCACCG
AGCTGAACGTGGGCATCGACTTCAACTGGGAGTACCCTTCCTCCAAGCACCAGCACAAGAAGCTGGTGAACCGCGAC
CTGAAGACCCAGTCCGGCTCCGAGATGAAGAAGTTCCTGTCCACCCTGACCATCGACGGCGTGACCCGCTCCGACCA
GGGCCTGTACACCTGCGCCGCCTCCTCCGGCCTGATGACCAAGAAGAACTCCACCTTCGTGCGCGTGCACGAGAAGT
AAGTCGAC

[0205] 融合蛋白BY24.10(κ,IgG4)的重链-VID融合亚基(BY24.10H)氨基酸序列(SEQ ID NO:103)：

[0206] METDTLLLWVLLLWVPGSTGDLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMGWI
SAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARGRGYSYGIDAFDIWGQGTLVTVSSASTKGP
SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTC
NVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVD
GVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN
HYTQKSLSLSLGGGGSGGGGSGGGGSASDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLKKFPLDTLI
PDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGIELSVGEKLVLNCTAR
TELNVGIDFNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHE
K

[0207] 融合蛋白BY24.11(κ,IgG4)的轻链亚基(BY24.11L)核苷酸序列(SEQ ID NO:104)：

[0208] CTCGAGGCCACCATGGAGACCGACACACTCCTCCTGTGGGTGCTGCTGCTGTGGGTGCCTGGCTCCACT
GGCGATGTCGTCATGACCCAGTCCCCTCTGTCTCTGCCCGTCACACTGGGACAGCCCGCATCCATTAGTTGTAGGTC
TAGCCAGAGCATTGTGCACAGTAACGGCAATACATACCTGGAGTGGTATCTTCAAAAGCCTGGCCAGTCTCCTCAGC
TGCTGATCTACAAGGTGAGTAATCGCTTTAGCGGCGTGCCTGATAGATTCAGCGGAAGTGGCTCCGGAACCGACTTC
ACACTCAAGATTTCTCGCGTGGAGGCCGAGGACGTCGGCGTGTACTACTGTTTTCAGGGGAGCCACGTGCCACTCAC
CTTTGGACAGGGCACTAAGGTGGAGATTAAGAGAACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCTCCCAGCGACG
AGCAGCTGAAGTCTGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCAAGGTGCAGTGG
AAGGTGGACAACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACTCCAAGGACAGCACCTACAG
CCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGG
GACTGTCTAGCCCCGTGACCAAGAGCTTCAACCGGGGCGAGTGCTAAGAATTC

[0209] 融合蛋白BY24.11(κ,IgG4)的轻链亚基(BY24.11L)氨基酸序列(SEQ ID NO:105)：

[0210] METDTLLLWVLLLWVPGSTGDVVMTQSPLSLPVTLGQPASISCRSSQSIVHSNGNTYLEWYLQKPGQSP
QLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHVPLTFGQGTKVEIKRTVAAPSVFIFPPS

DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTH
QGLSSPVTKSFNRGEC

[0211] 融合蛋白BY24.11(κ,IgG4)的重链-VID融合亚基(BY24.11H)核苷酸序列(SEQ ID NO:106)：

[0212] TCTAGAGCCACCATGGAGACCGACACCCTGCTGCTGTGGGTGCTGCTCCTGTGGGTGCCTGGCTCCACA
GGCCAGGGCCAGCTCGTGCAGAGTGGCGCAGAGGTGAAGAAGCCCGGAGCATCCGTCAAGGTCAGTTGCAAGGCCTC
TGGATACACCTTTACCGATTACGAGATGCACTGGGTGCGGCAGGCTCCTGGACAGGGACTCGAATGGATGGGCGTCA
TTGAGTCCGAGACCGGCGGAACAGCTTACAATCAGAAGTTTCAGGGACGGGTGACACTCACTGCCGATAAGTCTTCT
AGCACCGCCTACATGGAACTTTCCTCTCTGCGCTCAGAGGATACCGCTGTGTACTACTGTACACGCGAGGGAATCAC
AACTGTCGCAACCACATACTACTGGTACTTCGACGTGTGGGGCCAGGGAACCCTCGTGACAGTGTCTTCCGCCTCCA
CCAAGGGCCCTTCCGTGTTCCCTCTGGCCCCTTGCTCCCGCTCCACCTCCGAGTCCACCGCCGCCCTGGGCTGCCTG
GTGAAGGACTACTTCCCTGAGCCTGTGACCGTGTCCTGGAACTCCGGCGCCCTGACCTCCGGCGTGCACACCTTCCC
TGCCGTGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTGGTGACCGTGCCTTCCTCCTCCCTGGGCACCAAGA
CCTACACCTGCAACGTGGACCACAAGCCTTCCAACACCAAGGTGGACAAGCGCGTGGAGTCCAAGTACGGCCCTCCT
TGCCCTCCTTGCCCTGCCCCTGAGTTCCTGGGCGGCCCTTCCGTGTTCCTGTTCCCTCCTAAGCCTAAGGACACCCT
GATGATCTCCCGCACCCCTGAGGTGACCTGCGTGGTGGTGGACGTGTCCCAGGAGGACCCTGAGGTGCAGTTCAACT
GGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCAAGCCTCGCGAGGAGCAGTTCAACTCCACCTACCGCGTG
GTGTCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGTCCAACAAGGGCCT
GCCTTCCTCCATCGAGAAGACCATCTCCAAGGCCAAGGGCCAGCCTCGCGAGCCTCAGGTGTACACCCTGCCTCCTT
CCCAGGAGGAGATGACCAAGAACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCTTCCGACATCGCCGTG
GAGTGGGAGTCCAACGGCCAGCCTGAGAACAACTACAAGACCACCCCTCCTGTGCTGGACTCCGACGGCTCCTTCTT
CCTGTACTCCCGCCTGACCGTGGACAAGTCCCGCTGGCAGGAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGG
CCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCTGTCCCTGGGCGGCGGAGGATCTGGCGGCGGAGGCAGTGGA
GGCGGCGGAAGCGCTTCCGACACCGGCCGCCCTTTCGTGGAGATGTACTCCGAGATCCCTGAGATCATCCACATGAC
CGAGGGCCGCGAGCTGGTGATCCCTTGCCGCGTGACCTCCCCTAACATCACCGTGACCCTGAAGAAGTTCCCTCTGG
ACACCCTGATCCCTGACGGCAAGCGCATCATCTGGGACTCCCGCAAGGGCTTCATCATCTCCAACGCCACCTACAAG
GAGATCGGCCTGCTGACCTGCGAGGCCACCGTGAACGGCCACCTGTACAAGACCAACTACCTGACCCACCGCCAGAC
CAACACCATCATCGACGTGGTGCTGTCCCCTTCCCACGGCATCGAGCTGTCCGTGGGCGAGAAGCTGGTGCTGAACT
GCACCGCCCGCACCGAGCTGAACGTGGGCATCGACTTCAACTGGGAGTACCCTTCCTCCAAGCACCAGCACAAGAAG
CTGGTGAACCGCGACCTGAAGACCCAGTCCGGCTCCGAGATGAAGAAGTTCCTGTCCACCCTGACCATCGACGGCGT
GACCCGCTCCGACCAGGGCCTGTACACCTGCGCCGCCTCCTCCGGCCTGATGACCAAGAAGAACTCCACCTTCGTGC
GCGTGCACGAGAAGTAAGTCGAC

[0213] 融合蛋白BY24.11(κ,IgG4)的重链-VID融合亚基(BY24.11H)氨基酸序列(SEQ IDNO:107)：

[0214] METDTLLLWVLLLWVPGSTGQGQLVQSGAEVKKPGASVKVSCKASGYTFTDYEMHWVRQAPGQGLEWMG
VIESETGGTAYNQKFQGRVTLTADKSSSTAYMELSSLRSEDTAVYYCTREGITTVATTYYWYFDVWGQGTLVTVSSA
STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
KTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF
NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLP

PSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMH
EALHNHYTQKSLSLSLGGGGSGGGGSGGGGSASDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLKKFP
LDTLIPDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGIELSVGEKLVL
NCTARTELNVGIDFNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTF
VRVHEK

[0215] 融合蛋白BY24.12(κ,IgG4)的轻链亚基(BY24.12L)核苷酸序列(SEQ ID NO:108)：

[0216] CTCGAGGCCACCATGGAGACCGACACACTCCTCCTGTGGGTGCTGCTGCTGTGGGTGCCTGGCTCCACT
GGCGATATTGTGCTGACCCAGAGTCCCGCATCTCTCGCCGTCAGTCCTGGACAGCGCGCTACTATCACTTGCAGGGC
TTCTGAGAGCGTCGATAATTACGGCATTTCCTTTATGAACTGGTATCAGCAGAAGCCTGGCCAGCCTCCAAAGCTGC
TCATCTACACCTCTAGTAACAAGGATACAGGCGTGCCCGCAAGATTTAGCGGCTCCGGAAGTGGCACCGACTTCACA
CTCACAATCAACCCTATGGAGGCCGAGGATACCGCCGTGTACTACTGTCAGCAGTCTAAGGAGGTGCCTTGGACATT
CGGCGGCGGAACTAAGGTGGAGATTAAGAGAACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCTCCCAGCGACGAGC
AGCTGAAGTCTGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCAAGGTGCAGTGGAAG
GTGGACAACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACTCCAAGGACAGCACCTACAGCCT
GAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGAC
TGTCTAGCCCCGTGACCAAGAGCTTCAACCGGGGCGAGTGCTAAGAATTC

[0217] 融合蛋白BY24.12(κ,IgG4)的轻链亚基(BY24.12L)氨基酸序列(SEQ ID NO:109)：

[0218] METDTLLLWVLLLWVPGSTGDIVLTQSPASLAVSPGQRATITCRASESVDNYGISFMNWYQQKPGQPPK
LLIYTSSNKDTGVPARFSGSGSGTDFTLTINPMEAEDTAVYYCQQSKEVPWTFGGGTKVEIKRTVAAPSVFIFPPSD
EQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ
GLSSPVTKSFNRGEC

[0219] 融合蛋白BY24.12(κ,IgG4)的重链-VID融合亚基(BY24.12H)核苷酸序列(SEQ ID NO:110)：

[0220] TCTAGAGCCACCATGGAGACCGACACCCTGCTGCTGTGGGTGCTGCTCCTGTGGGTGCCTGGCTCCACA
GGCGAGGTCCAGCTCGTCGAGTCCGGCGGAGGCCTCGTGCAGCCCGGCGGATCTCTGAGACTCAGTTGTGCCGCTAG
TGGCTTTACATTTTCTTCCTACGGCATGTCTTGGGTGAGACAGGCTCCTGGAAAGGGATTAGAGTGGGTCGCAACTA
TTAGTGGCGGAGGAAGCGACACATACTACGCCGATTCCGTCAAGGGACGGTTCACCATCAGTCGCGATAACTCTAAG
AACACACTGTACCTACAGATGAATAGCCTGAGAGCAGAGGATACCGCTGTGTACTACTGCGCACGCCAGCTCAATTA
CGCATGGTTTGCTTACTGGGGCCAGGGCACCCTCGTGACAGTGTCTTCCGCCTCCACCAAGGGCCCTTCCGTGTTCC
CTCTGGCCCCTTGCTCCCGCTCCACCTCCGAGTCCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCTGAG
CCTGTGACCGTGTCCTGGAACTCCGGCGCCCTGACCTCCGGCGTGCACACCTTCCCTGCCGTGCTGCAGTCCTCCGG
CCTGTACTCCCTGTCCTCCGTGGTGACCGTGCCTTCCTCCTCCCTGGGCACCAAGACCTACACCTGCAACGTGGACC
ACAAGCCTTCCAACACCAAGGTGGACAAGCGCGTGGAGTCCAAGTACGGCCCTCCTTGCCCTCCTTGCCCTGCCCCT
GAGTTCCTGGGCGGCCCTTCCGTGTTCCTGTTCCCTCCTAAGCCTAAGGACACCCTGATGATCTCCCGCACCCCTGA
GGTGACCTGCGTGGTGGTGGACGTGTCCCAGGAGGACCCTGAGGTGCAGTTCAACTGGTACGTGGACGGCGTGGAGG
TGCACAACGCCAAGACCAAGCCTCGCGAGGAGCAGTTCAACTCCACCTACCGCGTGGTGTCCGTGCTGACCGTGCTG
CACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGTCCAACAAGGGCCTGCCTTCCTCCATCGAGAAGAC
CATCTCCAAGGCCAAGGGCCAGCCTCGCGAGCCTCAGGTGTACACCCTGCCTCCTTCCCAGGAGGAGATGACCAAGA
ACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCTTCCGACATCGCCGTGGAGTGGGAGTCCAACGGCCAG

CCTGAGAACAACTACAAGACCACCCCTCCTGTGCTGGACTCCGACGGCTCCTTCTTCCTGTACTCCCGCCTGACCGT
GGACAAGTCCCGCTGGCAGGAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCC
AGAAGTCCCTGTCCCTGTCCCTGGGCGGCGGAGGATCTGGCGGCGGAGGCAGTGGAGGCGGCGGAAGCGCTTCCGAC
ACCGGCCGCCCTTTCGTGGAGATGTACTCCGAGATCCCTGAGATCATCCACATGACCGAGGGCCGCGAGCTGGTGAT
CCCTTGCCGCGTGACCTCCCCTAACATCACCGTGACCCTGAAGAAGTTCCCTCTGGACACCCTGATCCCTGACGGCA
AGCGCATCATCTGGGACTCCCGCAAGGGCTTCATCATCTCCAACGCCACCTACAAGGAGATCGGCCTGCTGACCTGC
GAGGCCACCGTGAACGGCCACCTGTACAAGACCAACTACCTGACCCACCGCCAGACCAACACCATCATCGACGTGGT
GCTGTCCCCTTCCCACGGCATCGAGCTGTCCGTGGGCGAGAAGCTGGTGCTGAACTGCACCGCCCGCACCGAGCTGA
ACGTGGGCATCGACTTCAACTGGGAGTACCCTTCCTCCAAGCACCAGCACAAGAAGCTGGTGAACCGCGACCTGAAG
ACCCAGTCCGGCTCCGAGATGAAGAAGTTCCTGTCCACCCTGACCATCGACGGCGTGACCCGCTCCGACCAGGGCCT
GTACACCTGCGCCGCCTCCTCCGGCCTGATGACCAAGAAGAACTCCACCTTCGTGCGCGTGCACGAGAAGTAAGTCG
AC

[0221] 融合蛋白BY24.12(κ,IgG4)的重链-VID融合亚基(BY24.12H)氨基酸序列(SEQ ID NO:111)：

[0222] METDTLLLWVLLLWVPGSTGEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGKGLEWVA
TISGGGSDTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARQLNYAWFAYWGQGTLVTVSSASTKGPSV
FPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV
DHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGV
EVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHY
TQKSLSLSLGGGGSGGGGSGGGGSASDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLKKFPLDTLIPD
GKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGIELSVGEKLVLNCTARTE
LNVGIDFNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEK

[0223] 融合蛋白BY24.13(κ,IgG4)的轻链亚基(BY24.13L)核苷酸序列(SEQ ID NO:112)：

[0224] CTCGAGGCCACCATGGAGACCGACACACTCCTCCTGTGGGTGCTGCTGCTGTGGGTGCCTGGCTCCACT
GGCGATATTCAGATGACCCAGAGTCCATCTAGCGTGTCTGCTTCTGTGGGCGATCGGGTGACAATCACTTGTCGCGC
AAGTCAGGGAATTAGTAGTTGGCTCGCATGGTATCAGCAGAAGCCTGGCAAGGCACCTAAGCTCCTCATTAGCGCCG
CGTCATCCCTGCAATCCGGCGTGCCATCTAGGTTTAGTGGTTCCGGAAGCGGAACCGACTTTACACTCACTATCAGT
TCTCTCCAGCCCGAGGATTTCGCAACATACTACTGTCAGCAGGCCAACCACCTGCCTTTCACATTTGGAGGCGGCAC
ATTCGGCGGCGGAACTAAGGTGGAGATTAAGAGAACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCTCCCAGCGACG
AGCAGCTGAAGTCTGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCAAGGTGCAGTGG
AAGGTGGACAACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACTCCAAGGACAGCACCTACAG
CCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGG
GACTGTCTAGCCCCGTGACCAAGAGCTTCAACCGGGGCGAGTGCTAAGAATTC

[0225] 融合蛋白BY24.13(κ,IgG4)的轻链亚基(BY24.13L)氨基酸序列(SEQ ID NO:113)：

[0226] METDTLLLWVLLLWVPGSTGDIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIS
AASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANHLPFTFGGGTKVEIKRTVAAPSVFIFPPSDEQLK
SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS
PVTKSFNRGEC

[0227] 融合蛋白BY24.13(κ,IgG4)的重链-VID融合亚基(BY24.13H)核苷酸序列(SEQ ID NO:114)：

[0228] TCTAGAGCCACCATGGAGACCGACACCCTGCTGCTGTGGGTGCTGCTCCTGTGGGTGCCTGGCTCCACA
GGCCAGGTGCAGCTCGTCCAGTCTGGCGCTGAGGTCAAGAAGCCTGGATCTAGCGTGAAGGTGTCTTGTAAGGCAAG
TGGCGGAACCTTTTCTAGTTACGCTATTAGTTGGGTGCGGCAGGCTCCCGGCCAGGGCCTGGAGTGGATGGGACTCA
TCATTCCTATGTTCGATACCGCCGGCTACGCCCAGAAGTTTCAGGGACGGGTCGCAATCACCGTAGATGAGAGTACC
TCCACAGCATACATGGAGCTGAGTAGTCTCAGATCCGAGGACACTGCCGTGTACTACTGTGCTCGCGCAGAGCACTC
TAGCACCGGAACATTTGATTACTGGGGACAGGGCACCCTCGTGACAGTGTCTTCCGCCTCCACCAAGGGCCCTTCCG
TGTTCCCTCTGGCCCCTTGCTCCCGCTCCACCTCCGAGTCCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTC
CCTGAGCCTGTGACCGTGTCCTGGAACTCCGGCGCCCTGACCTCCGGCGTGCACACCTTCCCTGCCGTGCTGCAGTC
CTCCGGCCTGTACTCCCTGTCCTCCGTGGTGACCGTGCCTTCCTCCTCCCTGGGCACCAAGACCTACACCTGCAACG
TGGACCACAAGCCTTCCAACACCAAGGTGGACAAGCGCGTGGAGTCCAAGTACGGCCCTCCTTGCCCTCCTTGCCCT
GCCCCTGAGTTCCTGGGCGGCCCTTCCGTGTTCCTGTTCCCTCCTAAGCCTAAGGACACCCTGATGATCTCCCGCAC
CCCTGAGGTGACCTGCGTGGTGGTGGACGTGTCCCAGGAGGACCCTGAGGTGCAGTTCAACTGGTACGTGGACGGCG
TGGAGGTGCACAACGCCAAGACCAAGCCTCGCGAGGAGCAGTTCAACTCCACCTACCGCGTGGTGTCCGTGCTGACC
GTGCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGTCCAACAAGGGCCTGCCTTCCTCCATCGA
GAAGACCATCTCCAAGGCCAAGGGCCAGCCTCGCGAGCCTCAGGTGTACACCCTGCCTCCTTCCCAGGAGGAGATGA
CCAAGAACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCTTCCGACATCGCCGTGGAGTGGGAGTCCAAC
GGCCAGCCTGAGAACAACTACAAGACCACCCCTCCTGTGCTGGACTCCGACGGCTCCTTCTTCCTGTACTCCCGCCT
GACCGTGGACAAGTCCCGCTGGCAGGAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCACT
ACACCCAGAAGTCCCTGTCCCTGTCCCTGGGCGGCGGAGGATCTGGCGGCGGAGGCAGTGGAGGCGGCGGAAGCGCT
TCCGACACCGGCCGCCCTTTCGTGGAGATGTACTCCGAGATCCCTGAGATCATCCACATGACCGAGGGCCGCGAGCT
GGTGATCCCTTGCCGCGTGACCTCCCCTAACATCACCGTGACCCTGAAGAAGTTCCCTCTGGACACCCTGATCCCTG
ACGGCAAGCGCATCATCTGGGACTCCCGCAAGGGCTTCATCATCTCCAACGCCACCTACAAGGAGATCGGCCTGCTG
ACCTGCGAGGCCACCGTGAACGGCCACCTGTACAAGACCAACTACCTGACCCACCGCCAGACCAACACCATCATCGA
CGTGGTGCTGTCCCCTTCCCACGGCATCGAGCTGTCCGTGGGCGAGAAGCTGGTGCTGAACTGCACCGCCCGCACCG
AGCTGAACGTGGGCATCGACTTCAACTGGGAGTACCCTTCCTCCAAGCACCAGCACAAGAAGCTGGTGAACCGCGAC
CTGAAGACCCAGTCCGGCTCCGAGATGAAGAAGTTCCTGTCCACCCTGACCATCGACGGCGTGACCCGCTCCGACCA
GGGCCTGTACACCTGCGCCGCCTCCTCCGGCCTGATGACCAAGAAGAACTCCACCTTCGTGCGCGTGCACGAGAAGT
AAGTCGAC

[0229] 融合蛋白BY24.13(κ,IgG4)的重链-VID融合亚基(BY24.13H)氨基酸序列(SEQ ID NO:115)：

[0230] METDTLLLWVLLLWVPGSTGQVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMG
LIIPMFDTAGYAQKFQGRVAITVDESTSTAYMELSSLRSEDTAVYYCARAEHSSTGTFDYWGQGTLVTVSSASTKGP
SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTC
NVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVD
GVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHN
HYTQKSLSLSLGGGGSGGGGSGGGGSASDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLKKFPLDTLI

PDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGIELSVGEKLVLNCTAR
TELNVGIDFNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHE
K

[0231] 融合蛋白BY24.14(κ,IgG4)的轻链亚基(BY24.14L)核苷酸序列(SEQ ID NO:116)：

[0232] CTCGAGGCCACCATGGAGACCGACACACTCCTCCTGTGGGTGCTGCTGCTGTGGGTGCCTGGCTCCACT
GGCCAGAGCGCTCTCACTCAGCCTGCTTCCGTGTCTGGAAGTCCCGGCCAGAGTATCACTATTTCTTGTACAGGAAC
TTCCTCCGACGTCGGATTTTACAATTACGTCAGTTGGTATCAGCAGCACCCCGGAAAGGCACCTGAACTAATGATCT
ACGATGTGTCTAACCGCCCAAGCGGCGTGAGCGATAGGTTCAGTGGCAGTAAGAGTGGCAACACCGCATCCCTGACC
ATTAGTGGATTACAGGCCGAGGACGAGGCTGATTACTACTGTTCTAGCTACACAAATATCTCCACATGGGTCTTCGG
CGGAGGAACATTCGGCGGCGGAACTAAGGTGGAGATTAAGAGAACCGTGGCCGCCCCCAGCGTGTTCATCTTCCCTC
CCAGCGACGAGCAGCTGAAGTCTGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCAAG
GTGCAGTGGAAGGTGGACAACGCCCTGCAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACTCCAAGGACAG
CACCTACAGCCTGAGCAGCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGA
CCCACCAGGGACTGTCTAGCCCCGTGACCAAGAGCTTCAACCGGGGCGAGTGCTAAGAATTC

[0233] 融合蛋白BY24.14(κ,IgG4)的轻链亚基(BY24.14L)氨基酸序列(SEQ ID NO:117)：

[0234] METDTLLLWVLLLWVPGSTGQSALTQPASVSGSPGQSITISCTGTSSDVGFYNYVSWYQQHPGKAPELM
IYDVSNRPSGVSDRFSGSKSGNTASLTISGLQAEDEADYYCSSYTNISTWVFGGGTKVEIKRTVAAPSVFIFPPSDE
QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[0235] 融合蛋白BY24.14(κ,IgG4)的重链-VID融合亚基(BY24.14H)核苷酸序列(SEQ ID NO:118)：

[0236] TCTAGAGCCACCATGGAGACCGACACCCTGCTGCTGTGGGTGCTGCTCCTGTGGGTGCCTGGCTCCACA
GGCCAGCTCCAGCTTCAGGAGAGCGGACCCGGCCTGGTCAAGCCATCCGAGACTCTCACTCTGACATGCACCGTGAG
TGCTGATTCTATCAGTTCCACAACTTACTACTGGGTGTGGATTAGGCAGCCTCCCGGAAAGGGATTAGAATGGATCG
GCAGCATTTCTTACAGTGGCTCCACATACTACAATCCTAGTCTGAAGTCTCGCGTGACCGTGTCCGTGGATACATCT
AAGAACCAGTTTAGCCTCAAGCTGAATAGCGTCGCCGCAACAGATACCGCTCTGTACTACTGCGCACGCCACCTCGG
CTACAATGGACGCTATCTGCCCTTCGATTACTGGGGCCAGGGAAGCACCCTCGTGACAGTGTCTTCCGCCTCCACCA
AGGGCCCTTCCGTGTTCCCTCTGGCCCCTTGCTCCCGCTCCACCTCCGAGTCCACCGCCGCCCTGGGCTGCCTGGTG
AAGGACTACTTCCCTGAGCCTGTGACCGTGTCCTGGAACTCCGGCGCCCTGACCTCCGGCGTGCACACCTTCCCTGC
CGTGCTGCAGTCCTCCGGCCTGTACTCCCTGTCCTCCGTGGTGACCGTGCCTTCCTCCTCCCTGGGCACCAAGACCT
ACACCTGCAACGTGGACCACAAGCCTTCCAACACCAAGGTGGACAAGCGCGTGGAGTCCAAGTACGGCCCTCCTTGC
CCTCCTTGCCCTGCCCCTGAGTTCCTGGGCGGCCCTTCCGTGTTCCTGTTCCCTCCTAAGCCTAAGGACACCCTGAT
GATCTCCCGCACCCCTGAGGTGACCTGCGTGGTGGTGGACGTGTCCCAGGAGGACCCTGAGGTGCAGTTCAACTGGT
ACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCAAGCCTCGCGAGGAGCAGTTCAACTCCACCTACCGCGTGGTG
TCCGTGCTGACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGTCCAACAAGGGCCTGCC
TTCCTCCATCGAGAAGACCATCTCCAAGGCCAAGGGCCAGCCTCGCGAGCCTCAGGTGTACACCCTGCCTCCTTCCC
AGGAGGAGATGACCAAGAACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTACCCTTCCGACATCGCCGTGGAG
TGGGAGTCCAACGGCCAGCCTGAGAACAACTACAAGACCACCCCTCCTGTGCTGGACTCCGACGGCTCCTTCTTCCT
GTACTCCCGCCTGACCGTGGACAAGTCCCGCTGGCAGGAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCC

TGCACAACCACTACACCCAGAAGTCCCTGTCCCTGTCCCTGGGCGGCGGAGGATCTGGCGGCGGAGGCAGTGGAGGC
GGCGGAAGCGCTTCCGACACCGGCCGCCCTTTCGTGGAGATGTACTCCGAGATCCCTGAGATCATCCACATGACCGA
GGGCCGCGAGCTGGTGATCCCTTGCCGCGTGACCTCCCCTAACATCACCGTGACCCTGAAGAAGTTCCCTCTGGACA
CCCTGATCCCTGACGGCAAGCGCATCATCTGGGACTCCCGCAAGGGCTTCATCATCTCCAACGCCACCTACAAGGAG
ATCGGCCTGCTGACCTGCGAGGCCACCGTGAACGGCCACCTGTACAAGACCAACTACCTGACCCACCGCCAGACCAA
CACCATCATCGACGTGGTGCTGTCCCCTTCCCACGGCATCGAGCTGTCCGTGGGCGAGAAGCTGGTGCTGAACTGCA
CCGCCCGCACCGAGCTGAACGTGGGCATCGACTTCAACTGGGAGTACCCTTCCTCCAAGCACCAGCACAAGAAGCTG
GTGAACCGCGACCTGAAGACCCAGTCCGGCTCCGAGATGAAGAAGTTCCTGTCCACCCTGACCATCGACGGCGTGAC
CCGCTCCGACCAGGGCCTGTACACCTGCGCCGCCTCCTCCGGCCTGATGACCAAGAAGAACTCCACCTTCGTGCGCG
TGCACGAGAAGTAAGTCGAC

[0237] 融合蛋白BY24.14(κ,IgG4)的重链-VID融合亚基(BY24.14H)氨基酸序列(SEQ ID NO:119)：

[0238] METDTLLLWVLLLWVPGSTGQLQLQESGPGLVKPSETLTLTCTVSADSISSTTYYWVWIRQPPGKGLEW
IGSISYSGSTYYNPSLKSRVTVSVDTSKNQFSLKLNSVAATDTALYYCARHLGYNGRYLPFDYWGQGSTLVTVSSAS
TKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTK
TYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN
WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPP
SQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHE
ALHNHYTQKSLSLSLGGGGSGGGGSGGGGSASDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLKKFPL
DTLIPDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGIELSVGEKLVLN
CTARTELNVGIDFNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFV
RVHEK

[0239] 其中氨基酸序列“METDTLLLWVLLLWVPGSTG”为信号肽。

[0240] 使用上述实施例1(1)相同的方法，分别通过XhoI-EcoRI双酶切将BY24.3L、BY24.4L、LBY24.5L、BY24.6L、BY24.7L、BY24.8L、BY24.9L、BY24.10L、BY24.11L、BY24.12L、BY24.13L和BY24.14L编码核苷酸连接至具有双表达盒的谷氨酰胺合成酶高效表达载体(专利授权号：CN104195173B，获自北京比洋生物技术有限公司)；再通过XbaI-SalI双酶切将BY24.3H、BY24.4H、LBY24.5H、BY24.6H、BY24.7H、BY24.8H、BY24.9H、BY24.10H、BY24.11H、BY24.12H、BY24.13H和BY24.14H编码核苷酸分别克隆至已连接了相应的融合蛋白轻链亚基编码核苷酸的具有双表达盒的谷氨酰胺合成酶高效表达载体；或者反之亦然。将重组载体测序验证正确后用于表达。所表达的双靶向融合蛋白分别命名为融合蛋白BY24.3、BY24.4、BY24.5、BY24.6、BY24.7、BY24.8、BY24.9、BY24.10、BY24.11、BY24.12、BY24.13和BY24.14。

[0241] 实施例2、融合蛋白的表达和纯化

[0242] (1)融合蛋白的瞬时表达

[0243] 将293F(购自Invitrogen公司，目录号：11625-019)细胞悬浮培养于无血清CD 293培养液(购自Invitrogen公司，目录号：11913-019)中。转染前离心细胞培养物，获得细胞沉淀，用新鲜的无血清CD 293培养液悬浮细胞，将细胞浓度调整为1×10^6个细胞/ml。将细胞悬浮液置于摇瓶中。以100ml细胞悬浮液为例，分别将实施例1制备的重组表达载体质粒DNA 250ug和聚乙烯亚胺(polyethylenimine(PEI))(Sigma，目录号：408727)500ug加入1ml无血

清CD 293培养液中混匀,室温静置8分钟后,将PEI/DNA混悬液逐滴加入放置有100ml细胞悬浮液的摇瓶中。轻轻混匀,置于5%CO_2、37℃摇床培养(120转/分钟)。5天后收集培养上清。

[0244] 根据同样的方法,瞬时表达产生作为对照的抗体BY18.1和作为对照的蛋白301-8。

[0245] (2)表达蛋白的纯化

[0246] 用pH 7.4 PBS溶液平衡的HiTrap MabSelect SuRe 1ml柱(GE Healthcare Life Sciences产品,目录号:11-0034-93)纯化上述实施例2(1)收集的培养上清中存在的融合蛋白。简而言之,用pH 7.4的PBS溶液以10个柱床体积平衡HiTrap MabSelect SuRe 1ml柱,流速为0.5ml/分钟;将上述实施例2(1)收集的培养上清用0.45μm滤膜过滤后,载样至用pH 7.4 PBS溶液平衡的HiTrap MabSelect SuRe 1ml柱;装载上清液后,将该柱首先用pH 7.4的PBS溶液以流速0.5ml/分钟洗涤5-10个柱床体积,并随后用100mM柠檬酸缓冲液(pH 4.0)以流速0.5ml/分钟洗脱。收集洗脱峰,目的蛋白存在于洗脱峰中。

[0247] 在还原剂(5mM 1,4-二硫苏糖醇)存在下通过SDS-PAGE并用考马斯蓝染色,分析融合蛋白的纯度和分子量。结果如图2所示。分子量理论预测值与实际测定值见表5。因真核表达系统中存在对蛋白质的糖基化作用,故分子量实际测定值略高于理论预测值。

[0248] 表5经纯化的表达蛋白的分子量大小

[0249]

蛋白质名称	亚单位	理论预测分子量大小(kDa)	实际分子量大小(kDa)
蛋白 301-8	-	49	62
抗体 BY18.1	轻链	23	25
	重链	48	50
融合蛋白 BY24.7	轻链亚基	23	25
	重链-VID 融合亚基	62	70
融合蛋白 BY24.3、BY24.4、LBY24.5、BY24.6、BY24.8、BY24.9、BY24.10、BY24.11、Y24.12、BY24.13和 BY24.14	轻链亚基	23	25
	重链-VID 融合亚基	72	80

[0250] 实施例3、使用ELISA方法检测本发明的融合蛋白与人PD-1和重组人VEGF-A的结合

[0251] 将抗原PD-1(北京义翘神州生物技术有限公司产品,目录号:10377-H08H)和抗原$VEGF_{165}$(北京义翘神州生物技术有限公司产品,目录号:11066-HNAH)稀释至0.5μg/ml和0.02μg/ml并分别包被96孔ELISA板(购自Corning公司,货号:42592)。将上述实施例2(2)纯化的双靶向融合蛋白稀释至5μg/ml,然后进行3倍系列稀释,共稀释9个梯度,对每个浓度梯度进行复孔检测。将稀释样品50μl分别加入经抗原PD-1或抗原$VEGF_{165}$包被的96孔板中,37℃孵育2小时。洗涤3次后,加入辣根过氧化物酶标记的山羊抗人二级抗体(北京中衫金桥公司产品,产品号:ZDR-5301),37℃孵育1小时。洗涤3次后,加入3,3',5,5'-四甲基联苯胺(TMB)底物显色液(北京康为世纪生物科技有限公司,产品号:CW0050)50μl/孔。10分钟后,加入2N的H_2SO_4终止显色。使用ELISA读数仪在450nm处测定每孔的吸光度OD值。对作为对照

的抗体BY18.1、作为对照的蛋白301-8实施同样的ELISA操作。

[0252] ELISA结果显示，与作为对照的抗体BY18.1同样地，本发明的融合蛋白BY24.3、BY24.4、BY24.5、BY24.6、BY24.7、BY24.8、BY24.9、BY24.10、BY24.11、BY24.12、BY24.13、BY24.14能特异性地结合PD-1；与作为对照的蛋白301-8同样地，本发明的融合蛋白BY24.3、BY24.4、LBY24.5、BY24.6、BY24.7、BY24.8、BY24.9、BY24.10、BY24.11、BY24.12、BY24.13、BY24.14也能特异性地结合VEGF-A。

[0253] 应用GraphPadPrism5软件，将各融合蛋白的蛋白质浓度对吸光度OD值作图，并且拟合数据以产生融合蛋白介导的特异性结合作用的半数最大有效浓度EC_{50}值。结果如下表6所示。

[0254] 表6本发明的融合蛋白对PD-1、VEGF-A的结合作用

[0255]

蛋白质名称	对 PD-1 的结合 EC_{50} (μg/ml)	对 $VEGF_{165}$ 的结合 EC_{50} (μg/ml)
融合蛋白 BY24.3	3.991	0.1313
融合蛋白 BY24.4	1.236	0.1485
融合蛋白 BY24.5	0.5763	0.2099
融合蛋白 BY24.6	9.823	0.1633
融合蛋白 BY24.7	1.358	8.652
融合蛋白 BY24.8	0.322	0.1556

[0256]

融合蛋白 BY24.9	5.613	0.9444
融合蛋白 BY24.10	2.349	0.7762
融合蛋白 BY24.11	0.7454	0.3229
融合蛋白 BY24.12	1.583	0.4544
融合蛋白 BY24.13	5.633	0.1841
融合蛋白 BY24.14	0.7544	1.588
抗体 BY18.1	3.154	不结合
蛋白 301-8	不结合	0.0756

[0257] 根据表6的结果可见，本发明所构建的新型融合蛋白均能够以高亲和力结合PD-1，其中融合蛋白BY24.4、BY24.5、BY24.7、BY24.8、BY24.10、BY24.11、BY24.12、BY24.14以比抗体BY18.1大的、甚至融合蛋白BY24.8以比抗体BY18.1大约10倍的亲和力结合PD-1，融合蛋白BY24.3与抗体BY18.1对PD-1的亲和力基本一致；本发明所构建的新型融合蛋白也均能够以高亲和力结合VEGF-A，其中融合蛋白BY24.3显示与作为对照的蛋白301-8相似的高亲和力结合VEGF-A。

[0258] 实施例4、使用Biacore T100测定本发明的融合蛋白的亲和力

[0259] 在BIAcore®T100仪器(GE Healthcare Biosciences AB,瑞典)上于25℃进行表面等离子体共振测量。

[0260] 首先,通过酰胺偶联将抗IgG抗体(GE Healthcare Life Sciences,目录号:BR-1008-39)共价固定在CM5芯片上。使用60μl N-乙基-N'-(3-二甲基氨基丙基)碳二亚胺盐酸盐(EDC)和60μl N-羟基琥珀酰亚胺(NHS)活化CM5芯片,然后将5μl抗IgG抗体加95μl稀释缓冲液HBST(0.1M HEPES,1.5M NaCl,pH7.4,加0.005%吐温20)经0.2um滤膜过滤后,通过酰胺偶联将抗IgG抗体共价固定在CM5芯片上,产生约9000-14000共振单位(RU)的捕获系统。使用120μl乙醇胺封闭CM5芯片。

[0261] 然后,将实施例2制备的本发明的融合蛋白、抗体BY18.1和蛋白301-8分别稀释为5μg/ml,以流速10μL/分钟注射该稀释液2分钟,将1600RU的实施例2制备的本发明的融合蛋白、抗体BY18.1和蛋白301-8通过各自的Fc区非共价地捕获到CM5芯片表面上。通过与EDC/NHS交联来稳定所得的复合物,以避免在测量和再生期间的基线漂移。

[0262] 分别将结合抗原PD-1(北京义翘神州生物技术有限公司产品,目录号:10377-H08H)、$VEGF_{165}$(北京义翘神州生物技术有限公司产品,目录号:11066-HNAH)、VEGF-B(Biovision产品,目录号:4642-20)和PLGF-1(Biovision产品,目录号:4739-25)配制为如下浓度梯度:7nM、22nm、66nM、200nM、600nM。通过以流速30μl/分钟注射每个浓度180秒,解离时间600秒,测量结合。通过用3M $MgCl_2$溶液以流速10μL/分钟洗涤30秒使表面再生。使用BIA评价软件(BIAevaluation 4.1software,来自GE Healthcare Biosciences AB,瑞典)进行数据分析,获得下表7所示的亲和力数据。

[0263] 表7各蛋白质与VEGF家族分子、PD-1的结合

[0264]

蛋白质名称	靶标	ka (1/Ms)	kd (1/s)	KD (M)
融合蛋白 BY24.3	PD-1	6.35E+05	1.78 E-03	2.80 E-09
	VEGF-A	1.94E+07	1.86E-04	9.59E-12
	VEGF-B	4.62E+05	5.69E-04	1.23 E-09
	PLGF-1	5.33E+06	9.68E-04	1.82E-10
融合蛋白 BY 24.7	PD-1	1.15E+06	2.52 E-03	2.19 E-09
	VEGF-A	5.73E+04	1.72 E-03	3.02E-08
	VEGF-B	ND	ND	ND
	PLGF-1	ND	ND	ND
抗体 BY18.1	PD-1	1.76E+05	5.18E-04	2.94E-09
	VEGF-A	ND	ND	ND
	VEGF-B	ND	ND	ND
	PLGF-1	ND	ND	ND
蛋白 301-8	PD-1	无结合	无结合	无结合
	VEGF-A	5.65E+07	1.55E-04	2.74E-12
	VEGF-B	7.82E+05	3.79E-04	4.84 E-10
	PLGF-1	6.95E+06	4.88E-04	7.02E-11

[0265] 注:ND:未检测

[0266] 根据表7所示的数据可见,融合蛋白BY24.3以高的亲和力与VEGF-A、VEGF-B和PLGF-1结合,亲和力分别达到9.59×10^{-12}M、1.23×10^{-9}M和1.82×10^{-10}M,且对PD-1的亲和力(KD)与作为对照的抗体BY18.1基本一致,融合蛋白BY24.7以比抗体BY18.1大的亲和力(KD)结合PD-1;融合蛋白BY24.3显示与作为对照的蛋白301-8相似的高亲和力结合VEGF-A;融合蛋白BY24.3也以高亲和力结合VEGF-B和PLGF-1。

[0267] 由此表明了本发明的双靶向融合蛋白以与抗PD-1抗体类似的、或者更好的亲和力与PD-1结合,并具有极好的与多种VEGF结合的能力。

[0268] 表7的结果也表明了:实施例4的通过表面等离子体共振(SPR)技术测定的亲和力结果与实施例3的通过ELISA测定的亲和力结果呈现高度一致性。

[0269] 实施例5、本发明的融合蛋白在人源化B-hPD-1小鼠模型中对肿瘤生长的抑制作用

[0270] 将0.1mL DMEM培养基中的5×10^{5}个MC38鼠结肠癌细胞(获自ATCC,美国)接种于体重约18g,6周龄雌性B-hPD-1人源化小鼠(获自北京百奥赛图基因生物技术有限公司,产品编号:B-CM-001)右侧前胁肋部皮下。肿瘤在所述小鼠体内长大。待肿瘤体积达到约108mm^3时将荷瘤小鼠随机分组,每组6只,共4组,分别为:PBS溶剂对照组、蛋白301-8组(3.3mg/kg)、融合蛋白BY24.3组(6.4mg/kg)和抗体BY18.1组(5mg/kg),各给药组剂量以抗体BY18.1

组的剂量为标准，对蛋白301-8组、融合蛋白BY24.3组和抗体BY18.1组而言所施用的剂量在摩尔量上是等同的。将第一次给药的时间设定为第0天。所有组给药途径均为腹腔(i.p.)注射，每三天给药1次，连续给药6次，末次给药3天后结束实验。每周测量肿瘤体积及小鼠体重2次，记录小鼠体重和肿瘤体积。实验结束时，将动物安乐死，剥取肿瘤称重、拍照，计算肿瘤生长抑制率(Tumor Growth Inhibition%)和肿瘤重量抑制率(Inhibition Rate of Tumor Weight%)。计算TGI%使用的公式是：[1－(给药组肿瘤体积变化的均值/PBS溶剂对照组肿瘤体积变化的均值)]x100%，计算IRTW%使用的公式是：[1－(给药组肿瘤重量/PBS溶剂对照组肿瘤重量)]x100%。该实验在北京百奥赛图基因生物技术有限公司实施。

[0271] 结果见图3和图4。本实验观察了本发明的融合蛋白BY24.3以及作为药物对照的抗体BY18.1、蛋白301-8对MC38小鼠结肠癌皮下移植瘤生长的抑制作用。

[0272] 整个实验过程中，所有动物精神状态良好，无动物死亡。实验结束时(首次给药后的第21天)，各组动物体重平均约为19g。将本发明的融合蛋白BY24.3组以及作为药物对照的抗体BY18.1组、蛋白301-8组的动物与PBS溶剂对照组动物进行体重比较，没有显著性差异(P>0.05)，表明动物对本发明的融合蛋白BY24.3耐受良好(图3)。

[0273] 实验结束时，PBS溶剂对照组平均肿瘤体积±标准误为1386±170mm^3，而融合蛋白BY24.3和蛋白301-8组平均肿瘤体积±标准误分别为452±69、1023±256，TGI%分别为73.3%、28.1%，IRTW%分别为74.6%、25.7%。融合蛋白BY24.3与PBS溶剂对照组的肿瘤体积相比有明显差异(P<0.05)，表明融合蛋白BY24.3有显著的肿瘤抑制作用。蛋白301-8有一定的肿瘤抑制作用，但是与PBS溶剂对照组相比，未见显著性差异(P>0.05)。作为对照的抗体BY18.1平均肿瘤体积±标准误为739±128，TGI%为50.6%，IRTW%为46.0%，与PBS溶剂对照组的肿瘤体积相比有显著差异(P<0.05)。融合蛋白BY24.3显示极佳的肿瘤抑制作用，与作为药物对照的抗体BY18.1组、蛋白301-8组的肿瘤抑制作用相比较，具有显著性差异。本实验的抗肿瘤药效结果在对小鼠肿瘤称重的比较上也得到进一步证实。

[0274] 表8在人源化B-hPD-1小鼠模型中对肿瘤生长的抑制作用比较

[0275]

组别	平均肿瘤体积±标准误	肿瘤生长抑制率（TGI%）	肿瘤重量抑制率（IRTW%）
溶剂对照组	1386 ± 170 mm^3	-	-
蛋白 301-8 对照组	1023 ±256 mm^3	28.1%	25.7%
抗体 BY18.1 对照组	739 ± 128 mm^3	50.6%	46.0%
融合蛋白 BY24.3 组	452 ± 69 mm^3	73.3%	74.6%

[0276] 尽管已经出于说明本发明的目的显示了某些代表性实施方案和细节，但是本领域技术人员显而易见的是可以对它们进行多种变化和修改而不脱离主题发明的范围。在这个方面，本发明范围仅由以下权利要求限定。

[0001] 序列表

[0002] <110> 北京比洋生物技术有限公司

[0003] <120> 靶向PD-1或PD-L1且靶向VEGF家族的双靶向融合蛋白及其用途

[0004] <130>

[0005] <160> 121

[0006] <170> PatentIn版本3.3

[0007] <210> 1

[0008] <211> 106

[0009] <212> PRT

[0010] <213> 人工序列

[0011] <220>

[0012] <223> 融合蛋白中的一种抗PD-1抗体的重链可变区

[0013] <400> 1

[0014] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg

[0015] 1 5 10 15

[0016] Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe Ser Asn Ser

[0017] 20 25 30

[0018] Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

[0019] 35 40 45

[0020] Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser Val

[0021] 50 55 60

[0022] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe

[0023] 65 70 75 80

[0024] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

[0025] 85 90 95

[0026] Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly

[0027] 100 105

[0028] <210> 2

[0029] <211> 101

[0030] <212> PRT

[0031] <213> 人工序列

[0032] <220>

[0033] <223> 融合蛋白中的一种抗PD-1抗体的轻链可变区

[0034] <400> 2

[0035] Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly

[0036] 1 5 10 15

[0037] Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr

[0038] 20 25 30

[0039] Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile

[0040] 35 40 45

[0041] Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly

[0042] 50 55 60

[0043] Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro

[0044] 65 70 75 80

[0045] Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Ser Asn Trp Pro Arg

[0046] 85 90 95

[0047] Thr Phe Gly Gln Gly

[0048] 100

[0049] <210> 3

[0050] <211> 113

[0051] <212> PRT

[0052] <213> 人工序列

[0053] <220>

[0054] <223> 融合蛋白中的一种抗PD-1抗体的重链可变区

[0055] <400> 3

[0056] Gln Val Gln Leu Val Gln Ser Gly Val Glu Val Lys Lys Pro Gly Ala

[0057] 1 5 10 15

[0058] Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr

[0059] 20 25 30

[0060] Tyr Met Tyr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met

[0061] 35 40 45

[0062] Gly Gly Ile Asn Pro Ser Asn Gly Gly Thr Asn Phe Asn Glu Lys Phe

[0063] 50 55 60

[0064] Lys Asn Arg Val Thr Leu Thr Thr Asp Ser Ser Thr Thr Thr Ala Tyr

[0065] 65 70 75 80

[0066] Met Glu Leu Lys Ser Leu Gln Phe Asp Asp Thr Ala Val Tyr Tyr Cys

[0067] 85 90 95

[0068] Ala Arg Arg Asp Tyr Arg Phe Asp Met Gly Phe Asp Tyr Trp Gly Gln

[0069] 100 105 110

[0070] Gly

[0071] <210> 4

[0072] <211> 105

[0073] <212> PRT

[0074] <213> 人工序列

[0075] <220>

[0076] <223> 融合蛋白中的一种抗PD-1抗体的轻链可变区

[0077] <400> 4

[0078] Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly

[0079] 1 5 10 15

[0080] Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys Gly Val Ser Thr Ser

[0081] 20 25 30

[0082] Gly Tyr Ser Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro

[0083] 35 40 45

[0084] Arg Leu Leu Ile Tyr Leu Ala Ser Tyr Leu Glu Ser Gly Val Pro Ala
[0085] 50 55 60
[0086] Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
[0087] 65 70 75 80
[0088] Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Ser Arg
[0089] 85 90 95
[0090] Asp Leu Pro Leu Thr Phe Gly Gly Gly
[0091] 100 105
[0092] <210> 5
[0093] <211> 110
[0094] <212> PRT
[0095] <213> 人工序列
[0096] <220>
[0097] <223> 融合蛋白中的一种抗PD-1抗体的重链可变区
[0098] <400> 5
[0099] Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
[0100] 1 5 10 15
[0101] Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
[0102] 20 25 30
[0103] Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Gln Trp Met
[0104] 35 40 45
[0105] Gly Trp Ile Asn Thr Asp Ser Gly Glu Ser Thr Tyr Ala Glu Glu Phe
[0106] 50 55 60
[0107] Lys Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Asn Thr Ala Tyr
[0108] 65 70 75 80
[0109] Leu Gln Ile Thr Ser Leu Thr Ala Glu Asp Thr Gly Met Tyr Phe Cys
[0110] 85 90 95
[0111] Val Arg Val Gly Tyr Asp Ala Leu Asp Tyr Trp Gly Gln Gly
[0112] 100 105 110
[0113] <210> 6
[0114] <211> 100
[0115] <212> PRT
[0116] <213> 人工序列
[0117] <220>
[0118] <223> 融合蛋白中的一种抗PD-1抗体的轻链可变区
[0119] <400> 6
[0120] Glu Ile Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
[0121] 1 5 10 15
[0122] Asp Arg Val Thr Ile Thr Cys Ser Ala Arg Ser Ser Val Ser Tyr Met
[0123] 20 25 30
[0124] His Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Trp Ile Tyr
[0125] 35 40 45

[0126] Arg Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
[0127] 50 55 60
[0128] Gly Ser Gly Thr Ser Tyr Cys Leu Thr Ile Asn Ser Leu Gln Pro Glu
[0129] 65 70 75 80
[0130] Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Ser Phe Pro Leu Thr
[0131] 85 90 95
[0132] Phe Gly Gly Gly
[0133] 100
[0134] <210> 7
[0135] <211> 109
[0136] <212> PRT
[0137] <213> 人工序列
[0138] <220>
[0139] <223> 融合蛋白中的一种抗PD-1抗体的重链可变区
[0140] <400> 7
[0141] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[0142] 1 5 10 15
[0143] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
[0144] 20 25 30
[0145] Met Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[0146] 35 40 45
[0147] Ala Thr Ile Ser Gly Gly Gly Ala Asn Thr Tyr Tyr Pro Asp Ser Val
[0148] 50 55 60
[0149] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[0150] 65 70 75 80
[0151] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[0152] 85 90 95
[0153] Ala Arg Gln Leu Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly
[0154] 100 105
[0155] <210> 8
[0156] <211> 101
[0157] <212> PRT
[0158] <213> 人工序列
[0159] <220>
[0160] <223> 融合蛋白中的一种抗PD-1抗体的轻链可变区
[0161] <400> 8
[0162] Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
[0163] 1 5 10 15
[0164] Asp Arg Val Thr Ile Thr Cys Leu Ala Ser Gln Thr Ile Gly Thr Trp
[0165] 20 25 30
[0166] Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
[0167] 35 40 45

[0168] Tyr Thr Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
[0169] 50 55 60
[0170] Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
[0171] 65 70 75 80
[0172] Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Val Tyr Ser Ile Pro Trp
[0173] 85 90 95
[0174] Thr Phe Gly Gly Gly
[0175] 100
[0176] <210> 9
[0177] <211> 114
[0178] <212> PRT
[0179] <213> 人工序列
[0180] <220>
[0181] <223> 融合蛋白中的一种抗PD-1抗体的重链可变区
[0182] <400> 9
[0183] Gln Val Thr Leu Lys Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
[0184] 1 5 10 15
[0185] Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
[0186] 20 25 30
[0187] Gly Thr Cys Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
[0188] 35 40 45
[0189] Trp Leu Ala Thr Ile Cys Trp Glu Asp Ser Lys Gly Tyr Asn Pro Ser
[0190] 50 55 60
[0191] Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Ala
[0192] 65 70 75 80
[0193] Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
[0194] 85 90 95
[0195] Cys Ala Arg Arg Glu Asp Ser Gly Tyr Phe Trp Phe Pro Tyr Trp Gly
[0196] 100 105 110
[0197] Gln Gly
[0198] <210> 10
[0199] <211> 100
[0200] <212> PRT
[0201] <213> 人工序列
[0202] <220>
[0203] <223> 融合蛋白中的一种抗PD-1抗体的轻链可变区
[0204] <400> 10
[0205] Asn Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
[0206] 1 5 10 15
[0207] Asp Arg Val Thr Ile Thr Cys Lys Ala Gly Gln Asn Val Asn Asn Tyr
[0208] 20 25 30
[0209] Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Val Leu Ile

[0210] 35 40 45

[0211] Phe Asn Ala Asn Ser Leu Gln Thr Gly Val Pro Ser Arg Phe Ser Gly

[0212] 50 55 60

[0213] Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro

[0214] 65 70 75 80

[0215] Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Trp Thr Thr

[0216] 85 90 95

[0217] Phe Gly Gly Gly

[0218] 100

[0219] <210> 11

[0220] <211> 111

[0221] <212> PRT

[0222] <213> 人工序列

[0223] <220>

[0224] <223> 融合蛋白中的一种抗PD-1抗体的重链可变区

[0225] <400> 11

[0226] Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu

[0227] 1 5 10 15

[0228] Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ser Tyr

[0229] 20 25 30

[0230] Gly Val His Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu

[0231] 35 40 45

[0232] Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys

[0233] 50 55 60

[0234] Ser Arg Leu Thr Ile Ser Lys Asp Asn Ser Lys Ser Gln Val Ser Leu

[0235] 65 70 75 80

[0236] Lys Met Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala

[0237] 85 90 95

[0238] Arg Ala Tyr Gly Asn Tyr Trp Tyr Ile Asp Val Trp Gly Gln Gly

[0239] 100 105 110

[0240] <210> 12

[0241] <211> 101

[0242] <212> PRT

[0243] <213> 人工序列

[0244] <220>

[0245] <223> 融合蛋白中的一种抗PD-1抗体的轻链可变区

[0246] <400> 12

[0247] Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly

[0248] 1 5 10 15

[0249] Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Gln Ser Val Ser Asn Asp

[0250] 20 25 30

[0251] Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile

[0252] 35 40 45

[0253] Asn Tyr Ala Phe His Arg Phe Thr Gly Val Pro Asp Arg Phe Ser Gly

[0254] 50 55 60

[0255] Ser Gly Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala

[0256] 65 70 75 80

[0257] Glu Asp Val Ala Val Tyr Tyr Cys His Gln Ala Tyr Ser Ser Pro Tyr

[0258] 85 90 95

[0259] Thr Phe Gly Gly Gly

[0260] 100

[0261] <210> 13

[0262] <211> 105

[0263] <212> PRT

[0264] <213> 人工序列

[0265] <220>

[0266] <223> 融合蛋白中的一种抗PD-1抗体的重链可变区

[0267] <400> 13

[0268] Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser

[0269] 1 5 10 15

[0270] Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe Ser Asn Tyr Gly

[0271] 20 25 30

[0272] Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala

[0273] 35 40 45

[0274] Val Ile Trp Tyr Asp Ser Ser Arg Lys Tyr Tyr Ala Asp Ser Val Lys

[0275] 50 55 60

[0276] Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe Leu

[0277] 65 70 75 80

[0278] Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala

[0279] 85 90 95

[0280] Thr Asn Asn Asp Tyr Trp Gly Gln Gly

[0281] 100 105

[0282] <210> 14

[0283] <211> 101

[0284] <212> PRT

[0285] <213> 人工序列

[0286] <220>

[0287] <223> 融合蛋白中的一种抗PD-1抗体的轻链可变区

[0288] <400> 14

[0289] Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly

[0290] 1 5 10 15

[0291] Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Ser Asn Tyr

[0292] 20 25 30

[0293] Leu Asp Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile

[0294] 35 40 45

[0295] Tyr Asp Ala Ser Thr Arg Ala Thr Gly Val Pro Ser Arg Phe Ser Gly

[0296] 50 55 60

[0297] Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro

[0298] 65 70 75 80

[0299] Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Asn Met Gln Leu Pro Leu

[0300] 85 90 95

[0301] Thr Phe Gly Gln Gly

[0302] 100

[0303] <210> 15

[0304] <211> 113

[0305] <212> PRT

[0306] <213> 人工序列

[0307] <220>

[0308] <223> 融合蛋白中的一种抗PD-1抗体的重链可变区

[0309] <400> 15

[0310] Asp Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val

[0311] 1 5 10 15

[0312] Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Gly Ile

[0313] 20 25 30

[0314] Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Trp

[0315] 35 40 45

[0316] Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu Gln Gly

[0317] 50 55 60

[0318] Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr Met Glu

[0319] 65 70 75 80

[0320] Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys Ala Arg

[0321] 85 90 95

[0322] Gly Arg Gly Tyr Ser Tyr Gly Ile Asp Ala Phe Asp Ile Trp Gly Gln

[0323] 100 105 110

[0324] Gly

[0325] <210> 16

[0326] <211> 103

[0327] <212> PRT

[0328] <213> 人工序列

[0329] <220>

[0330] <223> 融合蛋白中的一种抗PD-1抗体的轻链可变区

[0331] <400> 16

[0332] Leu Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ser Pro Gly

[0333] 1 5 10 15

[0334] Gln Thr Ala Arg Ile Thr Cys Ser Gly Asp Ala Leu Pro Lys Gln Tyr

[0335] 20 25 30

[0336] Ala Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile
[0337] 35 40 45
[0338] Tyr Lys Asp Ser Glu Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly
[0339] 50 55 60
[0340] Ser Ser Ser Gly Thr Thr Val Thr Leu Thr Ile Ser Gly Val Gln Ala
[0341] 65 70 75 80
[0342] Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Ala Asp Ser Ser Gly Thr
[0343] 85 90 95
[0344] Tyr Val Val Phe Gly Gly Gly
[0345] 100
[0346] <210> 17
[0347] <211> 118
[0348] <212> PRT
[0349] <213> 人工序列
[0350] <220>
[0351] <223> 融合蛋白中的一种抗PD-1抗体的重链可变区
[0352] <400> 17
[0353] Gln Gly Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
[0354] 1 5 10 15
[0355] Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
[0356] 20 25 30
[0357] Glu Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
[0358] 35 40 45
[0359] Gly Val Ile Glu Ser Glu Thr Gly Gly Thr Ala Tyr Asn Gln Lys Phe
[0360] 50 55 60
[0361] Gln Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
[0362] 65 70 75 80
[0363] Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
[0364] 85 90 95
[0365] Thr Arg Glu Gly Ile Thr Thr Val Ala Thr Thr Tyr Tyr Trp Tyr Phe
[0366] 100 105 110
[0367] Asp Val Trp Gly Gln Gly
[0368] 115
[0369] <210> 18
[0370] <211> 106
[0371] <212> PRT
[0372] <213> 人工序列
[0373] <220>
[0374] <223> 融合蛋白中的一种抗PD-1抗体的轻链可变区
[0375] <400> 18
[0376] Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
[0377] 1 5 10 15

[0378] Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Ile Val His Ser
[0379] 20 25 30
[0380] Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
[0381] 35 40 45
[0382] Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
[0383] 50 55 60
[0384] Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
[0385] 65 70 75 80
[0386] Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln Gly
[0387] 85 90 95
[0388] Ser His Val Pro Leu Thr Phe Gly Gln Gly
[0389] 100 105
[0390] <210> 19
[0391] <211> 111
[0392] <212> PRT
[0393] <213> 人工序列
[0394] <220>
[0395] <223> 融合蛋白中的一种抗PD-1抗体的重链可变区
[0396] <400> 19
[0397] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
[0398] 1 5 10 15
[0399] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
[0400] 20 25 30
[0401] Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[0402] 35 40 45
[0403] Ala Thr Ile Ser Gly Gly Gly Ser Asp Thr Tyr Tyr Ala Asp Ser Val
[0404] 50 55 60
[0405] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[0406] 65 70 75 80
[0407] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[0408] 85 90 95
[0409] Ala Arg Gln Leu Asn Tyr Ala Trp Phe Ala Tyr Trp Gly Gln Gly
[0410] 100 105 110
[0411] <210> 20
[0412] <211> 105
[0413] <212> PRT
[0414] <213> 人工序列
[0415] <220>
[0416] <223> 融合蛋白中的一种抗PD-1抗体的轻链可变区
[0417] <400> 20
[0418] Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Pro Gly
[0419] 1 5 10 15

[0420] Gln Arg Ala Thr Ile Thr Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr
[0421] 20 25 30
[0422] Gly Ile Ser Phe Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
[0423] 35 40 45
[0424] Lys Leu Leu Ile Tyr Thr Ser Ser Asn Lys Asp Thr Gly Val Pro Ala
[0425] 50 55 60
[0426] Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn
[0427] 65 70 75 80
[0428] Pro Met Glu Ala Glu Asp Thr Ala Val Tyr Tyr Cys Gln Gln Ser Lys
[0429] 85 90 95
[0430] Glu Val Pro Trp Thr Phe Gly Gly Gly
[0431] 100 105
[0432] <210> 21
[0433] <211> 113
[0434] <212> PRT
[0435] <213> 人工序列
[0436] <220>
[0437] <223> 融合蛋白中的一种抗PD-1抗体的重链可变区
[0438] <400> 21
[0439] Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
[0440] 1 5 10 15
[0441] Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
[0442] 20 25 30
[0443] Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
[0444] 35 40 45
[0445] Gly Leu Ile Ile Pro Met Phe Asp Thr Ala Gly Tyr Ala Gln Lys Phe
[0446] 50 55 60
[0447] Gln Gly Arg Val Ala Ile Thr Val Asp Glu Ser Thr Ser Thr Ala Tyr
[0448] 65 70 75 80
[0449] Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
[0450] 85 90 95
[0451] Ala Arg Ala Glu His Ser Ser Thr Gly Thr Phe Asp Tyr Trp Gly Gln
[0452] 100 105 110
[0453] Gly
[0454] <210> 22
[0455] <211> 101
[0456] <212> PRT
[0457] <213> 人工序列
[0458] <220>
[0459] <223> 融合蛋白中的一种抗PD-1抗体的轻链可变区
[0460] <400> 22
[0461] Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly

[0462] 1 5 10 15
[0463] Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
[0464] 20 25 30
[0465] Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
[0466] 35 40 45
[0467] Ser Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
[0468] 50 55 60
[0469] Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
[0470] 65 70 75 80
[0471] Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn His Leu Pro Phe
[0472] 85 90 95
[0473] Thr Phe Gly Gly Gly
[0474] 100
[0475] <210> 23
[0476] <211> 116
[0477] <212> PRT
[0478] <213> 人工序列
[0479] <220>
[0480] <223> 融合蛋白中的一种抗PD-1抗体的重链可变区
[0481] <400> 23
[0482] Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
[0483] 1 5 10 15
[0484] Thr Leu Thr Leu Thr Cys Thr Val Ser Ala Asp Ser Ile Ser Ser Thr
[0485] 20 25 30
[0486] Thr Tyr Tyr Trp Val Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
[0487] 35 40 45
[0488] Trp Ile Gly Ser Ile Ser Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
[0489] 50 55 60
[0490] Leu Lys Ser Arg Val Thr Val Ser Val Asp Thr Ser Lys Asn Gln Phe
[0491] 65 70 75 80
[0492] Ser Leu Lys Leu Asn Ser Val Ala Ala Thr Asp Thr Ala Leu Tyr Tyr
[0493] 85 90 95
[0494] Cys Ala Arg His Leu Gly Tyr Asn Gly Arg Tyr Leu Pro Phe Asp Tyr
[0495] 100 105 110
[0496] Trp Gly Gln Gly
[0497] 115
[0498] <210> 24
[0499] <211> 104
[0500] <212> PRT
[0501] <213> 人工序列
[0502] <220>
[0503] <223> 融合蛋白中的一种抗PD-1抗体的轻链可变区

[0504] <400> 24

[0505] Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln

[0506] 1 5 10 15

[0507] Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Phe Tyr

[0508] 20 25 30

[0509] Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Glu Leu

[0510] 35 40 45

[0511] Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asp Arg Phe

[0512] 50 55 60

[0513] Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu

[0514] 65 70 75 80

[0515] Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Asn Ile

[0516] 85 90 95

[0517] Ser Thr Trp Val Phe Gly Gly Gly

[0518] 100

[0519] <210> 25

[0520] <211> 111

[0521] <212> PRT

[0522] <213> 人工序列

[0523] <220>

[0524] <223> 融合蛋白中的一种抗PD-L1抗体的重链可变区

[0525] <400> 25

[0526] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

[0527] 1 5 10 15

[0528] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ser

[0529] 20 25 30

[0530] Trp Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

[0531] 35 40 45

[0532] Ala Trp Ile Ser Pro Tyr Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val

[0533] 50 55 60

[0534] Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr

[0535] 65 70 75 80

[0536] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

[0537] 85 90 95

[0538] Ala Arg Arg His Trp Pro Gly Gly Phe Asp Tyr Trp Gly Gln Gly

[0539] 100 105 110

[0540] <210> 26

[0541] <211> 101

[0542] <212> PRT

[0543] <213> 人工序列

[0544] <220>

[0545] <223> 融合蛋白中的一种抗PD-L1抗体的轻链可变区

[0546] <400> 26

[0547] Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly

[0548] 1 5 10 15

[0549] Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Thr Ala

[0550] 20 25 30

[0551] Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile

[0552] 35 40 45

[0553] Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly

[0554] 50 55 60

[0555] Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro

[0556] 65 70 75 80

[0557] Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Leu Tyr His Pro Ala

[0558] 85 90 95

[0559] Thr Phe Gly Gln Gly

[0560] 100

[0561] <210> 27

[0562] <211> 114

[0563] <212> PRT

[0564] <213> 人工序列

[0565] <220>

[0566] <223> 融合蛋白中的一种抗PD-L1抗体的重链可变区

[0567] <400> 27

[0568] Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

[0569] 1 5 10 15

[0570] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr

[0571] 20 25 30

[0572] Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

[0573] 35 40 45

[0574] Ala Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val

[0575] 50 55 60

[0576] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr

[0577] 65 70 75 80

[0578] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

[0579] 85 90 95

[0580] Ala Arg Glu Gly Gly Trp Phe Gly Glu Leu Ala Phe Asp Tyr Trp Gly

[0581] 100 105 110

[0582] Gln Gly

[0583] <210> 28

[0584] <211> 102

[0585] <212> PRT

[0586] <213> 人工序列

[0587] <220>

[0588] <223> 融合蛋白中的一种抗PD-L1抗体的轻链可变区

[0589] <400> 28

[0590] Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly

[0591] 1 5 10 15

[0592] Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Arg Val Ser Ser Ser

[0593] 20 25 30

[0594] Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu

[0595] 35 40 45

[0596] Ile Tyr Asp Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser

[0597] 50 55 60

[0598] Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu

[0599] 65 70 75 80

[0600] Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Leu Pro

[0601] 85 90 95

[0602] Trp Thr Phe Gly Gln Gly

[0603] 100

[0604] <210> 29

[0605] <211> 113

[0606] <212> PRT

[0607] <213> 人工序列

[0608] <220>

[0609] <223> 融合蛋白中的一种抗PD-L1抗体的重链可变区

[0610] <400> 29

[0611] Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

[0612] 1 5 10 15

[0613] Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr

[0614] 20 25 30

[0615] Ile Met Met Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

[0616] 35 40 45

[0617] Ser Ser Ile Tyr Pro Ser Gly Gly Ile Thr Phe Tyr Ala Asp Thr Val

[0618] 50 55 60

[0619] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

[0620] 65 70 75 80

[0621] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

[0622] 85 90 95

[0623] Ala Arg Ile Lys Leu Gly Thr Val Thr Thr Val Asp Tyr Trp Gly Gln

[0624] 100 105 110

[0625] Gly

[0626] <210> 30

[0627] <211> 104

[0628] <212> PRT

[0629] <213> 人工序列

[0630] <220>

[0631] <223> 融合蛋白中的一种抗PD-L1抗体的轻链可变区

[0632] <400> 30

[0633] Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln

[0634] 1 5 10 15

[0635] Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr

[0636] 20 25 30

[0637] Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu

[0638] 35 40 45

[0639] Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe

[0640] 50 55 60

[0641] Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu

[0642] 65 70 75 80

[0643] Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Ser

[0644] 85 90 95

[0645] Ser Thr Arg Val Phe Gly Thr Gly

[0646] 100

[0647] <210> 31

[0648] <211> 113

[0649] <212> PRT

[0650] <213> 人工序列

[0651] <220>

[0652] <223> 融合蛋白中的一种抗PD-1抗体的轻链恒定区序列,κ型

[0653] <400> 31

[0654] Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile

[0655] 1 5 10 15

[0656] Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val

[0657] 20 25 30

[0658] Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys

[0659] 35 40 45

[0660] Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu

[0661] 50 55 60

[0662] Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu

[0663] 65 70 75 80

[0664] Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr

[0665] 85 90 95

[0666] His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu

[0667] 100 105 110

[0668] Cys

[0669] <210> 32

[0670] <211> 112

[0671] <212> PRT

[0672] <213> 人工序列

[0673] <220>

[0674] <223> 融合蛋白中的一种抗PD-1抗体的轻链恒定区序列,λ型

[0675] <400> 32

[0676] Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala Pro Ser Val Thr

[0677] 1 5 10 15

[0678] Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu

[0679] 20 25 30

[0680] Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp

[0681] 35 40 45

[0682] Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu Thr Thr Thr Pro

[0683] 50 55 60

[0684] Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu

[0685] 65 70 75 80

[0686] Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr

[0687] 85 90 95

[0688] His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser

[0689] 100 105 110

[0690] <210> 33

[0691] <211> 337

[0692] <212> PRT

[0693] <213> 人工序列

[0694] <220>

[0695] <223> 融合蛋白中的一种抗PD-1抗体的重链恒定区序列,IgG1型

[0696] <400> 33

[0697] Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe

[0698] 1 5 10 15

[0699] Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

[0700] 20 25 30

[0701] Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

[0702] 35 40 45

[0703] Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

[0704] 50 55 60

[0705] Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

[0706] 65 70 75 80

[0707] Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

[0708] 85 90 95

[0709] Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys

[0710] 100 105 110

[0711] Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro

[0712] 115 120 125

[0713] Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser

[0714] 130 135 140

[0715] Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp

[0716] 145 150 155 160

[0717] Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

[0718] 165 170 175

[0719] Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val

[0720] 180 185 190

[0721] Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu

[0722] 195 200 205

[0723] Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys

[0724] 210 215 220

[0725] Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr

[0726] 225 230 235 240

[0727] Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr

[0728] 245 250 255

[0729] Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu

[0730] 260 265 270

[0731] Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu

[0732] 275 280 285

[0733] Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys

[0734] 290 295 300

[0735] Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu

[0736] 305 310 315 320

[0737] Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly

[0738] 325 330 335

[0739] Lys

[0740] <210> 34

[0741] <211> 333

[0742] <212> PRT

[0743] <213> 人工序列

[0744] <220>

[0745] <223> 融合蛋白中的一种抗PD-1抗体的重链恒定区序列,IgG2型

[0746] <400> 34

[0747] Thr Thr Val Thr Val Ser Thr Ala Ser Thr Lys Gly Pro Ser Val Phe

[0748] 1 5 10 15

[0749] Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu

[0750] 20 25 30

[0751] Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp

[0752] 35 40 45

[0753] Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

[0754] 50 55 60

[0755] Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

[0756] 65 70 75 80
[0757] Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro
[0758] 85 90 95
[0759] Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val Glu
[0760] 100 105 110
[0761] Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu
[0762] 115 120 125
[0763] Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
[0764] 130 135 140
[0765] Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln
[0766] 145 150 155 160
[0767] Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
[0768] 165 170 175
[0769] Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu
[0770] 180 185 190
[0771] Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
[0772] 195 200 205
[0773] Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
[0774] 210 215 220
[0775] Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
[0776] 225 230 235 240
[0777] Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
[0778] 245 250 255
[0779] Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
[0780] 260 265 270
[0781] Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly
[0782] 275 280 285
[0783] Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
[0784] 290 295 300
[0785] Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
[0786] 305 310 315 320
[0787] His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[0788] 325 330
[0789] <210> 35
[0790] <211> 334
[0791] <212> PRT
[0792] <213> 人工序列
[0793] <220>
[0794] <223> 融合蛋白中的一种抗PD-1抗体的重链恒定区序列,IgG4型
[0795] <400> 35
[0796] Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
[0797] 1 5 10 15

[0798] Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu
[0799] 20 25 30
[0800] Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
[0801] 35 40 45
[0802] Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
[0803] 50 55 60
[0804] Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
[0805] 65 70 75 80
[0806] Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro
[0807] 85 90 95
[0808] Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro
[0809] 100 105 110
[0810] Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe
[0811] 115 120 125
[0812] Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
[0813] 130 135 140
[0814] Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val
[0815] 145 150 155 160
[0816] Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
[0817] 165 170 175
[0818] Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val
[0819] 180 185 190
[0820] Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
[0821] 195 200 205
[0822] Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser
[0823] 210 215 220
[0824] Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
[0825] 225 230 235 240
[0826] Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
[0827] 245 250 255
[0828] Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
[0829] 260 265 270
[0830] Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
[0831] 275 280 285
[0832] Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp
[0833] 290 295 300
[0834] Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
[0835] 305 310 315 320
[0836] Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
[0837] 325 330
[0838] <210> 36
[0839] <211> 16

[0840] <212> PRT
[0841] <213> 人工序列
[0842] <220>
[0843] <223> 融合蛋白中的一种肽接头
[0844] <400> 36
[0845] Ala Lys Thr Thr Pro Lys Leu Glu Glu Gly Glu Phe Ser Glu Ala Arg
[0846] 1 5 10 15
[0847] <210> 37
[0848] <211> 17
[0849] <212> PRT
[0850] <213> 人工序列
[0851] <220>
[0852] <223> 融合蛋白中的一种肽接头
[0853] <400> 37
[0854] Ala Lys Thr Thr Pro Lys Leu Glu Glu Gly Glu Phe Ser Glu Ala Arg
[0855] 1 5 10 15
[0856] Val
[0857] <210> 38
[0858] <211> 9
[0859] <212> PRT
[0860] <213> 人工序列
[0861] <220>
[0862] <223> 融合蛋白中的一种肽接头
[0863] <400> 38
[0864] Ala Lys Thr Thr Pro Lys Leu Gly Gly
[0865] 1 5
[0866] <210> 39
[0867] <211> 10
[0868] <212> PRT
[0869] <213> 人工序列
[0870] <220>
[0871] <223> 融合蛋白中的一种肽接头
[0872] <400> 39
[0873] Ser Ala Lys Thr Thr Pro Lys Leu Gly Gly
[0874] 1 5 10
[0875] <210> 40
[0876] <211> 6
[0877] <212> PRT
[0878] <213> 人工序列
[0879] <220>
[0880] <223> 融合蛋白中的一种肽接头
[0881] <400> 40

[0882] Ser Ala Lys Thr Thr Pro
[0883] 1 5
[0884] <210> 41
[0885] <211> 6
[0886] <212> PRT
[0887] <213> 人工序列
[0888] <220>
[0889] <223> 融合蛋白中的一种肽接头
[0890] <400> 41
[0891] Arg Ala Asp Ala Ala Pro
[0892] 1 5
[0893] <210> 42
[0894] <211> 9
[0895] <212> PRT
[0896] <213> 人工序列
[0897] <220>
[0898] <223> 融合蛋白中的一种肽接头
[0899] <400> 42
[0900] Arg Ala Asp Ala Ala Pro Thr Val Ser
[0901] 1 5
[0902] <210> 43
[0903] <211> 12
[0904] <212> PRT
[0905] <213> 人工序列
[0906] <220>
[0907] <223> 融合蛋白中的一种肽接头
[0908] <400> 43
[0909] Arg Ala Asp Ala Ala Ala Ala Gly Gly Pro Gly Ser
[0910] 1 5 10
[0911] <210> 44
[0912] <211> 7
[0913] <212> PRT
[0914] <213> 人工序列
[0915] <220>
[0916] <223> 融合蛋白中的一种肽接头
[0917] <400> 44
[0918] Arg Ala Asp Ala Ala Ala Ala
[0919] 1 5
[0920] <210> 45
[0921] <211> 18
[0922] <212> PRT
[0923] <213> 人工序列

[0924] <220>
[0925] <223> 融合蛋白中的一种肽接头
[0926] <400> 45
[0927] Ser Ala Lys Thr Thr Pro Lys Leu Glu Glu Gly Glu Phe Ser Glu Ala
[0928] 1 5 10 15
[0929] Arg Val
[0930] <210> 46
[0931] <211> 5
[0932] <212> PRT
[0933] <213> 人工序列
[0934] <220>
[0935] <223> 融合蛋白中的一种肽接头
[0936] <400> 46
[0937] Ala Asp Ala Ala Pro
[0938] 1 5
[0939] <210> 47
[0940] <211> 11
[0941] <212> PRT
[0942] <213> 人工序列
[0943] <220>
[0944] <223> 融合蛋白中的一种肽接头
[0945] <400> 47
[0946] Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro
[0947] 1 5 10
[0948] <210> 48
[0949] <211> 5
[0950] <212> PRT
[0951] <213> 人工序列
[0952] <220>
[0953] <223> 融合蛋白中的一种肽接头
[0954] <400> 48
[0955] Thr Val Ala Ala Pro
[0956] 1 5
[0957] <210> 49
[0958] <211> 12
[0959] <212> PRT
[0960] <213> 人工序列
[0961] <220>
[0962] <223> 融合蛋白中的一种肽接头
[0963] <400> 49
[0964] Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro
[0965] 1 5 10

[0966] <210> 50
[0967] <211> 6
[0968] <212> PRT
[0969] <213> 人工序列
[0970] <220>
[0971] <223> 融合蛋白中的一种肽接头
[0972] <400> 50
[0973] Gln Pro Lys Ala Ala Pro
[0974] 1 5
[0975] <210> 51
[0976] <211> 13
[0977] <212> PRT
[0978] <213> 人工序列
[0979] <220>
[0980] <223> 融合蛋白中的一种肽接头
[0981] <400> 51
[0982] Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro
[0983] 1 5 10
[0984] <210> 52
[0985] <211> 6
[0986] <212> PRT
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[0989] <223> 融合蛋白中的一种肽接头
[0990] <400> 52
[0991] Ala Lys Thr Thr Pro Pro
[0992] 1 5
[0993] <210> 53
[0994] <211> 13
[0995] <212> PRT
[0996] <213> 人工序列
[0997] <220>
[0998] <223> 融合蛋白中的一种肽接头
[0999] <400> 53
[1000] Ala Lys Thr Thr Pro Pro Ser Val Thr Pro Leu Ala Pro
[1001] 1 5 10
[1002] <210> 54
[1003] <211> 6
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[1005] <213> 人工序列
[1006] <220>
[1007] <223> 融合蛋白中的一种肽接头

[1008] <400> 54
[1009] Ala Lys Thr Thr Ala Pro
[1010] 1 5
[1011] <210> 55
[1012] <211> 13
[1013] <212> PRT
[1014] <213> 人工序列
[1015] <220>
[1016] <223> 融合蛋白中的一种肽接头
[1017] <400> 55
[1018] Ala Lys Thr Thr Ala Pro Ser Val Tyr Pro Leu Ala Pro
[1019] 1 5 10
[1020] <210> 56
[1021] <211> 6
[1022] <212> PRT
[1023] <213> 人工序列
[1024] <220>
[1025] <223> 融合蛋白中的一种肽接头
[1026] <400> 56
[1027] Ala Ser Thr Lys Gly Pro
[1028] 1 5
[1029] <210> 57
[1030] <211> 13
[1031] <212> PRT
[1032] <213> 人工序列
[1033] <220>
[1034] <223> 融合蛋白中的一种肽接头
[1035] <400> 57
[1036] Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
[1037] 1 5 10
[1038] <210> 58
[1039] <211> 15
[1040] <212> PRT
[1041] <213> 人工序列
[1042] <220>
[1043] <223> 融合蛋白中的一种肽接头
[1044] <400> 58
[1045] Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
[1046] 1 5 10 15
[1047] <210> 59
[1048] <211> 15
[1049] <212> PRT

[1050] <213> 人工序列
[1051] <220>
[1052] <223> 融合蛋白中的一种肽接头
[1053] <400> 59
[1054] Gly Glu Asn Lys Val Glu Tyr Ala Pro Ala Leu Met Ala Leu Ser
[1055] 1 5 10 15
[1056] <210> 60
[1057] <211> 15
[1058] <212> PRT
[1059] <213> 人工序列
[1060] <220>
[1061] <223> 融合蛋白中的一种肽接头
[1062] <400> 60
[1063] Gly Pro Ala Lys Glu Leu Thr Pro Leu Lys Glu Ala Lys Val Ser
[1064] 1 5 10 15
[1065] <210> 61
[1066] <211> 15
[1067] <212> PRT
[1068] <213> 人工序列
[1069] <220>
[1070] <223> 融合蛋白中的一种肽接头
[1071] <400> 61
[1072] Gly His Glu Ala Ala Ala Val Met Gln Val Gln Tyr Pro Ala Ser
[1073] 1 5 10 15
[1074] <210> 62
[1075] <211> 16
[1076] <212> PRT
[1077] <213> 人工序列
[1078] <220>
[1079] <223> 融合蛋白中的一种肽接头
[1080] <400> 62
[1081] Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
[1082] 1 5 10 15
[1083] <210> 63
[1084] <211> 205
[1085] <212> PRT
[1086] <213> 人工序列
[1087] <220>
[1088] <223> 融合蛋白中的一种VID的氨基酸序列
[1089] <400> 63
[1090] Ser Asp Thr Gly Arg Pro Phe Val Glu Met Tyr Ser Glu Ile Pro Glu
[1091] 1 5 10 15

[1092] Ile Ile His Met Thr Glu Gly Arg Glu Leu Val Ile Pro Cys Arg Val
[1093] 20 25 30
[1094] Thr Ser Pro Asn Ile Thr Val Thr Leu Lys Lys Phe Pro Leu Asp Thr
[1095] 35 40 45
[1096] Leu Ile Pro Asp Gly Lys Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe
[1097] 50 55 60
[1098] Ile Ile Ser Asn Ala Thr Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu
[1099] 65 70 75 80
[1100] Ala Thr Val Asn Gly His Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg
[1101] 85 90 95
[1102] Gln Thr Asn Thr Ile Ile Asp Val Val Leu Ser Pro Ser His Gly Ile
[1103] 100 105 110
[1104] Glu Leu Ser Val Gly Glu Lys Leu Val Leu Asn Cys Thr Ala Arg Thr
[1105] 115 120 125
[1106] Glu Leu Asn Val Gly Ile Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys
[1107] 130 135 140
[1108] His Gln His Lys Lys Leu Val Asn Arg Asp Leu Lys Thr Gln Ser Gly
[1109] 145 150 155 160
[1110] Ser Glu Met Lys Lys Phe Leu Ser Thr Leu Thr Ile Asp Gly Val Thr
[1111] 165 170 175
[1112] Arg Ser Asp Gln Gly Leu Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met
[1113] 180 185 190
[1114] Thr Lys Lys Asn Ser Thr Phe Val Arg Val His Glu Lys
[1115] 195 200 205
[1116] <210> 64
[1117] <211> 303
[1118] <212> PRT
[1119] <213> 人工序列
[1120] <220>
[1121] <223> 融合蛋白中的一种VID的氨基酸序列
[1122] <400> 64
[1123] Ser Asp Thr Gly Arg Pro Phe Val Glu Met Tyr Ser Glu Ile Pro Glu
[1124] 1 5 10 15
[1125] Ile Ile His Met Thr Glu Gly Arg Glu Leu Val Ile Pro Cys Arg Val
[1126] 20 25 30
[1127] Thr Ser Pro Asn Ile Thr Val Thr Leu Lys Lys Phe Pro Leu Asp Thr
[1128] 35 40 45
[1129] Leu Ile Pro Asp Gly Lys Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe
[1130] 50 55 60
[1131] Ile Ile Ser Asn Ala Thr Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu
[1132] 65 70 75 80
[1133] Ala Thr Val Asn Gly His Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg

[1134] 85 90 95
[1135] Gln Thr Asn Thr Ile Ile Asp Val Val Leu Ser Pro Ser His Gly Ile
[1136] 100 105 110
[1137] Glu Leu Ser Val Gly Glu Lys Leu Val Leu Asn Cys Thr Ala Arg Thr
[1138] 115 120 125
[1139] Glu Leu Asn Val Gly Ile Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys
[1140] 130 135 140
[1141] His Gln His Lys Lys Leu Val Asn Arg Asp Leu Lys Thr Gln Ser Gly
[1142] 145 150 155 160
[1143] Ser Glu Met Lys Lys Phe Leu Ser Thr Leu Thr Ile Asp Gly Val Thr
[1144] 165 170 175
[1145] Arg Ser Asp Gln Gly Leu Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met
[1146] 180 185 190
[1147] Thr Lys Lys Asn Ser Thr Phe Val Arg Val His Glu Lys Pro Phe Val
[1148] 195 200 205
[1149] Ala Phe Gly Ser Gly Met Glu Ser Leu Val Glu Ala Thr Val Gly Glu
[1150] 210 215 220
[1151] Arg Val Arg Ile Pro Ala Lys Tyr Leu Gly Tyr Pro Pro Pro Glu Ile
[1152] 225 230 235 240
[1153] Lys Trp Tyr Lys Asn Gly Ile Pro Leu Glu Ser Asn His Thr Ile Lys
[1154] 245 250 255
[1155] Ala Gly His Val Leu Thr Ile Met Glu Val Ser Glu Arg Asp Thr Gly
[1156] 260 265 270
[1157] Asn Tyr Thr Val Ile Leu Thr Asn Pro Ile Ser Lys Glu Lys Gln Ser
[1158] 275 280 285
[1159] His Val Val Ser Leu Val Val Tyr Val Pro Pro Gly Pro Gly Asp
[1160] 290 295 300
[1161] <210> 65
[1162] <211> 100
[1163] <212> PRT
[1164] <213> 人工序列
[1165] <220>
[1166] <223> 融合蛋白中的一种VID的氨基酸序列
[1167] <400> 65
[1168] Ser Asp Thr Gly Arg Pro Phe Val Glu Met Tyr Ser Glu Ile Pro Glu
[1169] 1 5 10 15
[1170] Ile Ile His Met Thr Glu Gly Arg Glu Leu Val Ile Pro Cys Arg Val
[1171] 20 25 30
[1172] Thr Ser Pro Asn Ile Thr Val Thr Leu Lys Lys Phe Pro Leu Asp Thr
[1173] 35 40 45
[1174] Leu Ile Pro Asp Gly Lys Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe
[1175] 50 55 60

[1176] Ile Ile Ser Asn Ala Thr Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu
[1177] 65 70 75 80
[1178] Ala Thr Val Asn Gly His Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg
[1179] 85 90 95
[1180] Gln Thr Asn Thr
[1181] 100
[1182] <210> 66
[1183] <211> 723
[1184] <212> DNA
[1185] <213> 人工序列
[1186] <220>
[1187] <223> 抗PD1抗体BY18.1的轻链(BY18.1L)核苷酸序列
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[1190] ggctccactg gcgagattgt gctgacacag tcccccgcta ctctgagcct gagccctggc 120
[1191] gagagggcta cactgtcttg cagagcttct cagtccgtgt cttcttacct cgcttggtat 180
[1192] cagcagaagc ccggccaggc tccaagactg ctgatctatg acgcttctaa ccgcgctaca 240
[1193] ggcattcctg ctaggttcag cggcagcggc tctggcaccg acttcacact cacaattagc 300
[1194] tctcttgaac ctgaggactt cgccgtgtac tactgccagc agtctagcaa ctggcctaga 360
[1195] acattcggcc agggcactaa ggtggagatt aagagaaccg tggccgcccc cagcgtgttc 420
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[1197] aacaacttct acccccgcga ggccaaggtg cagtggaagg tggacaacgc cctgcagagc 540
[1198] ggcaacagcc aggagagcgt gaccgagcag gactccaagg acagcaccta cagcctgagc 600
[1199] agcaccctga ccctgagcaa ggccgactac gagaagcaca aggtgtacgc ctgcgaggtg 660
[1200] acccaccagg gactgtctag ccccgtgacc aagagcttca accggggcga gtgctaagaa 720
[1201] ttc 723
[1202] <210> 67
[1203] <211> 234
[1204] <212> PRT
[1205] <213> 人工序列
[1206] <220>
[1207] <223> 抗PD1抗体BY18.1的轻链(BY18.1L)氨基酸序列
[1208] <400> 67
[1209] Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
[1210] 1 5 10 15
[1211] Gly Ser Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
[1212] 20 25 30
[1213] Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
[1214] 35 40 45
[1215] Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
[1216] 50 55 60
[1217] Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala

[1218] 65 70 75 80
[1219] Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
[1220] 85 90 95
[1221] Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Ser
[1222] 100 105 110
[1223] Asn Trp Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
[1224] 115 120 125
[1225] Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
[1226] 130 135 140
[1227] Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
[1228] 145 150 155 160
[1229] Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
[1230] 165 170 175
[1231] Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
[1232] 180 185 190
[1233] Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
[1234] 195 200 205
[1235] His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
[1236] 210 215 220
[1237] Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
[1238] 225 230
[1239] <210> 68
[1240] <211> 1401
[1241] <212> DNA
[1242] <213> 人工序列
[1243] <220>
[1244] <223> 抗PD1抗体BY18.1的重链(BY18.1H)核苷酸序列
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[1248] tccctcagac tggactgcaa ggcatccggc attacattct ctaactctgg aatgcactgg 180
[1249] gtgagacagg ctcctggcaa gggcctggaa tgggtggccg tgatttggta cgacggctct 240
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[1251] aacactctgt tcctccagat gaacagcctg agagccgagg acaccgctgt gtactactgc 360
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[1257] aacgtggacc acaagccttc caacaccaag gtggacaagc gcgtggagtc caagtacggc 720
[1258] cctccttgcc ctccttgccc tgcccctgag ttcctgggcg gcccttccgt gttcctgttc 780
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[1267] ttcttcctgt actcccgcct gaccgtggac aagtcccgct ggcaggaggg caacgtgttc 1320
[1268] tcctgctccg tgatgcacga ggccctgcac aaccactaca cccagaagtc cctgtccctg 1380
[1269] tccctgggca agtaagtcga c 1401
[1270] <210> 69
[1271] <211> 460
[1272] <212> PRT
[1273] <213> 人工序列
[1274] <220>
[1275] <223> 抗PD1抗体BY18.1的重链(BY18.1H)氨基酸序列
[1276] <400> 69
[1277] Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
[1278] 1 5 10 15
[1279] Gly Ser Thr Gly Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val
[1280] 20 25 30
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[1282] 35 40 45
[1283] Phe Ser Asn Ser Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly
[1284] 50 55 60
[1285] Leu Glu Trp Val Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr
[1286] 65 70 75 80
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[1288] 85 90 95
[1289] Asn Thr Leu Phe Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala
[1290] 100 105 110
[1291] Val Tyr Tyr Cys Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu
[1292] 115 120 125
[1293] Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
[1294] 130 135 140
[1295] Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys
[1296] 145 150 155 160
[1297] Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
[1298] 165 170 175
[1299] Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
[1300] 180 185 190
[1301] Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser

[1302] 195 200 205
[1303] Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn
[1304] 210 215 220
[1305] Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro
[1306] 225 230 235 240
[1307] Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe
[1308] 245 250 255
[1309] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
[1310] 260 265 270
[1311] Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe
[1312] 275 280 285
[1313] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[1314] 290 295 300
[1315] Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[1316] 305 310 315 320
[1317] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[1318] 325 330 335
[1319] Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala
[1320] 340 345 350
[1321] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln
[1322] 355 360 365
[1323] Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
[1324] 370 375 380
[1325] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
[1326] 385 390 395 400
[1327] Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[1328] 405 410 415
[1329] Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu
[1330] 420 425 430
[1331] Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[1332] 435 440 445
[1333] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
[1334] 450 455 460
[1335] <210> 70
[1336] <211> 1365
[1337] <212> DNA
[1338] <213> 人工序列
[1339] <220>
[1340] <223> 蛋白301-8的编码核苷酸序列
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[1343] ggctccaccg gatccgacac cggccgccct ttcgtggaga tgtactccga gatccctgag 120

[1344] atcatccaca tgaccgaggg ccgcgagctg gtgatccctt gccgcgtgac ctcccctaac 180
[1345] atcaccgtga ccctgaagaa gttccctctg gacaccctga tccctgacgg caagcgcatc 240
[1346] atctgggact cccgcaaggg cttcatcatc tccaacgcca cctacaagga gatcggcctg 300
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[1348] cagaccaaca ccatcatcga cgtggtgctg tcccccttccc acggcatcga gctgtccgtg 420
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[1366] <211> 451
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[1368] <213> 人工序列
[1369] <220>
[1370] <223> 蛋白301-8的氨基酸序列
[1371] <400> 71
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[1374] Gly Ser Thr Gly Ser Asp Thr Gly Arg Pro Phe Val Glu Met Tyr Ser
[1375] 20 25 30
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[1377] 35 40 45
[1378] Pro Cys Arg Val Thr Ser Pro Asn Ile Thr Val Thr Leu Lys Lys Phe
[1379] 50 55 60
[1380] Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys Arg Ile Ile Trp Asp Ser
[1381] 65 70 75 80
[1382] Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr Tyr Lys Glu Ile Gly Leu
[1383] 85 90 95
[1384] Leu Thr Cys Glu Ala Thr Val Asn Gly His Leu Tyr Lys Thr Asn Tyr
[1385] 100 105 110

[1386] Leu Thr His Arg Gln Thr Asn Thr Ile Ile Asp Val Val Leu Ser Pro
[1387] 115 120 125
[1388] Ser His Gly Ile Glu Leu Ser Val Gly Glu Lys Leu Val Leu Asn Cys
[1389] 130 135 140
[1390] Thr Ala Arg Thr Glu Leu Asn Val Gly Ile Asp Phe Asn Trp Glu Tyr
[1391] 145 150 155 160
[1392] Pro Ser Ser Lys His Gln His Lys Lys Leu Val Asn Arg Asp Leu Lys
[1393] 165 170 175
[1394] Thr Gln Ser Gly Ser Glu Met Lys Lys Phe Leu Ser Thr Leu Thr Ile
[1395] 180 185 190
[1396] Asp Gly Val Thr Arg Ser Asp Gln Gly Leu Tyr Thr Cys Ala Ala Ser
[1397] 195 200 205
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[1400] Lys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
[1401] 225 230 235 240
[1402] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
[1403] 245 250 255
[1404] Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
[1405] 260 265 270
[1406] His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
[1407] 275 280 285
[1408] Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
[1409] 290 295 300
[1410] Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
[1411] 305 310 315 320
[1412] Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
[1413] 325 330 335
[1414] Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
[1415] 340 345 350
[1416] Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
[1417] 355 360 365
[1418] Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[1419] 370 375 380
[1420] Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
[1421] 385 390 395 400
[1422] Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
[1423] 405 410 415
[1424] Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
[1425] 420 425 430
[1426] Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
[1427] 435 440 445

[1428] Ser Pro Gly
[1429] 450
[1430] <210> 72
[1431] <211> 723
[1432] <212> DNA
[1433] <213> 人工序列
[1434] <220>
[1435] <223> 融合蛋白BY24.3(κ,IgG4)的轻链亚基(BY24.3L)核苷酸序列
[1436] <400> 72
[1437] ctcgaggcca ccatggagac cgacacactc ctcctgtggg tgctgctgct gtgggtgcct 60
[1438] ggctccactg gcgagattgt gctgacacag tcccccgcta ctctgagcct gagccctggc 120
[1439] gagagggcta cactgtcttg cagagcttct cagtccgtgt cttcttacct cgcttggtat 180
[1440] cagcagaagc ccggccaggc tccaagactg ctgatctatg acgcttctaa ccgcgctaca 240
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[1446] ggcaacagcc aggagagcgt gaccgagcag gactccaagg acagcaccta cagcctgagc 600
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[1448] acccaccagg gactgtctag ccccgtgacc aagagcttca accggggcga gtgctaagaa 720
[1449] ttc 723
[1450] <210> 73
[1451] <211> 234
[1452] <212> PRT
[1453] <213> 人工序列
[1454] <220>
[1455] <223> 融合蛋白BY24.3(κ,IgG4)的轻链亚基(BY24.3L)氨基酸序列
[1456] <400> 73
[1457] Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
[1458] 1 5 10 15
[1459] Gly Ser Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
[1460] 20 25 30
[1461] Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
[1462] 35 40 45
[1463] Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
[1464] 50 55 60
[1465] Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala
[1466] 65 70 75 80
[1467] Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
[1468] 85 90 95
[1469] Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Ser

[1470] 100 105 110

[1471] Asn Trp Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg

[1472] 115 120 125

[1473] Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln

[1474] 130 135 140

[1475] Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr

[1476] 145 150 155 160

[1477] Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser

[1478] 165 170 175

[1479] Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr

[1480] 180 185 190

[1481] Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys

[1482] 195 200 205

[1483] His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro

[1484] 210 215 220

[1485] Val Thr Lys Ser Phe Asn Arg Gly Glu Cys

[1486] 225 230

[1487] <210> 74

[1488] <211> 2058

[1489] <212> DNA

[1490] <213> 人工序列

[1491] <220>

[1492] <223> 融合蛋白BY24.3(κ,IgG4)的重链-VID融合亚基(BY24.3H)核苷酸序列

[1493] <400> 74

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[1495] ggctccacag gccaggtgca gctcgtggag tccggcggcg gcgtggtgca gcccggcaga 120

[1496] tccctcagac tggactgcaa ggcatccggc attacattct ctaactctgg aatgcactgg 180

[1497] gtgagacagg ctcctggcaa gggcctggaa tgggtggccg tgatttggta cgacggctct 240

[1498] aagagatact acgctgactc cgtgaagggc cggttcacaa ttagcagaga caactccaag 300

[1499] aacactctgt tcctccagat gaacagcctg agagccgagg acaccgctgt gtactactgc 360

[1500] gccaccaacg acgactactg gggccagggc accctcgtga cagtgtcttc cgcctccacc 420

[1501] aagggccctt ccgtgttccc tctggccct tgctcccgct ccacctccga gtccaccgcc 480

[1502] gccctgggct gcctggtgaa ggactacttc cctgagcctg tgaccgtgtc ctggaactcc 540

[1503] ggcgccctga cctccggcgt gcacaccttc cctgccgtgc tgcagtcctc cggcctgtac 600

[1504] tccctgtcct ccgtggtgac cgtgccttcc tcctccctgg gcaccaagac ctacacctgc 660

[1505] aacgtggacc acaagccttc caacaccaag gtggacaagc gcgtggagtc caagtacggc 720

[1506] cctccttgcc ctccttgccc tgcccctgag ttcctgggcg gcccttccgt gttcctgttc 780

[1507] cctcctaagc ctaaggacac cctgatgatc tcccgcaccc ctgaggtgac ctgcgtggtg 840

[1508] gtggacgtgt cccaggagga ccctgaggtg cagttcaact ggtacgtgga cggcgtggag 900

[1509] gtgcacaacg ccaagaccaa gcctcgcgag gagcagttca actccaccta ccgcgtggtg 960

[1510] tccgtgctga ccgtgctgca ccaggactgg ctgaacggca aggagtacaa gtgcaaggtg 1020

[1511] tccaacaagg gcctgccttc ctccatcgag aagaccatct ccaaggccaa gggccagcct 1080

[1512] cgcgagcctc aggtgtacac cctgcctcct tcccaggagg agatgaccaa gaaccaggtg 1140
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[1514] aacggccagc ctgagaacaa ctacaagacc acccctcctg tgctggactc cgacggctcc 1260
[1515] ttcttcctgt actcccgcct gaccgtggac aagtcccgct ggcaggaggg caacgtgttc 1320
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[1527] tacacctgcg ccgcctcctc cggcctgatg accaagaaga actccacctt cgtgcgcgtg 2040
[1528] cacgagaagt aagtcgac 2058
[1529] <210> 75
[1530] <211> 679
[1531] <212> PRT
[1532] <213> 人工序列
[1533] <220>
[1534] <223> 融合蛋白BY24.3(κ,IgG4)的重链-VID融合亚基(BY24.3H)氨基酸序列
[1535] <400> 75
[1536] Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
[1537] 1 5 10 15
[1538] Gly Ser Thr Gly Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val
[1539] 20 25 30
[1540] Gln Pro Gly Arg Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr
[1541] 35 40 45
[1542] Phe Ser Asn Ser Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly
[1543] 50 55 60
[1544] Leu Glu Trp Val Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr
[1545] 65 70 75 80
[1546] Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys
[1547] 85 90 95
[1548] Asn Thr Leu Phe Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala
[1549] 100 105 110
[1550] Val Tyr Tyr Cys Ala Thr Asn Asp Asp Tyr Trp Gly Gln Gly Thr Leu
[1551] 115 120 125
[1552] Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
[1553] 130 135 140

[1554] Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys
[1555] 145 150 155 160
[1556] Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
[1557] 165 170 175
[1558] Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
[1559] 180 185 190
[1560] Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
[1561] 195 200 205
[1562] Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn
[1563] 210 215 220
[1564] Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro
[1565] 225 230 235 240
[1566] Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe
[1567] 245 250 255
[1568] Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
[1569] 260 265 270
[1570] Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe
[1571] 275 280 285
[1572] Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
[1573] 290 295 300
[1574] Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
[1575] 305 310 315 320
[1576] Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
[1577] 325 330 335
[1578] Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala
[1579] 340 345 350
[1580] Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln
[1581] 355 360 365
[1582] Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
[1583] 370 375 380
[1584] Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
[1585] 385 390 395 400
[1586] Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
[1587] 405 410 415
[1588] Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu
[1589] 420 425 430
[1590] Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
[1591] 435 440 445
[1592] Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Gly Gly Gly Ser Gly
[1593] 450 455 460
[1594] Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ser Asp Thr Gly Arg Pro
[1595] 465 470 475 480

[1596] Phe Val Glu Met Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu
[1597] 485 490 495
[1598] Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr
[1599] 500 505 510
[1600] Val Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys
[1601] 515 520 525
[1602] Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr
[1603] 530 535 540
[1604] Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His
[1605] 545 550 555 560
[1606] Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile
[1607] 565 570 575
[1608] Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu
[1609] 580 585 590
[1610] Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile
[1611] 595 600 605
[1612] Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu
[1613] 610 615 620
[1614] Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe
[1615] 625 630 635 640
[1616] Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu
[1617] 645 650 655
[1618] Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr
[1619] 660 665 670
[1620] Phe Val Arg Val His Glu Lys
[1621] 675
[1622] <210> 76
[1623] <211> 786
[1624] <212> DNA
[1625] <213> 人工序列
[1626] <220>
[1627] <223> 融合蛋白BY24.7(κ,IgG2)的轻链亚基(BY24.7L)核苷酸序列
[1628] <400> 76
[1629] ctcgaggcca ccatggagac cgacacactc ctcctgtggg tgctgctgct gtgggtgcct 60
[1630] ggctccactg gcgagatcaa gcggaccgtg gccgccccat ccgtgttcat tttcccacct 120
[1631] tccgagattg tgctgacaca gtcccccgct actctgagcc tgagccctgg cgagagggct 180
[1632] acactgtctt gcagagcttc caagggcgtg agcacatccg gctactccta cctccactgg 240
[1633] tatcagcaga agccaggcca ggccccaaga ctgctgatat acctcgcttc ttacttagag 300
[1634] tctggcgtgc ccgctcggtt cagcggctcc ggctctggca ccgacttcac cctgacaatt 360
[1635] tctagcctgg agcccgagga cttcgccgtg tactactgcc agcactctag ggacctgcct 420
[1636] ctcacattcg gcggcggcac taaggtggag attaagagaa ccgtggccgc ccccagcgtg 480
[1637] ttcatcttcc ctcccagcga cgagcagctg aagtctggca ccgccagcgt ggtgtgcctg 540

[1638] ctgaacaact tctacccccg cgaggccaag gtgcagtgga aggtggacaa cgccctgcag 600
[1639] agcggcaaca gccaggagag cgtgaccgag caggactcca aggacagcac ctacagcctg 660
[1640] agcagcaccc tgaccctgag caaggccgac tacgagaagc acaaggtgta cgcctgcgag 720
[1641] gtgacccacc agggactgtc tagccccgtg accaagagct tcaaccgggg cgagtgctaa 780
[1642] gaattc 786
[1643] <210> 77
[1644] <211> 238
[1645] <212> PRT
[1646] <213> 人工序列
[1647] <220>
[1648] <223> 融合蛋白BY24.7(κ,IgG2)的轻链亚基(BY24.7L)氨基酸序列
[1649] <400> 77
[1650] Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
[1651] 1 5 10 15
[1652] Gly Ser Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
[1653] 20 25 30
[1654] Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Lys Gly
[1655] 35 40 45
[1656] Val Ser Thr Ser Gly Tyr Ser Tyr Leu His Trp Tyr Gln Gln Lys Pro
[1657] 50 55 60
[1658] Gly Gln Ala Pro Arg Leu Leu Ile Tyr Leu Ala Ser Tyr Leu Glu Ser
[1659] 65 70 75 80
[1660] Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
[1661] 85 90 95
[1662] Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
[1663] 100 105 110
[1664] Gln His Ser Arg Asp Leu Pro Leu Thr Phe Gly Gly Gly Thr Lys Val
[1665] 115 120 125
[1666] Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro
[1667] 130 135 140
[1668] Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu
[1669] 145 150 155 160
[1670] Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn
[1671] 165 170 175
[1672] Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser
[1673] 180 185 190
[1674] Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala
[1675] 195 200 205
[1676] Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly
[1677] 210 215 220
[1678] Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
[1679] 225 230 235

[1680] <210> 78

[1681] <211> 1761

[1682] <212> DNA

[1683] <213> 人工序列

[1684] <220>

[1685] <223> 融合蛋白BY24.7(κ,IgG2)的重链-VID融合亚基(BY24.7H)核苷酸序列

[1686] <400> 78

[1687] tctagagcca ccatggagac cgacaccctg ctgctgtggg tgctgctcct gtgggtgcct 60

[1688] ggctccacag gccaggtgca gctcgtgcag tctggcgtgg aggtgaagaa gcctggcgcc 120

[1689] tctgtgaagg tgtcttgcaa ggcttccggc tacactttca ctaactacta catgtactgg 180

[1690] gtgagacagg ctcccggcca gggcctagag tggatgggcg gcattaaccc tagcaacggc 240

[1691] ggcacaaact tcaacgagaa gttcaagaac cgcgtgaccc tgaccacaga ctctagcaca 300

[1692] acaactgctt acatggagct gaagtctctc cagttcgacg acaccgctgt gtactactgc 360

[1693] gctcggaggg actacagatt cgacatgggc ttcgactact ggggccaggg caccactgtg 420

[1694] acagtgtcta cagcctccac caagggccct tccgtgttcc ctctggcccc ttgctcccgc 480

[1695] tccacctccg agtccaccgc cgccctgggc tgcctggtga aggactactt ccctgagcct 540

[1696] gtgaccgtgt cctggaactc cggcgccctg acctccggcg tgcacacctt ccctgccgtg 600

[1697] ctgcagtcct ccggcctgta ctccctgtcc tccgtggtga ccgtgccttc ctccaacttc 660

[1698] ggcacccaga catacacatg caacgtggac cacaagcctt ctaacacaaa ggtggacaag 720

[1699] accgtggagc ggaagtgctg cgtggagtgc ccaccttgcc ccgctcctcc tgtggccggc 780

[1700] ccttctgtgt tcctgttccc acctaagcca aaggacacac tcatgatcag cagaacccct 840

[1701] gaggtgacct gcgtggtggt ggacgtgagc cacgaggacc ccgaggtgca gttcaactgg 900

[1702] tatgtggacg gcgtggaggt gcacaacgct aagaccaagc ctagagaaga acagttcaac 960

[1703] agcacattca gagtggtgtc cgtgctcacc gtggtgcacc aggactggct gaacggcaaa 1020

[1704] gagtacaagt gcaaggtgtc caacaagggc ctgccagccc ctatcgaaaa aacaatcagc 1080

[1705] aagaccaagg gccagcctag agagcctcag gtgtacacac tgcctccatc tcgggaagaa 1140

[1706] atgacaaaga accaggtgtc cctcacatgc ctcgtgaagg gcttctaccc atccgacatc 1200

[1707] gctgtggagt gggagtctaa cggccagccc gagaacaact acaagaccac ccctcctatg 1260

[1708] ctcgactccg acggctcttt cttcctgtac tctaagctga ccgtggacaa gtccagatgg 1320

[1709] cagcagggca acgtgttctc ttgcagcgtg atgcacgagg ctctccacaa ccactacacc 1380

[1710] cagaagtccc tgagcctgtc tccaggcggc ggaggatctg gcggcggagg cagtggaggc 1440

[1711] ggcggaagcg cttccgacac cggccgccct ttcgtggaga tgtactccga gatccctgag 1500

[1712] atcatccaca tgaccgaggg ccgcgagctg gtgatccctt gccgcgtgac ctcccctaac 1560

[1713] atcaccgtga ccctgaagaa gttccctctg gacaccctga tccctgacgg caagcgcatc 1620

[1714] atctgggact cccgcaaggg cttcatcatc tccaacgcca cctacaagga gatcggcctg 1680

[1715] ctgacctgcg aggccaccgt gaacggccac ctgtacaaga ccaactacct gacccaccgc 1740

[1716] cagaccaaca cctaagtcga c 1761

[1717] <210> 79

[1718] <211> 580

[1719] <212> PRT

[1720] <213> 人工序列

[1721] <220>

[1722] <223> 融合蛋白BY24.7(κ,IgG2)的重链-VID融合亚基(BY24.7H)氨基酸序列

[1723] <400> 79

[1724] Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro

[1725] 1 5 10 15

[1726] Gly Ser Thr Gly Gln Val Gln Leu Val Gln Ser Gly Val Glu Val Lys

[1727] 20 25 30

[1728] Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr

[1729] 35 40 45

[1730] Phe Thr Asn Tyr Tyr Met Tyr Trp Val Arg Gln Ala Pro Gly Gln Gly

[1731] 50 55 60

[1732] Leu Glu Trp Met Gly Gly Ile Asn Pro Ser Asn Gly Gly Thr Asn Phe

[1733] 65 70 75 80

[1734] Asn Glu Lys Phe Lys Asn Arg Val Thr Leu Thr Thr Asp Ser Ser Thr

[1735] 85 90 95

[1736] Thr Thr Ala Tyr Met Glu Leu Lys Ser Leu Gln Phe Asp Asp Thr Ala

[1737] 100 105 110

[1738] Val Tyr Tyr Cys Ala Arg Arg Asp Tyr Arg Phe Asp Met Gly Phe Asp

[1739] 115 120 125

[1740] Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Thr Ala Ser Thr Lys

[1741] 130 135 140

[1742] Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu

[1743] 145 150 155 160

[1744] Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro

[1745] 165 170 175

[1746] Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr

[1747] 180 185 190

[1748] Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val

[1749] 195 200 205

[1750] Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn

[1751] 210 215 220

[1752] Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg

[1753] 225 230 235 240

[1754] Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly

[1755] 245 250 255

[1756] Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile

[1757] 260 265 270

[1758] Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu

[1759] 275 280 285

[1760] Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His

[1761] 290 295 300

[1762] Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg

[1763] 305 310 315 320

[1764] Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
[1765] 325 330 335
[1766] Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
[1767] 340 345 350
[1768] Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
[1769] 355 360 365
[1770] Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
[1771] 370 375 380
[1772] Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
[1773] 385 390 395 400
[1774] Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
[1775] 405 410 415
[1776] Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
[1777] 420 425 430
[1778] Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
[1779] 435 440 445
[1780] Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
[1781] 450 455 460
[1782] Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala
[1783] 465 470 475 480
[1784] Ser Asp Thr Gly Arg Pro Phe Val Glu Met Tyr Ser Glu Ile Pro Glu
[1785] 485 490 495
[1786] Ile Ile His Met Thr Glu Gly Arg Glu Leu Val Ile Pro Cys Arg Val
[1787] 500 505 510
[1788] Thr Ser Pro Asn Ile Thr Val Thr Leu Lys Lys Phe Pro Leu Asp Thr
[1789] 515 520 525
[1790] Leu Ile Pro Asp Gly Lys Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe
[1791] 530 535 540
[1792] Ile Ile Ser Asn Ala Thr Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu
[1793] 545 550 555 560
[1794] Ala Thr Val Asn Gly His Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg
[1795] 565 570 575
[1796] Gln Thr Asn Thr
[1797] 580
[1798] <210> 80
[1799] <211> 720
[1800] <212> DNA
[1801] <213> 人工序列
[1802] <220>
[1803] <223> 融合蛋白BY24.4(κ,IgG4)的轻链亚基(BY24.4L)核苷酸序列
[1804] <400> 80
[1805] ctcgaggcca ccatggagac cgacacactc ctcctgtggg tgctgctgct gtgggtgcct 60

[1806] ggctccactg gcgagatcgt gctgacacag agtcctagtt ccctgagcgc atccgtcggc 120
[1807] gatagggtga ctatcacttg tagcgcacgc agtagcgtgt cttacatgca ctggtttcag 180
[1808] cagaagcccg gcaaggcacc caagctgtgg atctaccgga ccagtaacct cgcctctgga 240
[1809] gtgccatcca ggtttagtgg ctccggaagt ggaacttctt actgcctcac aattaatagt 300
[1810] ctccagcccg aggattttgc aacatactac tgtcagcagc ggtctagctt tcccctgaca 360
[1811] ttcggcggag gcactaaggt ggagattaag agaaccgtgg ccgcccccag cgtgttcatc 420
[1812] ttccctccca gcgacgagca gctgaagtct ggcaccgcca gcgtggtgtg cctgctgaac 480
[1813] aacttctacc cccgcgaggc caaggtgcag tggaaggtgg acaacgccct gcagagcggc 540
[1814] aacagccagg agagcgtgac cgagcaggac tccaaggaca gcacctacag cctgagcagc 600
[1815] accctgaccc tgagcaaggc cgactacgag aagcacaagg tgtacgcctg cgaggtgacc 660
[1816] caccagggac tgtctagccc cgtgaccaag agcttcaacc ggggcgagtg ctaagaattc 720
[1817] <210> 81
[1818] <211> 233
[1819] <212> PRT
[1820] <213> 人工序列
[1821] <220>
[1822] <223> 融合蛋白BY24.4(κ,IgG4)的轻链亚基(BY24.4L)氨基酸序列
[1823] <400> 81
[1824] Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
[1825] 1 5 10 15
[1826] Gly Ser Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ser Ser Leu Ser
[1827] 20 25 30
[1828] Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Ser Ala Arg Ser Ser
[1829] 35 40 45
[1830] Val Ser Tyr Met His Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys
[1831] 50 55 60
[1832] Leu Trp Ile Tyr Arg Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg
[1833] 65 70 75 80
[1834] Phe Ser Gly Ser Gly Ser Gly Thr Ser Tyr Cys Leu Thr Ile Asn Ser
[1835] 85 90 95
[1836] Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Ser
[1837] 100 105 110
[1838] Phe Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr
[1839] 115 120 125
[1840] Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu
[1841] 130 135 140
[1842] Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro
[1843] 145 150 155 160
[1844] Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly
[1845] 165 170 175
[1846] Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr
[1847] 180 185 190

[1848] Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His
[1849] 195 200 205
[1850] Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val
[1851] 210 215 220
[1852] Thr Lys Ser Phe Asn Arg Gly Glu Cys
[1853] 225 230
[1854] <210> 82
[1855] <211> 2070
[1856] <212> DNA
[1857] <213> 人工序列
[1858] <220>
[1859] <223> 融合蛋白BY24.4(κ,IgG4)的重链-VID融合亚基(BY24.4H)核苷酸序列
[1860] <400> 82
[1861] tctagagcca ccatggagac cgacaccctg ctgctgtggg tgctgctcct gtgggtgcct 60
[1862] ggctccacag gccaggtgca gctggtccag agcggaagcg agcttaagaa gcctggagca 120
[1863] tctgtcaaga ttagttgtaa ggcaagtggc tacacattta ccaactacgg aatgaattgg 180
[1864] gtgcgccagg cacccggaca gggcctccag tggatgggat ggatcaatac cgatagcggc 240
[1865] gagtctacat acgctgagga gtttaagggc cggttcgtgt tcagtctcga tacaagcgtg 300
[1866] aacacagctt acctccaaat cacttctctg actgctgagg acaccggcat gtacttttgc 360
[1867] gtccgcgtcg gctacgacgc actcgattac tggggacagg gcaccctcgt gacagtgtct 420
[1868] tccgcctcca ccaagggccc ttccgtgttc cctctggccc cttgctcccg ctccacctcc 480
[1869] gagtccaccg ccgccctggg ctgcctggtg aaggactact tccctgagcc tgtgaccgtg 540
[1870] tcctggaact ccggcgccct gacctccggc gtgcacacct tccctgccgt gctgcagtcc 600
[1871] tccggcctgt actccctgtc ctccgtggtg accgtgcctt cctcctccct gggcaccaag 660
[1872] acctacacct gcaacgtgga ccacaagcct tccaacacca aggtggacaa gcgcgtggag 720
[1873] tccaagtacg gccctccttg ccctccttgc cctgcccctg agttcctggg cggcccttcc 780
[1874] gtgttcctgt tccctcctaa gcctaaggac accctgatga tctcccgcac ccctgaggtg 840
[1875] acctgcgtgg tggtggacgt gtcccaggag gaccctgagg tgcagttcaa ctggtacgtg 900
[1876] gacggcgtgg aggtgcacaa cgccaagacc aagcctcgcg aggagcagtt caactccacc 960
[1877] taccgcgtgg tgtccgtgct gaccgtgctg caccaggact ggctgaacgg caaggagtac 1020
[1878] aagtgcaagg tgtccaacaa gggcctgcct tcctccatcg agaagaccat ctccaaggcc 1080
[1879] aagggccagc ctcgcgagcc tcaggtgtac accctgcctc cttcccagga ggagatgacc 1140
[1880] aagaaccagg tgtccctgac ctgcctggtg aagggcttct acccttccga catcgccgtg 1200
[1881] gagtgggagt ccaacggcca gcctgagaac aactacaaga ccacccctcc tgtgctggac 1260
[1882] tccgacggct ccttcttcct gtactcccgc ctgaccgtgg acaagtcccg ctggcaggag 1320
[1883] ggcaacgtgt tctcctgctc cgtgatgcac gaggccctgc acaaccacta cacccagaag 1380
[1884] tccctgtccc tgtccctggg cggcggagga tctggcggcg gaggcagtgg aggcggcgga 1440
[1885] agcgcttccg acaccggccg ccctttcgtg gagatgtact ccgagatccc tgagatcatc 1500
[1886] cacatgaccg agggccgcga gctggtgatc ccttgccgcg tgacctcccc taacatcacc 1560
[1887] gtgaccctga agaagttccc tctggacacc ctgatccctg acggcaagcg catcatctgg 1620
[1888] gactcccgca agggcttcat catctccaac gccacctaca aggagatcgg cctgctgacc 1680
[1889] tgcgaggcca ccgtgaacgg ccacctgtac aagaccaact acctgaccca ccgccagacc 1740

[1890] aacaccatca tcgacgtggt gctgtcccct tcccacggca tcgagctgtc cgtgggcgag 1800
[1891] aagctggtgc tgaactgcac cgcccgcacc gagctgaacg tgggcatcga cttcaactgg 1860
[1892] gagtaccctt cctccaagca ccagcacaag aagctggtga accgcgacct gaagacccag 1920
[1893] tccggctccg agatgaagaa gttcctgtcc accctgacca tcgacggcgt gacccgctcc 1980
[1894] gaccagggcc tgtacacctg cgccgcctcc tccggcctga tgaccaagaa gaactccacc 2040
[1895] ttcgtgcgcg tgcacgagaa gtaagtcgac 2070
[1896] <210> 83
[1897] <211> 683
[1898] <212> PRT
[1899] <213> 人工序列
[1900] <220>
[1901] <223> 融合蛋白BY24.4(κ,IgG4)的重链-VID融合亚基(BY24.4H)氨基酸序列
[1902] <400> 83
[1903] Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
[1904] 1 5 10 15
[1905] Gly Ser Thr Gly Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys
[1906] 20 25 30
[1907] Lys Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr
[1908] 35 40 45
[1909] Phe Thr Asn Tyr Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly
[1910] 50 55 60
[1911] Leu Gln Trp Met Gly Trp Ile Asn Thr Asp Ser Gly Glu Ser Thr Tyr
[1912] 65 70 75 80
[1913] Ala Glu Glu Phe Lys Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val
[1914] 85 90 95
[1915] Asn Thr Ala Tyr Leu Gln Ile Thr Ser Leu Thr Ala Glu Asp Thr Gly
[1916] 100 105 110
[1917] Met Tyr Phe Cys Val Arg Val Gly Tyr Asp Ala Leu Asp Tyr Trp Gly
[1918] 115 120 125
[1919] Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
[1920] 130 135 140
[1921] Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala
[1922] 145 150 155 160
[1923] Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
[1924] 165 170 175
[1925] Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
[1926] 180 185 190
[1927] Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
[1928] 195 200 205
[1929] Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His
[1930] 210 215 220
[1931] Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly

[1932] 225 230 235 240
[1933] Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser
[1934] 245 250 255
[1935] Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
[1936] 260 265 270
[1937] Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro
[1938] 275 280 285
[1939] Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
[1940] 290 295 300
[1941] Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val
[1942] 305 310 315 320
[1943] Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
[1944] 325 330 335
[1945] Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr
[1946] 340 345 350
[1947] Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
[1948] 355 360 365
[1949] Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
[1950] 370 375 380
[1951] Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
[1952] 385 390 395 400
[1953] Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
[1954] 405 410 415
[1955] Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser
[1956] 420 425 430
[1957] Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
[1958] 435 440 445
[1959] Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Gly
[1960] 450 455 460
[1961] Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ser Asp
[1962] 465 470 475 480
[1963] Thr Gly Arg Pro Phe Val Glu Met Tyr Ser Glu Ile Pro Glu Ile Ile
[1964] 485 490 495
[1965] His Met Thr Glu Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser
[1966] 500 505 510
[1967] Pro Asn Ile Thr Val Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu Ile
[1968] 515 520 525
[1969] Pro Asp Gly Lys Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile
[1970] 530 535 540
[1971] Ser Asn Ala Thr Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr
[1972] 545 550 555 560
[1973] Val Asn Gly His Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln Thr

[1974] 565 570 575

[1975] Asn Thr Ile Ile Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu

[1976] 580 585 590

[1977] Ser Val Gly Glu Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu

[1978] 595 600 605

[1979] Asn Val Gly Ile Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln

[1980] 610 615 620

[1981] His Lys Lys Leu Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu

[1982] 625 630 635 640

[1983] Met Lys Lys Phe Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser

[1984] 645 650 655

[1985] Asp Gln Gly Leu Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys

[1986] 660 665 670

[1987] Lys Asn Ser Thr Phe Val Arg Val His Glu Lys

[1988] 675 680

[1989] <210> 84

[1990] <211> 723

[1991] <212> DNA

[1992] <213> 人工序列

[1993] <220>

[1994] <223> 融合蛋白BY24.5(κ,IgG4)的轻链亚基(BY24.5L)核苷酸序列

[1995] <400> 84

[1996] ctcgaggcca ccatggagac cgacacactc ctcctgtggg tgctgctgct gtgggtgcct 60

[1997] ggctccactg gcgacattca gatgacccag tctccaagct ctctgagcgc ttccgtgggc 120

[1998] gaccgcgtga caattacatg cctcgcatct cagaccattg gcacctggct gacatggtat 180

[1999] cagcagaagc ctggcaaggc ccctaagctg ctgatttaca ccgctacctc cctcgccgac 240

[2000] ggcgtgccat ctaggttctc tggctccggc tccggcacag acttcacact cactatttct 300

[2001] tccctccagc ccgaggactt cgccacatac tactgccagc aggtgtactc tatcccttgg 360

[2002] actttcggcg gcggcactaa ggtggagatt aagagaaccg tggccgcccc cagcgtgttc 420

[2003] atcttccctc ccagcgacga gcagctgaag tctggcaccg ccagcgtggt gtgcctgctg 480

[2004] aacaacttct acccccgcga ggccaaggtg cagtggaagg tggacaacgc cctgcagagc 540

[2005] ggcaacagcc aggagagcgt gaccgagcag gactccaagg acagcaccta cagcctgagc 600

[2006] agcaccctga ccctgagcaa ggccgactac gagaagcaca aggtgtacgc ctgcgaggtg 660

[2007] acccaccagg gactgtctag ccccgtgacc aagagcttca accggggcga gtgctaagaa 720

[2008] ttc 723

[2009] <210> 85

[2010] <211> 234

[2011] <212> PRT

[2012] <213> 人工序列

[2013] <220>

[2014] <223> 融合蛋白BY24.5(κ,IgG4)的轻链亚基(BY24.5L)氨基酸序列

[2015] <400> 85

[2016] Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
[2017] 1 5 10 15
[2018] Gly Ser Thr Gly Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser
[2019] 20 25 30
[2020] Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Leu Ala Ser Gln Thr
[2021] 35 40 45
[2022] Ile Gly Thr Trp Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
[2023] 50 55 60
[2024] Lys Leu Leu Ile Tyr Thr Ala Thr Ser Leu Ala Asp Gly Val Pro Ser
[2025] 65 70 75 80
[2026] Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
[2027] 85 90 95
[2028] Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Val Tyr
[2029] 100 105 110
[2030] Ser Ile Pro Trp Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
[2031] 115 120 125
[2032] Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
[2033] 130 135 140
[2034] Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
[2035] 145 150 155 160
[2036] Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
[2037] 165 170 175
[2038] Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
[2039] 180 185 190
[2040] Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
[2041] 195 200 205
[2042] His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
[2043] 210 215 220
[2044] Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
[2045] 225 230
[2046] <210> 86
[2047] <211> 2067
[2048] <212> DNA
[2049] <213> 人工序列
[2050] <220>
[2051] <223> 融合蛋白BY24.5(κ,IgG4)的重链-VID融合亚基(BY24.5H)核苷酸序列
[2052] <400> 86
[2053] tctagagcca ccatggagac cgacaccctg ctgctgtggg tgctgctcct gtgggtgcct 60
[2054] ggctccacag gcgaggtcca gctcgtcgag agtggaggcg gcctcgtgca gcccggcgga 120
[2055] agcctcagac tgtcttgtgc tgcatctggc ttcactttct ctagttacat gatgagttgg 180
[2056] gtgagacagg caccaggaaa gggattggag tgggtcgcaa caatcagtgg cggaggagca 240
[2057] aacacatact accccgatag cgtcaaggga cggttcacca ttagtcgcga taacgctaag 300

[2058] aactccctgt accttcagat gaatagtctc cgcgctgagg ataccgccgt gtactactgc 360
[2059] gcacggcagc tctactactt cgattactgg ggccagggca ccctcgtgac agtgtcttcc 420
[2060] gcctccacca agggcccttc cgtgttccct ctggcccctt gctcccgctc cacctccgag 480
[2061] tccaccgccg ccctgggctg cctggtgaag gactacttcc ctgagcctgt gaccgtgtcc 540
[2062] tggaactccg gcgccctgac ctccggcgtg cacaccttcc ctgccgtgct gcagtcctcc 600
[2063] ggcctgtact ccctgtcctc cgtggtgacc gtgccttcct cctccctggg caccaagacc 660
[2064] tacacctgca acgtggacca caagccttcc aacaccaagg tggacaagcg cgtggagtcc 720
[2065] aagtacggcc ctccttgccc tccttgccct gcccctgagt tcctgggcgg cccttccgtg 780
[2066] ttcctgttcc ctcctaagcc taaggacacc ctgatgatct cccgcacccc tgaggtgacc 840
[2067] tgcgtggtgg tggacgtgtc ccaggaggac cctgaggtgc agttcaactg gtacgtggac 900
[2068] ggcgtggagg tgcacaacgc caagaccaag cctcgcgagg agcagttcaa ctccacctac 960
[2069] cgcgtggtgt ccgtgctgac cgtgctgcac caggactggc tgaacggcaa ggagtacaag 1020
[2070] tgcaaggtgt ccaacaaggg cctgccttcc tccatcgaga agaccatctc caaggccaag 1080
[2071] ggccagcctc gcgagcctca ggtgtacacc ctgcctcctt cccaggagga gatgaccaag 1140
[2072] aaccaggtgt ccctgacctg cctggtgaag ggcttctacc cttccgacat cgccgtggag 1200
[2073] tgggagtcca acggccagcc tgagaacaac tacaagacca cccctcctgt gctggactcc 1260
[2074] gacggctcct tcttcctgta ctcccgcctg accgtggaca agtcccgctg gcaggagggc 1320
[2075] aacgtgttct cctgctccgt gatgcacgag gccctgcaca accactacac ccagaagtcc 1380
[2076] ctgtccctgt ccctgggcgg cggaggatct ggcggcggag gcagtggagg cggcggaagc 1440
[2077] gcttccgaca ccggccgccc tttcgtggag atgtactccg agatccctga gatcatccac 1500
[2078] atgaccgagg gccgcgagct ggtgatccct tgccgcgtga cctcccctaa catcaccgtg 1560
[2079] accctgaaga agttccctct ggacaccctg atccctgacg gcaagcgcat catctgggac 1620
[2080] tcccgcaagg gcttcatcat ctccaacgcc acctacaagg agatcggcct gctgacctgc 1680
[2081] gaggccaccg tgaacggcca cctgtacaag accaactacc tgacccaccg ccagaccaac 1740
[2082] accatcatcg acgtggtgct gtcccttcc cacggcatcg agctgtccgt gggcgagaag 1800
[2083] ctggtgctga actgcaccgc ccgcaccgag ctgaacgtgg gcatcgactt caactgggag 1860
[2084] taccttcct ccaagcacca gcacaagaag ctggtgaacc gcgacctgaa gacccagtcc 1920
[2085] ggctccgaga tgaagaagtt cctgtccacc ctgaccatcg acggcgtgac ccgctccgac 1980
[2086] cagggcctgt acacctgcgc cgcctcctcc ggcctgatga ccaagaagaa ctccaccttc 2040
[2087] gtgcgcgtgc acgagaagta agtcgac 2067
[2088] <210> 87
[2089] <211> 682
[2090] <212> PRT
[2091] <213> 人工序列
[2092] <220>
[2093] <223> 融合蛋白BY24.5(κ,IgG4)的重链-VID融合亚基(BY24.5H)氨基酸序列
[2094] <400> 87
[2095] Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
[2096] 1 5 10 15
[2097] Gly Ser Thr Gly Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
[2098] 20 25 30
[2099] Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr

[2100] 35 40 45
[2101] Phe Ser Ser Tyr Met Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly
[2102] 50 55 60
[2103] Leu Glu Trp Val Ala Thr Ile Ser Gly Gly Gly Ala Asn Thr Tyr Tyr
[2104] 65 70 75 80
[2105] Pro Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys
[2106] 85 90 95
[2107] Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala
[2108] 100 105 110
[2109] Val Tyr Tyr Cys Ala Arg Gln Leu Tyr Tyr Phe Asp Tyr Trp Gly Gln
[2110] 115 120 125
[2111] Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
[2112] 130 135 140
[2113] Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
[2114] 145 150 155 160
[2115] Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
[2116] 165 170 175
[2117] Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
[2118] 180 185 190
[2119] Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
[2120] 195 200 205
[2121] Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
[2122] 210 215 220
[2123] Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
[2124] 225 230 235 240
[2125] Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
[2126] 245 250 255
[2127] Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
[2128] 260 265 270
[2129] Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
[2130] 275 280 285
[2131] Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
[2132] 290 295 300
[2133] Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
[2134] 305 310 315 320
[2135] Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
[2136] 325 330 335
[2137] Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
[2138] 340 345 350
[2139] Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
[2140] 355 360 365
[2141] Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu

[2142] 370 375 380
[2143] Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
[2144] 385 390 395 400
[2145] Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
[2146] 405 410 415
[2147] Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
[2148] 420 425 430
[2149] Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
[2150] 435 440 445
[2151] His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Gly Gly
[2152] 450 455 460
[2153] Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ser Asp Thr
[2154] 465 470 475 480
[2155] Gly Arg Pro Phe Val Glu Met Tyr Ser Glu Ile Pro Glu Ile Ile His
[2156] 485 490 495
[2157] Met Thr Glu Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser Pro
[2158] 500 505 510
[2159] Asn Ile Thr Val Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro
[2160] 515 520 525
[2161] Asp Gly Lys Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser
[2162] 530 535 540
[2163] Asn Ala Thr Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr Val
[2164] 545 550 555 560
[2165] Asn Gly His Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln Thr Asn
[2166] 565 570 575
[2167] Thr Ile Ile Asp Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser
[2168] 580 585 590
[2169] Val Gly Glu Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn
[2170] 595 600 605
[2171] Val Gly Ile Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His
[2172] 610 615 620
[2173] Lys Lys Leu Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met
[2174] 625 630 635 640
[2175] Lys Lys Phe Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp
[2176] 645 650 655
[2177] Gln Gly Leu Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys
[2178] 660 665 670
[2179] Asn Ser Thr Phe Val Arg Val His Glu Lys
[2180] 675 680
[2181] <210> 88
[2182] <211> 720
[2183] <212> DNA

[2184] <213> 人工序列
[2185] <220>
[2186] <223> 融合蛋白BY24.6(κ,IgG2)的轻链亚基(BY24.6L)核苷酸序列
[2187] <400> 88
[2188] ctcgaggcca ccatggagac cgacacactc ctcctgtggg tgctgctgct gtgggtgcct 60
[2189] ggctccactg gcaatattca gatgacccag agtcctagta gcctgagcgc atccgtcggc 120
[2190] gaccgcgtga ccattacatg taaggccgga cagaacgtga ataattacct cgcttggtat 180
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[2201] <211> 233
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[2223] Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu
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[2225] Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro

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[2230] 180 185 190
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[2290] Lys Pro Thr Gln Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser
[2291] 35 40 45
[2292] Leu Ser Thr Ser Gly Thr Cys Val Ser Trp Ile Arg Gln Pro Pro Gly
[2293] 50 55 60
[2294] Lys Ala Leu Glu Trp Leu Ala Thr Ile Cys Trp Glu Asp Ser Lys Gly
[2295] 65 70 75 80
[2296] Tyr Asn Pro Ser Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser
[2297] 85 90 95
[2298] Lys Asn Gln Ala Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr
[2299] 100 105 110
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[2301] 115 120 125
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[2303] 130 135 140
[2304] Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser
[2305] 145 150 155 160
[2306] Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
[2307] 165 170 175
[2308] Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
[2309] 180 185 190

[2310] Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
[2311] 195 200 205
[2312] Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys
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[2315] 225 230 235 240
[2316] Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu
[2317] 245 250 255
[2318] Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
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[2345] 465 470 475 480
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[2351] 515 520 525

[2352] Asp Thr Leu Ile Pro Asp Gly Lys Arg Ile Ile Trp Asp Ser Arg Lys
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[2354] Gly Phe Ile Ile Ser Asn Ala Thr Tyr Lys Glu Ile Gly Leu Leu Thr
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[2356] Cys Glu Ala Thr Val Asn Gly His Leu Tyr Lys Thr Asn Tyr Leu Thr
[2357] 565 570 575
[2358] His Arg Gln Thr Asn Thr Ile Ile Asp Val Val Leu Ser Pro Ser His
[2359] 580 585 590
[2360] Gly Ile Glu Leu Ser Val Gly Glu Lys Leu Val Leu Asn Cys Thr Ala
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[2362] Arg Thr Glu Leu Asn Val Gly Ile Asp Phe Asn Trp Glu Tyr Pro Ser
[2363] 610 615 620
[2364] Ser Lys His Gln His Lys Lys Leu Val Asn Arg Asp Leu Lys Thr Gln
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[2366] Ser Gly Ser Glu Met Lys Lys Phe Leu Ser Thr Leu Thr Ile Asp Gly
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[2368] Val Thr Arg Ser Asp Gln Gly Leu Tyr Thr Cys Ala Ala Ser Ser Gly
[2369] 660 665 670
[2370] Leu Met Thr Lys Lys Asn Ser Thr Phe Val Arg Val His Glu Lys
[2371] 675 680 685
[2372] <210> 92
[2373] <211> 723
[2374] <212> DNA
[2375] <213> 人工序列
[2376] <220>
[2377] <223> 融合蛋白BY24.8(κ,IgG4)的轻链亚基(BY24.8L)核苷酸序列
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[2382] cagcagaagc ctggacagcc acctaagctg ctcattaact acgccttcca cagattcact 240
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[2391] ttc 723
[2392] <210> 93
[2393] <211> 234

[2394] <212> PRT

[2395] <213> 人工序列

[2396] <220>

[2397] <223> 融合蛋白BY24.8(κ,IgG4)的轻链亚基(BY24.8L)氨基酸序列

[2398] <400> 93

[2399] Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro

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[2402] 20 25 30

[2403] Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Gln Ser

[2404] 35 40 45

[2405] Val Ser Asn Asp Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro

[2406] 50 55 60

[2407] Lys Leu Leu Ile Asn Tyr Ala Phe His Arg Phe Thr Gly Val Pro Asp

[2408] 65 70 75 80

[2409] Arg Phe Ser Gly Ser Gly Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser

[2410] 85 90 95

[2411] Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys His Gln Ala Tyr

[2412] 100 105 110

[2413] Ser Ser Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg

[2414] 115 120 125

[2415] Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln

[2416] 130 135 140

[2417] Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr

[2418] 145 150 155 160

[2419] Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser

[2420] 165 170 175

[2421] Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr

[2422] 180 185 190

[2423] Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys

[2424] 195 200 205

[2425] His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro

[2426] 210 215 220

[2427] Val Thr Lys Ser Phe Asn Arg Gly Glu Cys

[2428] 225 230

[2429] <210> 94

[2430] <211> 2073

[2431] <212> DNA

[2432] <213> 人工序列

[2433] <220>

[2434] <223> 融合蛋白BY24.8(κ,IgG4)的重链-VID融合亚基(BY24.8H)核苷酸序列

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[2440] actaactaca acccatctct caagtctagg ctcacaatca gcaaggataa tagtaagagt 300
[2441] caggtgtccc tgaagatgag ttccgtcacc gctgccgata ccgctgtgta ctactgcgca 360
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[2445] gtgtcctgga actccggcgc cctgacctcc ggcgtgcaca ccttccctgc cgtgctgcag 600
[2446] tcctccggcc tgtactccct gtcctccgtg gtgaccgtgc cttcctcctc cctgggcacc 660
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[2448] gagtccaagt acggccctcc ttgccctcct tgccctgccc ctgagttcct gggcggccct 780
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[2453] tacaagtgca aggtgtccaa caagggcctg ccttcctcca tcgagaagac catctccaag 1080
[2454] gccaagggcc agcctcgcga gcctcaggtg tacaccctgc ctccttccca ggaggagatg 1140
[2455] accaagaacc aggtgtccct gacctgcctg gtgaagggct tctaccttc cgacatcgcc 1200
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[2468] cagtccggct ccgagatgaa gaagttcctg tccaccctga ccatcgacgg cgtgacccgc 1980
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[2471] <210> 95
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[2473] <212> PRT
[2474] <213> 人工序列
[2475] <220>
[2476] <223> 融合蛋白BY24.8(κ,IgG4)的重链-VID融合亚基(BY24.8H)氨基酸序列
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[2481] 20 25 30
[2482] Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser
[2483] 35 40 45
[2484] Leu Thr Ser Tyr Gly Val His Trp Ile Arg Gln Pro Pro Gly Lys Gly
[2485] 50 55 60
[2486] Leu Glu Trp Leu Gly Val Ile Trp Ala Gly Gly Ser Thr Asn Tyr Asn
[2487] 65 70 75 80
[2488] Pro Ser Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Asn Ser Lys Ser
[2489] 85 90 95
[2490] Gln Val Ser Leu Lys Met Ser Ser Val Thr Ala Ala Asp Thr Ala Val
[2491] 100 105 110
[2492] Tyr Tyr Cys Ala Arg Ala Tyr Gly Asn Tyr Trp Tyr Ile Asp Val Trp
[2493] 115 120 125
[2494] Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
[2495] 130 135 140
[2496] Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
[2497] 145 150 155 160
[2498] Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
[2499] 165 170 175
[2500] Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
[2501] 180 185 190
[2502] Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
[2503] 195 200 205
[2504] Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
[2505] 210 215 220
[2506] His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
[2507] 225 230 235 240
[2508] Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro
[2509] 245 250 255
[2510] Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
[2511] 260 265 270
[2512] Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
[2513] 275 280 285
[2514] Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
[2515] 290 295 300
[2516] Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
[2517] 305 310 315 320
[2518] Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
[2519] 325 330 335

[2520] Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
[2521] 340 345 350
[2522] Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
[2523] 355 360 365
[2524] Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
[2525] 370 375 380
[2526] Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
[2527] 385 390 395 400
[2528] Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
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[2530] Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
[2531] 420 425 430
[2532] Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
[2533] 435 440 445
[2534] Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
[2535] 450 455 460
[2536] Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ser
[2537] 465 470 475 480
[2538] Asp Thr Gly Arg Pro Phe Val Glu Met Tyr Ser Glu Ile Pro Glu Ile
[2539] 485 490 495
[2540] Ile His Met Thr Glu Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr
[2541] 500 505 510
[2542] Ser Pro Asn Ile Thr Val Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu
[2543] 515 520 525
[2544] Ile Pro Asp Gly Lys Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile
[2545] 530 535 540
[2546] Ile Ser Asn Ala Thr Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala
[2547] 545 550 555 560
[2548] Thr Val Asn Gly His Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln
[2549] 565 570 575
[2550] Thr Asn Thr Ile Ile Asp Val Val Leu Ser Pro Ser His Gly Ile Glu
[2551] 580 585 590
[2552] Leu Ser Val Gly Glu Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu
[2553] 595 600 605
[2554] Leu Asn Val Gly Ile Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His
[2555] 610 615 620
[2556] Gln His Lys Lys Leu Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser
[2557] 625 630 635 640
[2558] Glu Met Lys Lys Phe Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg
[2559] 645 650 655
[2560] Ser Asp Gln Gly Leu Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr
[2561] 660 665 670

[2562] Lys Lys Asn Ser Thr Phe Val Arg Val His Glu Lys
[2563] 675 680
[2564] <210> 96
[2565] <211> 723
[2566] <212> DNA
[2567] <213> 人工序列
[2568] <220>
[2569] <223> 融合蛋白BY24.9(κ,IgG4)的轻链亚基(BY24.9L)核苷酸序列
[2570] <400> 96
[2571] ctcgaggcca ccatggagac cgacacactc ctcctgtggg tgctgctgct gtgggtgcct 60
[2572] ggctccactg gcgatattca gatgacacag tccccaagtt ccctgagcgc ctccgtcgga 120
[2573] gaccgggtca ccattacttg tcgcgcttct cagagcgtga gtaattacct cgattggtat 180
[2574] cagcagaagc caggaaaggc tcctaagctg ctcatctacg acgcatccac ccgcgcaaca 240
[2575] ggcgtgccta gccggtttag cggatctgga agtggcactg atttcacact cacaatctct 300
[2576] agtctgcaac ccgaggactt tgctacatac tactgtcagc agaacatgca gctgccactg 360
[2577] acattcggcc agggaactaa ggtggagatt aagagaaccg tggccgcccc cagcgtgttc 420
[2578] atcttccctc ccagcgacga gcagctgaag tctggcaccg ccagcgtggt gtgcctgctg 480
[2579] aacaacttct acccccgcga ggccaaggtg cagtggaagg tggacaacgc cctgcagagc 540
[2580] ggcaacagcc aggagagcgt gaccgagcag gactccaagg acagcaccta cagcctgagc 600
[2581] agcaccctga ccctgagcaa ggccgactac gagaagcaca aggtgtacgc ctgcgaggtg 660
[2582] acccaccagg gactgtctag ccccgtgacc aagagcttca accggggcga gtgctaagaa 720
[2583] ttc 723
[2584] <210> 97
[2585] <211> 234
[2586] <212> PRT
[2587] <213> 人工序列
[2588] <220>
[2589] <223> 融合蛋白BY24.9(κ,IgG4)的轻链亚基(BY24.9L)氨基酸序列
[2590] <400> 97
[2591] Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
[2592] 1 5 10 15
[2593] Gly Ser Thr Gly Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser
[2594] 20 25 30
[2595] Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser
[2596] 35 40 45
[2597] Val Ser Asn Tyr Leu Asp Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
[2598] 50 55 60
[2599] Lys Leu Leu Ile Tyr Asp Ala Ser Thr Arg Ala Thr Gly Val Pro Ser
[2600] 65 70 75 80
[2601] Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
[2602] 85 90 95
[2603] Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Asn Met

[2604] 100 105 110

[2605] Gln Leu Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg

[2606] 115 120 125

[2607] Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln

[2608] 130 135 140

[2609] Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr

[2610] 145 150 155 160

[2611] Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser

[2612] 165 170 175

[2613] Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr

[2614] 180 185 190

[2615] Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys

[2616] 195 200 205

[2617] His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro

[2618] 210 215 220

[2619] Val Thr Lys Ser Phe Asn Arg Gly Glu Cys

[2620] 225 230

[2621] <210> 98

[2622] <211> 2055

[2623] <212> DNA

[2624] <213> 人工序列

[2625] <220>

[2626] <223> 融合蛋白BY24.9(κ,IgG4)的重链-VID融合亚基(BY24.9H)核苷酸序列

[2627] <400> 98

[2628] tctagagcca ccatggagac cgacaccctg ctgctgtggg tgctgctcct gtgggtgcct 60

[2629] ggctccacag gcgtgcagct cgtcgagtcc ggcggaggcg tggtccagcc aggacgcagt 120

[2630] ctgcgcctgg attgtaaggc aagcggcatc acctttagta actacggtat gcactgggtg 180

[2631] agacaggctc ccggaaaggg cctagaatgg gtggccgtca tttggtacga ctcttctagg 240

[2632] aagtactacg ccgatagtgt caagggacgg ttcacaatct ctcgcgataa tagcaagaat 300

[2633] acactgtttt tgcaaatgaa ctccctcaga gctgaggata ccgctgtgta ctactgcgca 360

[2634] accaacaatg attactgggg acagggcacc ctcgtgacag tgtcttccgc ctccaccaag 420

[2635] ggcccttccg tgttccctct ggcccccttgc tcccgctcca cctccgagtc caccgccgcc 480

[2636] ctgggctgcc tggtgaagga ctacttccct gagcctgtga ccgtgtcctg gaactccggc 540

[2637] gccctgacct ccggcgtgca caccttccct gccgtgctgc agtcctccgg cctgtactcc 600

[2638] ctgtcctccg tggtgaccgt gccttcctcc tccctgggca ccaagaccta cacctgcaac 660

[2639] gtggaccaca agccttccaa caccaaggtg gacaagcgcg tggagtccaa gtacggccct 720

[2640] ccttgccctc cttgccctgc ccctgagttc ctgggcggcc cttccgtgtt cctgttccct 780

[2641] cctaagccta aggacaccct gatgatctcc cgcacccctg aggtgacctg cgtggtggtg 840

[2642] gacgtgtccc aggaggaccc tgaggtgcag ttcaactggt acgtggacgg cgtggaggtg 900

[2643] cacaacgcca agaccaagcc tcgcgaggag cagttcaact ccacctaccg cgtggtgtcc 960

[2644] gtgctgaccg tgctgcacca ggactggctg aacggcaagg agtacaagtg caaggtgtcc 1020

[2645] aacaagggcc tgccttcctc catcgagaag accatctcca aggccaaggg ccagcctcgc 1080

[2646] gagcctcagg tgtacaccct gcctccttcc caggaggaga tgaccaagaa ccaggtgtcc 1140
[2647] ctgacctgcc tggtgaaggg cttctaccct tccgacatcg ccgtggagtg ggagtccaac 1200
[2648] ggccagcctg agaacaacta caagaccacc cctcctgtgc tggactccga cggctccttc 1260
[2649] ttcctgtact cccgcctgac cgtggacaag tcccgctggc aggagggcaa cgtgttctcc 1320
[2650] tgctccgtga tgcacgaggc cctgcacaac cactacaccc agaagtccct gtccctgtcc 1380
[2651] ctgggcggcg gaggatctgg cggcggaggc agtggaggcg gcggaagcgc ttccgacacc 1440
[2652] ggccgccctt tcgtggagat gtactccgag atccctgaga tcatccacat gaccgagggc 1500
[2653] cgcgagctgg tgatcccttg ccgcgtgacc tcccctaaca tcaccgtgac cctgaagaag 1560
[2654] ttccctctgg acaccctgat ccctgacggc aagcgcatca tctgggactc ccgcaagggc 1620
[2655] ttcatcatct ccaacgccac ctacaaggag atcggcctgc tgacctgcga ggccaccgtg 1680
[2656] aacggccacc tgtacaagac caactacctg acccaccgcc agaccaacac catcatcgac 1740
[2657] gtggtgctgt ccccttccca cggcatcgag ctgtccgtgg gcgagaagct ggtgctgaac 1800
[2658] tgcaccgccc gcaccgagct gaacgtgggc atcgacttca actgggagta cccttcctcc 1860
[2659] aagcaccagc acaagaagct ggtgaaccgc gacctgaaga cccagtccgg ctccgagatg 1920
[2660] aagaagttcc tgtccaccct gaccatcgac ggcgtgaccc gctccgacca gggcctgtac 1980
[2661] acctgcgccg cctcctccgg cctgatgacc aagaagaact ccaccttcgt gcgcgtgcac 2040
[2662] gagaagtaag tcgac 2055
[2663] <210> 99
[2664] <211> 678
[2665] <212> PRT
[2666] <213> 人工序列
[2667] <220>
[2668] <223> 融合蛋白BY24.9(κ,IgG4)的重链-VID融合亚基(BY24.9H)氨基酸序列
[2669] <400> 99
[2670] Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
[2671] 1 5 10 15
[2672] Gly Ser Thr Gly Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
[2673] 20 25 30
[2674] Pro Gly Arg Ser Leu Arg Leu Asp Cys Lys Ala Ser Gly Ile Thr Phe
[2675] 35 40 45
[2676] Ser Asn Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
[2677] 50 55 60
[2678] Glu Trp Val Ala Val Ile Trp Tyr Asp Ser Ser Arg Lys Tyr Tyr Ala
[2679] 65 70 75 80
[2680] Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
[2681] 85 90 95
[2682] Thr Leu Phe Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
[2683] 100 105 110
[2684] Tyr Tyr Cys Ala Thr Asn Asn Asp Tyr Trp Gly Gln Gly Thr Leu Val
[2685] 115 120 125
[2686] Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
[2687] 130 135 140

[2688] Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu
[2689] 145 150 155 160
[2690] Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
[2691] 165 170 175
[2692] Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
[2693] 180 185 190
[2694] Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
[2695] 195 200 205
[2696] Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr
[2697] 210 215 220
[2698] Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro
[2699] 225 230 235 240
[2700] Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
[2701] 245 250 255
[2702] Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
[2703] 260 265 270
[2704] Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn
[2705] 275 280 285
[2706] Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
[2707] 290 295 300
[2708] Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
[2709] 305 310 315 320
[2710] Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
[2711] 325 330 335
[2712] Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys
[2713] 340 345 350
[2714] Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu
[2715] 355 360 365
[2716] Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
[2717] 370 375 380
[2718] Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
[2719] 385 390 395 400
[2720] Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
[2721] 405 410 415
[2722] Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly
[2723] 420 425 430
[2724] Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
[2725] 435 440 445
[2726] Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Gly Gly Gly Ser Gly Gly
[2727] 450 455 460
[2728] Gly Gly Ser Gly Gly Gly Gly Ser Ala Ser Asp Thr Gly Arg Pro Phe
[2729] 465 470 475 480

[2730] Val Glu Met Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu Gly
[2731] 485 490 495
[2732] Arg Glu Leu Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr Val
[2733] 500 505 510
[2734] Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys Arg
[2735] 515 520 525
[2736] Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr Tyr
[2737] 530 535 540
[2738] Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His Leu
[2739] 545 550 555 560
[2740] Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile Asp
[2741] 565 570 575
[2742] Val Val Leu Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu Lys
[2743] 580 585 590
[2744] Leu Val Leu Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile Asp
[2745] 595 600 605
[2746] Phe Asn Trp Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu Val
[2747] 610 615 620
[2748] Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe Leu
[2749] 625 630 635 640
[2750] Ser Thr Leu Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu Tyr
[2751] 645 650 655
[2752] Thr Cys Ala Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr Phe
[2753] 660 665 670
[2754] Val Arg Val His Glu Lys
[2755] 675
[2756] <210> 100
[2757] <211> 729
[2758] <212> DNA
[2759] <213> 人工序列
[2760] <220>
[2761] <223> 融合蛋白BY24.10(κ,IgG4)的轻链亚基(BY24.10L)核苷酸序列
[2762] <400> 100
[2763] ctcgaggcca ccatggagac cgacacactc ctcctgtggg tgctgctgct gtgggtgcct 60
[2764] ggctccactg gcctcagtta cgtcctcaca cagcctccat ccgtgtctgt gagtcccgga 120
[2765] cagaccgcaa gaatcacatg tagcggcgac gcactgccta agcagtacgc ttactggtat 180
[2766] cagcagaagc caggacaggc acctgtgctg gtgatctaca aggatagcga gcgcccaagt 240
[2767] ggcattcccg agagatttag tggctcttct agtggaacaa ccgtcaccct gactatttcc 300
[2768] ggcgtgcagg ccgaggatga ggccgattac tactgtcagt ctgctgactc tagcggaaca 360
[2769] tacgtcgtgt ttggaggcgg aactaaggtg gagattaaga gaaccgtggc cgcccccagc 420
[2770] gtgttcatct tccctcccag cgacgagcag ctgaagtctg gcaccgccag cgtggtgtgc 480
[2771] ctgctgaaca acttctaccc ccgcgaggcc aaggtgcagt ggaaggtgga caacgccctg 540

[2772] cagagcggca acagccagga gagcgtgacc gagcaggact ccaaggacag cacctacagc 600
[2773] ctgagcagca ccctgaccct gagcaaggcc gactacgaga agcacaaggt gtacgcctgc 660
[2774] gaggtgaccc accagggact gtctagcccc gtgaccaaga gcttcaaccg gggcgagtgc 720
[2775] taagaattc 729
[2776] <210> 101
[2777] <211> 236
[2778] <212> PRT
[2779] <213> 人工序列
[2780] <220>
[2781] <223> 融合蛋白BY24.10(κ,IgG4)的轻链亚基(BY24.10L)氨基酸序列
[2782] <400> 101
[2783] Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
[2784] 1 5 10 15
[2785] Gly Ser Thr Gly Leu Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser
[2786] 20 25 30
[2787] Val Ser Pro Gly Gln Thr Ala Arg Ile Thr Cys Ser Gly Asp Ala Leu
[2788] 35 40 45
[2789] Pro Lys Gln Tyr Ala Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
[2790] 50 55 60
[2791] Val Leu Val Ile Tyr Lys Asp Ser Glu Arg Pro Ser Gly Ile Pro Glu
[2792] 65 70 75 80
[2793] Arg Phe Ser Gly Ser Ser Ser Gly Thr Thr Val Thr Leu Thr Ile Ser
[2794] 85 90 95
[2795] Gly Val Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Ala Asp
[2796] 100 105 110
[2797] Ser Ser Gly Thr Tyr Val Val Phe Gly Gly Gly Thr Lys Val Glu Ile
[2798] 115 120 125
[2799] Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
[2800] 130 135 140
[2801] Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
[2802] 145 150 155 160
[2803] Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
[2804] 165 170 175
[2805] Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
[2806] 180 185 190
[2807] Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
[2808] 195 200 205
[2809] Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
[2810] 210 215 220
[2811] Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
[2812] 225 230 235
[2813] <210> 102

[2814] <211> 2079

[2815] <212> DNA

[2816] <213> 人工序列

[2817] <220>

[2818] <223> 融合蛋白BY24.10(κ,IgG4)的重链-VID融合亚基(BY24.10H)核苷酸序列

[2819] <400> 102

[2820] tctagagcca ccatggagac cgacaccctg ctgctgtggg tgctgctcct gtgggtgcct 60

[2821] ggctccacag gcgacctcgt gcagtccggc gccgaggtga agaagcccgg cgcatccgtc 120

[2822] aaggtgtctt gcaaggcaag tggctacact ttcaccagtt acggaatcag ttgggtcaga 180

[2823] caggcacctg gccagggcct ggagtggatg ggctggatta gcgcttacaa cggaaacacc 240

[2824] aattacgctc agaagctcca gggtcgggtg actatgacaa ccgacacatc taccagcacc 300

[2825] gcatacatgg agctgcgtag tctgagatcc gacgataccg ccgtgtacta ctgtgctcgc 360

[2826] ggcagaggat actcctacgg aattgatgca ttcgatattt ggggacaggg aaccctcgtg 420

[2827] acagtgtctt ccgcctccac caagggccct tccgtgttcc ctctggcccc ttgctcccgc 480

[2828] tccacctccg agtccaccgc cgccctgggc tgcctggtga aggactactt ccctgagcct 540

[2829] gtgaccgtgt cctggaactc cggcgccctg acctccggcg tgcacacctt ccctgccgtg 600

[2830] ctgcagtcct ccggcctgta ctccctgtcc tccgtggtga ccgtgccttc ctcctccctg 660

[2831] ggcaccaaga cctacacctg caacgtggac cacaagcctt ccaacaccaa ggtggacaag 720

[2832] cgcgtggagt ccaagtacgg ccctccttgc cctccttgcc ctgcccctga gttcctgggc 780

[2833] ggcccttccg tgttcctgtt ccctcctaag cctaaggaca ccctgatgat ctcccgcacc 840

[2834] cctgaggtga cctgcgtggt ggtggacgtg tcccaggagg accctgaggt gcagttcaac 900

[2835] tggtacgtgg acggcgtgga ggtgcacaac gccaagacca agcctcgcga ggagcagttc 960

[2836] aactccacct accgcgtggt gtccgtgctg accgtgctgc accaggactg gctgaacggc 1020

[2837] aaggagtaca agtgcaaggt gtccaacaag ggcctgcctt cctccatcga gaagaccatc 1080

[2838] tccaaggcca agggccagcc tcgcgagcct caggtgtaca ccctgcctcc ttcccaggag 1140

[2839] gagatgacca agaaccaggt gtccctgacc tgcctggtga agggcttcta cccttccgac 1200

[2840] atcgccgtgg agtgggagtc caacggccag cctgagaaca actacaagac cacccctcct 1260

[2841] gtgctggact ccgacggctc cttcttcctg tactcccgcc tgaccgtgga caagtcccgc 1320

[2842] tggcaggagg gcaacgtgtt ctcctgctcc gtgatgcacg aggccctgca caaccactac 1380

[2843] acccagaagt ccctgtccct gtccctgggc ggcggaggat ctggcggcgg aggcagtgga 1440

[2844] ggcggcggaa gcgcttccga caccggccgc cctttcgtgg agatgtactc cgagatccct 1500

[2845] gagatcatcc acatgaccga gggccgcgag ctggtgatcc cttgccgcgt gacctccct 1560

[2846] aacatcaccg tgaccctgaa gaagttccct ctggacaccc tgatccctga cggcaagcgc 1620

[2847] atcatctggg actcccgcaa gggcttcatc atctccaacg ccacctacaa ggagatcggc 1680

[2848] ctgctgacct gcgaggccac cgtgaacggc cacctgtaca agaccaacta cctgacccac 1740

[2849] cgccagacca acaccatcat cgacgtggtg ctgtcccctt cccacggcat cgagctgtcc 1800

[2850] gtgggcgaga agctggtgct gaactgcacc gcccgcaccg agctgaacgt gggcatcgac 1860

[2851] ttcaactggg agtaccttc ctccaagcac cagcacaaga agctggtgaa ccgcgacctg 1920

[2852] aagacccagt ccggctccga gatgaagaag ttcctgtcca ccctgaccat cgacggcgtg 1980

[2853] acccgctccg accagggcct gtacacctgc gccgcctcct ccggcctgat gaccaagaag 2040

[2854] aactccacct tcgtgcgcgt gcacgagaag taagtcgac 2079

[2855] <210> 103

[2856] <211> 686

[2857] <212> PRT

[2858] <213> 人工序列

[2859] <220>

[2860] <223> 融合蛋白BY24.10(κ,IgG4)的重链-VID融合亚基(BY24.10H)氨基酸序列

[2861] <400> 103

[2862] Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro

[2863] 1 5 10 15

[2864] Gly Ser Thr Gly Asp Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro

[2865] 20 25 30

[2866] Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr

[2867] 35 40 45

[2868] Ser Tyr Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu

[2869] 50 55 60

[2870] Trp Met Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln

[2871] 65 70 75 80

[2872] Lys Leu Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr

[2873] 85 90 95

[2874] Ala Tyr Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr

[2875] 100 105 110

[2876] Tyr Cys Ala Arg Gly Arg Gly Tyr Ser Tyr Gly Ile Asp Ala Phe Asp

[2877] 115 120 125

[2878] Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys

[2879] 130 135 140

[2880] Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu

[2881] 145 150 155 160

[2882] Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro

[2883] 165 170 175

[2884] Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr

[2885] 180 185 190

[2886] Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val

[2887] 195 200 205

[2888] Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn

[2889] 210 215 220

[2890] Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser

[2891] 225 230 235 240

[2892] Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly

[2893] 245 250 255

[2894] Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met

[2895] 260 265 270

[2896] Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln

[2897] 275 280 285

[2898] Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
[2899] 290 295 300
[2900] His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr
[2901] 305 310 315 320
[2902] Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
[2903] 325 330 335
[2904] Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
[2905] 340 345 350
[2906] Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
[2907] 355 360 365
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[2909] 370 375 380
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[2913] 405 410 415
[2914] Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val
[2915] 420 425 430
[2916] Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
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[2918] His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
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[2921] 465 470 475 480
[2922] Ala Ser Asp Thr Gly Arg Pro Phe Val Glu Met Tyr Ser Glu Ile Pro
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[2924] Glu Ile Ile His Met Thr Glu Gly Arg Glu Leu Val Ile Pro Cys Arg
[2925] 500 505 510
[2926] Val Thr Ser Pro Asn Ile Thr Val Thr Leu Lys Lys Phe Pro Leu Asp
[2927] 515 520 525
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[2929] 530 535 540
[2930] Phe Ile Ile Ser Asn Ala Thr Tyr Lys Glu Ile Gly Leu Leu Thr Cys
[2931] 545 550 555 560
[2932] Glu Ala Thr Val Asn Gly His Leu Tyr Lys Thr Asn Tyr Leu Thr His
[2933] 565 570 575
[2934] Arg Gln Thr Asn Thr Ile Ile Asp Val Val Leu Ser Pro Ser His Gly
[2935] 580 585 590
[2936] Ile Glu Leu Ser Val Gly Glu Lys Leu Val Leu Asn Cys Thr Ala Arg
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[2938] Thr Glu Leu Asn Val Gly Ile Asp Phe Asn Trp Glu Tyr Pro Ser Ser
[2939] 610 615 620

[2940] Lys His Gln His Lys Lys Leu Val Asn Arg Asp Leu Lys Thr Gln Ser
[2941] 625 630 635 640
[2942] Gly Ser Glu Met Lys Lys Phe Leu Ser Thr Leu Thr Ile Asp Gly Val
[2943] 645 650 655
[2944] Thr Arg Ser Asp Gln Gly Leu Tyr Thr Cys Ala Ala Ser Ser Gly Leu
[2945] 660 665 670
[2946] Met Thr Lys Lys Asn Ser Thr Phe Val Arg Val His Glu Lys
[2947] 675 680 685
[2948] <210> 104
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[2950] <212> DNA
[2951] <213> 人工序列
[2952] <220>
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[2954] <400> 104
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[2965] acctacagcc tgagcagcac cctgaccctg agcaaggccg actacgagaa gcacaaggtg 660
[2966] tacgcctgcg aggtgaccca ccagggactg tctagccccg tgaccaagag cttcaaccgg 720
[2967] ggcgagtgct aagaattc 738
[2968] <210> 105
[2969] <211> 239
[2970] <212> PRT
[2971] <213> 人工序列
[2972] <220>
[2973] <223> 融合蛋白BY24.11(κ,IgG4)的轻链亚基(BY24.11L)氨基酸序列
[2974] <400> 105
[2975] Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
[2976] 1 5 10 15
[2977] Gly Ser Thr Gly Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro
[2978] 20 25 30
[2979] Val Thr Leu Gly Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser
[2980] 35 40 45
[2981] Ile Val His Ser Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys

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[2983] Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe

[2984] 65 70 75 80

[2985] Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe

[2986] 85 90 95

[2987] Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr

[2988] 100 105 110

[2989] Cys Phe Gln Gly Ser His Val Pro Leu Thr Phe Gly Gln Gly Thr Lys

[2990] 115 120 125

[2991] Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro

[2992] 130 135 140

[2993] Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu

[2994] 145 150 155 160

[2995] Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp

[2996] 165 170 175

[2997] Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp

[2998] 180 185 190

[2999] Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys

[3000] 195 200 205

[3001] Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln

[3002] 210 215 220

[3003] Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys

[3004] 225 230 235

[3005] <210> 106

[3006] <211> 2094

[3007] <212> DNA

[3008] <213> 人工序列

[3009] <220>

[3010] <223> 融合蛋白BY24.11(κ,IgG4)的重链-VID融合亚基(BY24.11H)核苷酸序列

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[3013] ggctccacag gccagggcca gctcgtgcag agtggcgcag aggtgaagaa gcccggagca 120

[3014] tccgtcaagg tcagttgcaa ggcctctgga tacaccttta ccgattacga gatgcactgg 180

[3015] gtgcggcagg ctcctggaca gggactcgaa tggatgggcg tcattgagtc cgagaccggc 240

[3016] ggaacagctt acaatcagaa gtttcaggga cgggtgacac tcactgccga taagtcttct 300

[3017] agcaccgcct acatggaact ttcctctctg cgctcagagg ataccgctgt gtactactgt 360

[3018] acacgcgagg gaatcacaac tgtcgcaacc acatactact ggtacttcga cgtgtggggc 420

[3019] cagggaaccc tcgtgacagt gtcttccgcc tccaccaagg gcccttccgt gttccctctg 480

[3020] gcccccttgct cccgctccac ctccgagtcc accgccgccc tgggctgcct ggtgaaggac 540

[3021] tacttccctg agcctgtgac cgtgtcctgg aactccggcg ccctgacctc cggcgtgcac 600

[3022] accttccctg ccgtgctgca gtcctccggc ctgtactccc tgtcctccgt ggtgaccgtg 660

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[3032] ttctaccctt ccgacatcgc cgtggagtgg gagtccaacg gccagcctga gaacaactac 1260
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[3047] <210> 107
[3048] <211> 691
[3049] <212> PRT
[3050] <213> 人工序列
[3051] <220>
[3052] <223> 融合蛋白BY24.11(κ,IgG4)的重链-VID融合亚基(BY24.11H)氨基酸序列
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[3054] Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
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[3057] 20 25 30
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[3059] 35 40 45
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[3061] 50 55 60
[3062] Leu Glu Trp Met Gly Val Ile Glu Ser Glu Thr Gly Gly Thr Ala Tyr
[3063] 65 70 75 80
[3064] Asn Gln Lys Phe Gln Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Ser
[3065] 85 90 95

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[3067] 100 105 110
[3068] Val Tyr Tyr Cys Thr Arg Glu Gly Ile Thr Thr Val Ala Thr Thr Tyr
[3069] 115 120 125
[3070] Tyr Trp Tyr Phe Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser
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[3072] Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser
[3073] 145 150 155 160
[3074] Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
[3075] 165 170 175
[3076] Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
[3077] 180 185 190
[3078] Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
[3079] 195 200 205
[3080] Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys
[3081] 210 215 220
[3082] Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp
[3083] 225 230 235 240
[3084] Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala
[3085] 245 250 255
[3086] Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
[3087] 260 265 270
[3088] Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
[3089] 275 280 285
[3090] Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val
[3091] 290 295 300
[3092] Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
[3093] 305 310 315 320
[3094] Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
[3095] 325 330 335
[3096] Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly
[3097] 340 345 350
[3098] Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
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[3104] Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
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[3106] Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
[3107] 420 425 430

[3108] Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe
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[3111] 450 455 460
[3112] Ser Leu Ser Leu Ser Leu Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
[3113] 465 470 475 480
[3114] Gly Gly Gly Gly Ser Ala Ser Asp Thr Gly Arg Pro Phe Val Glu Met
[3115] 485 490 495
[3116] Tyr Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu Gly Arg Glu Leu
[3117] 500 505 510
[3118] Val Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr Val Thr Leu Lys
[3119] 515 520 525
[3120] Lys Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys Arg Ile Ile Trp
[3121] 530 535 540
[3122] Asp Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr Tyr Lys Glu Ile
[3123] 545 550 555 560
[3124] Gly Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His Leu Tyr Lys Thr
[3125] 565 570 575
[3126] Asn Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile Asp Val Val Leu
[3127] 580 585 590
[3128] Ser Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu Lys Leu Val Leu
[3129] 595 600 605
[3130] Asn Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile Asp Phe Asn Trp
[3131] 610 615 620
[3132] Glu Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu Val Asn Arg Asp
[3133] 625 630 635 640
[3134] Leu Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe Leu Ser Thr Leu
[3135] 645 650 655
[3136] Thr Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu Tyr Thr Cys Ala
[3137] 660 665 670
[3138] Ala Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr Phe Val Arg Val
[3139] 675 680 685
[3140] His Glu Lys
[3141] 690
[3142] <210> 108
[3143] <211> 735
[3144] <212> DNA
[3145] <213> 人工序列
[3146] <220>
[3147] <223> 融合蛋白BY24.12(κ,IgG4)的轻链亚基(BY24.12L)核苷酸序列
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[3161] gagtgctaag aattc 735
[3162] <210> 109
[3163] <211> 238
[3164] <212> PRT
[3165] <213> 人工序列
[3166] <220>
[3167] <223> 融合蛋白BY24.12(κ,IgG4)的轻链亚基(BY24.12L)氨基酸序列
[3168] <400> 109
[3169] Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
[3170] 1 5 10 15
[3171] Gly Ser Thr Gly Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala
[3172] 20 25 30
[3173] Val Ser Pro Gly Gln Arg Ala Thr Ile Thr Cys Arg Ala Ser Glu Ser
[3174] 35 40 45
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[3176] 50 55 60
[3177] Gly Gln Pro Pro Lys Leu Leu Ile Tyr Thr Ser Ser Asn Lys Asp Thr
[3178] 65 70 75 80
[3179] Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
[3180] 85 90 95
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[3182] 100 105 110
[3183] Gln Gln Ser Lys Glu Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Val
[3184] 115 120 125
[3185] Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro
[3186] 130 135 140
[3187] Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu
[3188] 145 150 155 160
[3189] Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn
[3190] 165 170 175
[3191] Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser

[3192] 180 185 190

[3193] Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala

[3194] 195 200 205

[3195] Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly

[3196] 210 215 220

[3197] Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys

[3198] 225 230 235

[3199] <210> 110

[3200] <211> 2073

[3201] <212> DNA

[3202] <213> 人工序列

[3203] <220>

[3204] <223> 融合蛋白BY24.12(κ,IgG4)的重链-VID融合亚基(BY24.12H)核苷酸序列

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[3209] gtgagacagg ctcctggaaa gggattagag tgggtcgcaa ctattagtgg cggaggaagc 240

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[3211] aacacactgt acctacagat gaatagcctg agagcagagg ataccgctgt gtactactgc 360

[3212] gcacgccagc tcaattacgc atggtttgct tactggggcc agggcaccct cgtgacagtg 420

[3213] tcttccgcct ccaccaaggg cccttccgtg ttccctctgg ccccttgctc ccgctccacc 480

[3214] tccgagtcca ccgccgccct gggctgcctg gtgaaggact acttccctga gcctgtgacc 540

[3215] gtgtcctgga actccggcgc cctgacctcc ggcgtgcaca ccttccctgc cgtgctgcag 600

[3216] tcctccggcc tgtactccct gtcctccgtg gtgaccgtgc cttcctcctc cctgggcacc 660

[3217] aagacctaca cctgcaacgt ggaccacaag ccttccaaca ccaaggtgga caagcgcgtg 720

[3218] gagtccaagt acggccctcc ttgccctcct tgccctgccc ctgagttcct gggcggccct 780

[3219] tccgtgttcc tgttccctcc taagcctaag gacaccctga tgatctcccg cacccctgag 840

[3220] gtgacctgcg tggtggtgga cgtgtcccag gaggaccctg aggtgcagtt caactggtac 900

[3221] gtggacggcg tggaggtgca caacgccaag accaagcctc gcgaggagca gttcaactcc 960

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[3223] tacaagtgca aggtgtccaa caagggcctg ccttcctcca tcgagaagac catctccaag 1080

[3224] gccaagggcc agcctcgcga gcctcaggtg tacaccctgc ctccttccca ggaggagatg 1140

[3225] accaagaacc aggtgtccct gacctgcctg gtgaagggct tctacccttc cgacatcgcc 1200

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[3227] gactccgacg gctccttctt cctgtactcc cgcctgaccg tggacaagtc ccgctggcag 1320

[3228] gagggcaacg tgttctcctg ctccgtgatg cacgaggccc tgcacaacca ctacacccag 1380

[3229] aagtccctgt ccctgtccct gggcggcgga ggatctggcg gcggaggcag tggaggcggc 1440

[3230] ggaagcgctt ccgacaccgg ccgccctttc gtggagatgt actccgagat ccctgagatc 1500

[3231] atccacatga ccgagggccg cgagctggtg atcccttgcc gcgtgacctc ccctaacatc 1560

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[3237] tgggagtacc cttcctccaa gcaccagcac aagaagctgg tgaaccgcga cctgaagacc 1920
[3238] cagtccggct ccgagatgaa gaagttcctg tccaccctga ccatcgacgg cgtgacccgc 1980
[3239] tccgaccagg gcctgtacac ctgcgccgcc tcctccggcc tgatgaccaa gaagaactcc 2040
[3240] accttcgtgc gcgtgcacga gaagtaagtc gac 2073
[3241] <210> 111
[3242] <211> 684
[3243] <212> PRT
[3244] <213> 人工序列
[3245] <220>
[3246] <223> 融合蛋白BY24.12(κ,IgG4)的重链-VID融合亚基(BY24.12H)氨基酸序列
[3247] <400> 111
[3248] Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
[3249] 1 5 10 15
[3250] Gly Ser Thr Gly Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
[3251] 20 25 30
[3252] Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr
[3253] 35 40 45
[3254] Phe Ser Ser Tyr Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly
[3255] 50 55 60
[3256] Leu Glu Trp Val Ala Thr Ile Ser Gly Gly Gly Ser Asp Thr Tyr Tyr
[3257] 65 70 75 80
[3258] Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys
[3259] 85 90 95
[3260] Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala
[3261] 100 105 110
[3262] Val Tyr Tyr Cys Ala Arg Gln Leu Asn Tyr Ala Trp Phe Ala Tyr Trp
[3263] 115 120 125
[3264] Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
[3265] 130 135 140
[3266] Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
[3267] 145 150 155 160
[3268] Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
[3269] 165 170 175
[3270] Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
[3271] 180 185 190
[3272] Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
[3273] 195 200 205
[3274] Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp
[3275] 210 215 220

[3276] His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr
[3277] 225 230 235 240
[3278] Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro
[3279] 245 250 255
[3280] Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
[3281] 260 265 270
[3282] Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp
[3283] 275 280 285
[3284] Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
[3285] 290 295 300
[3286] Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val
[3287] 305 310 315 320
[3288] Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
[3289] 325 330 335
[3290] Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys
[3291] 340 345 350
[3292] Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
[3293] 355 360 365
[3294] Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
[3295] 370 375 380
[3296] Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
[3297] 385 390 395 400
[3298] Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
[3299] 405 410 415
[3300] Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys
[3301] 420 425 430
[3302] Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu
[3303] 435 440 445
[3304] Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly
[3305] 450 455 460
[3306] Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ser
[3307] 465 470 475 480
[3308] Asp Thr Gly Arg Pro Phe Val Glu Met Tyr Ser Glu Ile Pro Glu Ile
[3309] 485 490 495
[3310] Ile His Met Thr Glu Gly Arg Glu Leu Val Ile Pro Cys Arg Val Thr
[3311] 500 505 510
[3312] Ser Pro Asn Ile Thr Val Thr Leu Lys Lys Phe Pro Leu Asp Thr Leu
[3313] 515 520 525
[3314] Ile Pro Asp Gly Lys Arg Ile Ile Trp Asp Ser Arg Lys Gly Phe Ile
[3315] 530 535 540
[3316] Ile Ser Asn Ala Thr Tyr Lys Glu Ile Gly Leu Leu Thr Cys Glu Ala
[3317] 545 550 555 560

[3318] Thr Val Asn Gly His Leu Tyr Lys Thr Asn Tyr Leu Thr His Arg Gln
[3319] 565 570 575
[3320] Thr Asn Thr Ile Ile Asp Val Val Leu Ser Pro Ser His Gly Ile Glu
[3321] 580 585 590
[3322] Leu Ser Val Gly Glu Lys Leu Val Leu Asn Cys Thr Ala Arg Thr Glu
[3323] 595 600 605
[3324] Leu Asn Val Gly Ile Asp Phe Asn Trp Glu Tyr Pro Ser Ser Lys His
[3325] 610 615 620
[3326] Gln His Lys Lys Leu Val Asn Arg Asp Leu Lys Thr Gln Ser Gly Ser
[3327] 625 630 635 640
[3328] Glu Met Lys Lys Phe Leu Ser Thr Leu Thr Ile Asp Gly Val Thr Arg
[3329] 645 650 655
[3330] Ser Asp Gln Gly Leu Tyr Thr Cys Ala Ala Ser Ser Gly Leu Met Thr
[3331] 660 665 670
[3332] Lys Lys Asn Ser Thr Phe Val Arg Val His Glu Lys
[3333] 675 680
[3334] <210> 112
[3335] <211> 738
[3336] <212> DNA
[3337] <213> 人工序列
[3338] <220>
[3339] <223> 融合蛋白BY24.13(κ,IgG4)的轻链亚基(BY24.13L)核苷酸序列
[3340] <400> 112
[3341] ctcgaggcca ccatggagac cgacacactc ctcctgtggg tgctgctgct gtgggtgcct 60
[3342] ggctccactg gcgatattca gatgacccag agtccatcta gcgtgtctgc ttctgtgggc 120
[3343] gatcgggtga caatcacttg tcgcgcaagt cagggaatta gtagttggct cgcatggtat 180
[3344] cagcagaagc ctggcaaggc acctaagctc ctcattagcg ccgcgtcatc cctgcaatcc 240
[3345] ggcgtgccat ctaggtttag tggttccgga agcggaaccg actttacact cactatcagt 300
[3346] tctctccagc ccgaggattt cgcaacatac tactgtcagc aggccaacca cctgcctttc 360
[3347] acatttggag gcggcacatt cggcggcgga actaaggtgg agattaagag aaccgtggcc 420
[3348] gcccccagcg tgttcatctt ccctcccagc gacgagcagc tgaagtctgg caccgccagc 480
[3349] gtggtgtgcc tgctgaacaa cttctacccc cgcgaggcca aggtgcagtg gaaggtggac 540
[3350] aacgccctgc agagcggcaa cagccaggag agcgtgaccg agcaggactc caaggacagc 600
[3351] acctacagcc tgagcagcac cctgaccctg agcaaggccg actacgagaa gcacaaggtg 660
[3352] tacgcctgcg aggtgaccca ccagggactg tctagccccg tgaccaagag cttcaaccgg 720
[3353] ggcgagtgct aagaattc 738
[3354] <210> 113
[3355] <211> 234
[3356] <212> PRT
[3357] <213> 人工序列
[3358] <220>
[3359] <223> 融合蛋白BY24.13(κ,IgG4)的轻链亚基(BY24.13L)氨基酸序列

[3360] <400> 113

[3361] Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
[3362] 1 5 10 15
[3363] Gly Ser Thr Gly Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
[3364] 20 25 30
[3365] Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly
[3366] 35 40 45
[3367] Ile Ser Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
[3368] 50 55 60
[3369] Lys Leu Leu Ile Ser Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser
[3370] 65 70 75 80
[3371] Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
[3372] 85 90 95
[3373] Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn
[3374] 100 105 110
[3375] His Leu Pro Phe Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
[3376] 115 120 125
[3377] Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
[3378] 130 135 140
[3379] Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
[3380] 145 150 155 160
[3381] Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
[3382] 165 170 175
[3383] Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
[3384] 180 185 190
[3385] Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
[3386] 195 200 205
[3387] His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
[3388] 210 215 220
[3389] Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
[3390] 225 230

[3391] <210> 114
[3392] <211> 2079
[3393] <212> DNA
[3394] <213> 人工序列
[3395] <220>
[3396] <223> 融合蛋白BY24.13(κ,IgG4)的重链-VID融合亚基(BY24.13H)核苷酸序列
[3397] <400> 114

[3398] tctagagcca ccatggagac cgacaccctg ctgctgtggg tgctgctcct gtgggtgcct 60
[3399] ggctccacag gccaggtgca gctcgtccag tctggcgctg aggtcaagaa gcctggatct 120
[3400] agcgtgaagg tgtcttgtaa ggcaagtggc ggaacctttt ctagttacgc tattagttgg 180
[3401] gtgcggcagg ctcccggcca gggcctggag tggatgggac tcatcattcc tatgttcgat 240

[3402] accgccggct acgcccagaa gtttcaggga cgggtcgcaa tcaccgtaga tgagagtacc 300
[3403] tccacagcat acatggagct gagtagtctc agatccgagg acactgccgt gtactactgt 360
[3404] gctcgcgcag agcactctag caccggaaca tttgattact ggggacaggg caccctcgtg 420
[3405] acagtgtctt ccgcctccac caagggccct tccgtgttcc ctctggcccc ttgctcccgc 480
[3406] tccacctccg agtccaccgc cgccctgggc tgcctggtga aggactactt ccctgagcct 540
[3407] gtgaccgtgt cctggaactc cggcgccctg acctccggcg tgcacacctt ccctgccgtg 600
[3408] ctgcagtcct ccggcctgta ctccctgtcc tccgtggtga ccgtgccttc ctcctccctg 660
[3409] ggcaccaaga cctacacctg caacgtggac cacaagcctt ccaacaccaa ggtggacaag 720
[3410] cgcgtggagt ccaagtacgg ccctccttgc cctccttgcc ctgcccctga gttcctgggc 780
[3411] ggcccttccg tgttcctgtt ccctcctaag cctaaggaca ccctgatgat ctcccgcacc 840
[3412] cctgaggtga cctgcgtggt ggtggacgtg tcccaggagg accctgaggt gcagttcaac 900
[3413] tggtacgtgg acggcgtgga ggtgcacaac gccaagacca agcctcgcga ggagcagttc 960
[3414] aactccacct accgcgtggt gtccgtgctg accgtgctgc accaggactg gctgaacggc 1020
[3415] aaggagtaca agtgcaaggt gtccaacaag ggcctgcctt cctccatcga gaagaccatc 1080
[3416] tccaaggcca agggccagcc tcgcgagcct caggtgtaca ccctgcctcc ttcccaggag 1140
[3417] gagatgacca agaaccaggt gtccctgacc tgcctggtga agggcttcta cccttccgac 1200
[3418] atcgccgtgg agtgggagtc caacggccag cctgagaaca actacaagac cacccctcct 1260
[3419] gtgctggact ccgacggctc cttcttcctg tactcccgcc tgaccgtgga caagtcccgc 1320
[3420] tggcaggagg gcaacgtgtt ctcctgctcc gtgatgcacg aggccctgca caaccactac 1380
[3421] acccagaagt ccctgtccct gtccctgggc ggcggaggat ctggcggcgg aggcagtgga 1440
[3422] ggcggcggaa gcgcttccga caccggccgc cctttcgtgg agatgtactc cgagatccct 1500
[3423] gagatcatcc acatgaccga gggccgcgag ctggtgatcc cttgccgcgt gacctccct 1560
[3424] aacatcaccg tgaccctgaa gaagttccct ctggacaccc tgatccctga cggcaagcgc 1620
[3425] atcatctggg actcccgcaa gggcttcatc atctccaacg ccacctacaa ggagatcggc 1680
[3426] ctgctgacct gcgaggccac cgtgaacggc cacctgtaca agaccaacta cctgacccac 1740
[3427] cgccagacca acaccatcat cgacgtggtg ctgtcccctt cccacggcat cgagctgtcc 1800
[3428] gtgggcgaga agctggtgct gaactgcacc gcccgcaccg agctgaacgt gggcatcgac 1860
[3429] ttcaactggg agtacccttc ctccaagcac cagcacaaga agctggtgaa ccgcgacctg 1920
[3430] aagacccagt ccggctccga gatgaagaag ttcctgtcca ccctgaccat cgacggcgtg 1980
[3431] acccgctccg accagggcct gtacacctgc gccgcctcct ccggcctgat gaccaagaag 2040
[3432] aactccacct tcgtgcgcgt gcacgagaag taagtcgac 2079
[3433] <210> 115
[3434] <211> 686
[3435] <212> PRT
[3436] <213> 人工序列
[3437] <220>
[3438] <223> 融合蛋白BY24.13(κ,IgG4)的重链-VID融合亚基(BY24.13H)氨基酸序列
[3439] <400> 115
[3440] Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
[3441] 1 5 10 15
[3442] Gly Ser Thr Gly Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys
[3443] 20 25 30

[3444] Lys Pro Gly Ser Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr
[3445] 35 40 45
[3446] Phe Ser Ser Tyr Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly
[3447] 50 55 60
[3448] Leu Glu Trp Met Gly Leu Ile Ile Pro Met Phe Asp Thr Ala Gly Tyr
[3449] 65 70 75 80
[3450] Ala Gln Lys Phe Gln Gly Arg Val Ala Ile Thr Val Asp Glu Ser Thr
[3451] 85 90 95
[3452] Ser Thr Ala Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala
[3453] 100 105 110
[3454] Val Tyr Tyr Cys Ala Arg Ala Glu His Ser Ser Thr Gly Thr Phe Asp
[3455] 115 120 125
[3456] Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
[3457] 130 135 140
[3458] Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu
[3459] 145 150 155 160
[3460] Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
[3461] 165 170 175
[3462] Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
[3463] 180 185 190
[3464] Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
[3465] 195 200 205
[3466] Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn
[3467] 210 215 220
[3468] Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser
[3469] 225 230 235 240
[3470] Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly
[3471] 245 250 255
[3472] Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
[3473] 260 265 270
[3474] Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln
[3475] 275 280 285
[3476] Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
[3477] 290 295 300
[3478] His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr
[3479] 305 310 315 320
[3480] Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
[3481] 325 330 335
[3482] Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile
[3483] 340 345 350
[3484] Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
[3485] 355 360 365

[3486] Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser
[3487] 370 375 380
[3488] Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
[3489] 385 390 395 400
[3490] Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
[3491] 405 410 415
[3492] Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val
[3493] 420 425 430
[3494] Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met
[3495] 435 440 445
[3496] His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
[3497] 450 455 460
[3498] Leu Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
[3499] 465 470 475 480
[3500] Ala Ser Asp Thr Gly Arg Pro Phe Val Glu Met Tyr Ser Glu Ile Pro
[3501] 485 490 495
[3502] Glu Ile Ile His Met Thr Glu Gly Arg Glu Leu Val Ile Pro Cys Arg
[3503] 500 505 510
[3504] Val Thr Ser Pro Asn Ile Thr Val Thr Leu Lys Lys Phe Pro Leu Asp
[3505] 515 520 525
[3506] Thr Leu Ile Pro Asp Gly Lys Arg Ile Ile Trp Asp Ser Arg Lys Gly
[3507] 530 535 540
[3508] Phe Ile Ile Ser Asn Ala Thr Tyr Lys Glu Ile Gly Leu Leu Thr Cys
[3509] 545 550 555 560
[3510] Glu Ala Thr Val Asn Gly His Leu Tyr Lys Thr Asn Tyr Leu Thr His
[3511] 565 570 575
[3512] Arg Gln Thr Asn Thr Ile Ile Asp Val Val Leu Ser Pro Ser His Gly
[3513] 580 585 590
[3514] Ile Glu Leu Ser Val Gly Glu Lys Leu Val Leu Asn Cys Thr Ala Arg
[3515] 595 600 605
[3516] Thr Glu Leu Asn Val Gly Ile Asp Phe Asn Trp Glu Tyr Pro Ser Ser
[3517] 610 615 620
[3518] Lys His Gln His Lys Lys Leu Val Asn Arg Asp Leu Lys Thr Gln Ser
[3519] 625 630 635 640
[3520] Gly Ser Glu Met Lys Lys Phe Leu Ser Thr Leu Thr Ile Asp Gly Val
[3521] 645 650 655
[3522] Thr Arg Ser Asp Gln Gly Leu Tyr Thr Cys Ala Ala Ser Ser Gly Leu
[3523] 660 665 670
[3524] Met Thr Lys Lys Asn Ser Thr Phe Val Arg Val His Glu Lys
[3525] 675 680 685
[3526] <210> 116
[3527] <211> 747

[3528] <212> DNA
[3529] <213> 人工序列
[3530] <220>
[3531] <223> 融合蛋白BY24.14(κ,IgG4)的轻链亚基(BY24.14L)核苷酸序列
[3532] <400> 116
[3533] ctcgaggcca ccatggagac cgacacactc ctcctgtggg tgctgctgct gtgggtgcct 60
[3534] ggctccactg gccagagcgc tctcactcag cctgcttccg tgtctggaag tcccggccag 120
[3535] agtatcacta tttcttgtac aggaacttcc tccgacgtcg gattttacaa ttacgtcagt 180
[3536] tggtatcagc agcaccccgg aaaggcacct gaactaatga tctacgatgt gtctaaccgc 240
[3537] ccaagcggcg tgagcgatag gttcagtggc agtaagagtg gcaacaccgc atccctgacc 300
[3538] attagtggat tacaggccga ggacgaggct gattactact gttctagcta cacaaatatc 360
[3539] tccacatggg tcttcggcgg aggaacattc ggcggcggaa ctaaggtgga gattaagaga 420
[3540] accgtggccg cccccagcgt gttcatcttc cctcccagcg acgagcagct gaagtctggc 480
[3541] accgccagcg tggtgtgcct gctgaacaac ttctaccccc gcgaggccaa ggtgcagtgg 540
[3542] aaggtggaca acgccctgca gagcggcaac agccaggaga gcgtgaccga gcaggactcc 600
[3543] aaggacagca cctacagcct gagcagcacc ctgaccctga gcaaggccga ctacgagaag 660
[3544] cacaaggtgt acgcctgcga ggtgacccac cagggactgt ctagccccgt gaccaagagc 720
[3545] ttcaaccggg gcgagtgcta agaattc 747
[3546] <210> 117
[3547] <211> 237
[3548] <212> PRT
[3549] <213> 人工序列
[3550] <220>
[3551] <223> 融合蛋白BY24.14(κ,IgG4)的轻链亚基(BY24.14L)氨基酸序列
[3552] <400> 117
[3553] Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
[3554] 1 5 10 15
[3555] Gly Ser Thr Gly Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly
[3556] 20 25 30
[3557] Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp
[3558] 35 40 45
[3559] Val Gly Phe Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys
[3560] 50 55 60
[3561] Ala Pro Glu Leu Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val
[3562] 65 70 75 80
[3563] Ser Asp Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr
[3564] 85 90 95
[3565] Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser
[3566] 100 105 110
[3567] Tyr Thr Asn Ile Ser Thr Trp Val Phe Gly Gly Gly Thr Lys Val Glu
[3568] 115 120 125
[3569] Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser

[3570] 130 135 140

[3571] Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn

[3572] 145 150 155 160

[3573] Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala

[3574] 165 170 175

[3575] Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys

[3576] 180 185 190

[3577] Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp

[3578] 195 200 205

[3579] Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu

[3580] 210 215 220

[3581] Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys

[3582] 225 230 235

[3583] <210> 118

[3584] <211> 2091

[3585] <212> DNA

[3586] <213> 人工序列

[3587] <220>

[3588] <223> 融合蛋白BY24.14(κ,IgG4)的重链-VID融合亚基(BY24.14H)核苷酸序列

[3589] <400> 118

[3590] tctagagcca ccatggagac cgacaccctg ctgctgtggg tgctgctcct gtgggtgcct 60

[3591] ggctccacag gccagctcca gcttcaggag agcggacccg gcctggtcaa gccatccgag 120

[3592] actctcactc tgacatgcac cgtgagtgct gattctatca gttccacaac ttactactgg 180

[3593] gtgtggatta ggcagcctcc cggaaaggga ttagaatgga tcggcagcat ttcttacagt 240

[3594] ggctccacat actacaatcc tagtctgaag tctcgcgtga ccgtgtccgt ggatacatct 300

[3595] aagaaccagt ttagcctcaa gctgaatagc gtcgccgcaa cagataccgc tctgtactac 360

[3596] tgcgcacgcc acctcggcta caatggacgc tatctgccct tcgattactg gggccaggga 420

[3597] agcaccctcg tgacagtgtc ttccgcctcc accaagggcc cttccgtgtt ccctctggcc 480

[3598] ccttgctccc gctccacctc cgagtccacc gccgccctgg gctgcctggt gaaggactac 540

[3599] ttccctgagc ctgtgaccgt gtcctggaac tccggcgccc tgacctccgg cgtgcacacc 600

[3600] ttccctgccg tgctgcagtc ctccggcctg tactccctgt cctccgtggt gaccgtgcct 660

[3601] tcctcctccc tgggcaccaa gacctacacc tgcaacgtgg accacaagcc ttccaacacc 720

[3602] aaggtggaca agcgcgtgga gtccaagtac ggccctcctt gccctccttg ccctgccccc 780

[3603] gagttcctgg gcggcccttc cgtgttcctg ttccctccta agcctaagga caccctgatg 840

[3604] atctcccgca cccctgaggt gacctgcgtg gtggtggacg tgtcccagga ggaccctgag 900

[3605] gtgcagttca actggtacgt ggacggcgtg gaggtgcaca acgccaagac caagcctcgc 960

[3606] gaggagcagt tcaactccac ctaccgcgtg gtgtccgtgc tgaccgtgct gcaccaggac 1020

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[3615] tccgagatcc ctgagatcat ccacatgacc gagggccgcg agctggtgat cccttgccgc 1560
[3616] gtgacctccc ctaacatcac cgtgaccctg aagaagttcc ctctggacac cctgatccct 1620
[3617] gacggcaagc gcatcatctg ggactcccgc aagggcttca tcatctccaa cgccacctac 1680
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[3622] aaccgcgacc tgaagaccca gtccggctcc gagatgaaga agttcctgtc caccctgacc 1980
[3623] atcgacggcg tgacccgctc cgaccagggc ctgtacacct gcgccgcctc ctccggcctg 2040
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[3625] <210> 119
[3626] <211> 690
[3627] <212> PRT
[3628] <213> 人工序列
[3629] <220>
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[3634] Gly Ser Thr Gly Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val
[3635] 20 25 30
[3636] Lys Pro Ser Glu Thr Leu Thr Leu Thr Cys Thr Val Ser Ala Asp Ser
[3637] 35 40 45
[3638] Ile Ser Ser Thr Thr Tyr Tyr Trp Val Trp Ile Arg Gln Pro Pro Gly
[3639] 50 55 60
[3640] Lys Gly Leu Glu Trp Ile Gly Ser Ile Ser Tyr Ser Gly Ser Thr Tyr
[3641] 65 70 75 80
[3642] Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Val Ser Val Asp Thr Ser
[3643] 85 90 95
[3644] Lys Asn Gln Phe Ser Leu Lys Leu Asn Ser Val Ala Ala Thr Asp Thr
[3645] 100 105 110
[3646] Ala Leu Tyr Tyr Cys Ala Arg His Leu Gly Tyr Asn Gly Arg Tyr Leu
[3647] 115 120 125
[3648] Pro Phe Asp Tyr Trp Gly Gln Gly Ser Thr Leu Val Thr Val Ser Ser
[3649] 130 135 140
[3650] Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
[3651] 145 150 155 160
[3652] Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
[3653] 165 170 175

[3654] Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
[3655] 180 185 190
[3656] Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
[3657] 195 200 205
[3658] Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
[3659] 210 215 220
[3660] Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
[3661] 225 230 235 240
[3662] Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
[3663] 245 250 255
[3664] Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
[3665] 260 265 270
[3666] Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
[3667] 275 280 285
[3668] Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
[3669] 290 295 300
[3670] Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
[3671] 305 310 315 320
[3672] Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
[3673] 325 330 335
[3674] Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
[3675] 340 345 350
[3676] Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
[3677] 355 360 365
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[3679] 370 375 380
[3680] Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
[3681] 385 390 395 400
[3682] Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
[3683] 405 410 415
[3684] Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
[3685] 420 425 430
[3686] Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
[3687] 435 440 445
[3688] Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
[3689] 450 455 460
[3690] Leu Ser Leu Ser Leu Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
[3691] 465 470 475 480
[3692] Gly Gly Gly Ser Ala Ser Asp Thr Gly Arg Pro Phe Val Glu Met Tyr
[3693] 485 490 495
[3694] Ser Glu Ile Pro Glu Ile Ile His Met Thr Glu Gly Arg Glu Leu Val
[3695] 500 505 510

[3696] Ile Pro Cys Arg Val Thr Ser Pro Asn Ile Thr Val Thr Leu Lys Lys
[3697] 515 520 525
[3698] Phe Pro Leu Asp Thr Leu Ile Pro Asp Gly Lys Arg Ile Ile Trp Asp
[3699] 530 535 540
[3700] Ser Arg Lys Gly Phe Ile Ile Ser Asn Ala Thr Tyr Lys Glu Ile Gly
[3701] 545 550 555 560
[3702] Leu Leu Thr Cys Glu Ala Thr Val Asn Gly His Leu Tyr Lys Thr Asn
[3703] 565 570 575
[3704] Tyr Leu Thr His Arg Gln Thr Asn Thr Ile Ile Asp Val Val Leu Ser
[3705] 580 585 590
[3706] Pro Ser His Gly Ile Glu Leu Ser Val Gly Glu Lys Leu Val Leu Asn
[3707] 595 600 605
[3708] Cys Thr Ala Arg Thr Glu Leu Asn Val Gly Ile Asp Phe Asn Trp Glu
[3709] 610 615 620
[3710] Tyr Pro Ser Ser Lys His Gln His Lys Lys Leu Val Asn Arg Asp Leu
[3711] 625 630 635 640
[3712] Lys Thr Gln Ser Gly Ser Glu Met Lys Lys Phe Leu Ser Thr Leu Thr
[3713] 645 650 655
[3714] Ile Asp Gly Val Thr Arg Ser Asp Gln Gly Leu Tyr Thr Cys Ala Ala
[3715] 660 665 670
[3716] Ser Ser Gly Leu Met Thr Lys Lys Asn Ser Thr Phe Val Arg Val His
[3717] 675 680 685
[3718] Glu Lys
[3719] 690
[3720] <210> 120
[3721] <211> 106
[3722] <212> PRT
[3723] <213> 人工序列
[3724] <220>
[3725] <223> 融合蛋白中的一种抗PD-1抗体的重链可变区
[3726] <400> 120
[3727] Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
[3728] 1 5 10 15
[3729] Ser Leu Arg Leu Thr Cys Lys Ala Ser Gly Leu Thr Phe Ser Ser Ser
[3730] 20 25 30
[3731] Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[3732] 35 40 45
[3733] Ala Val Ile Trp Tyr Asp Gly Ser Lys Arg Tyr Tyr Ala Asp Ser Val
[3734] 50 55 60
[3735] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
[3736] 65 70 75 80
[3737] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys

[3738] 85 90 95

[3739] Ala Thr Asn Asn Asp Tyr Trp Gly Gln Gly

[3740] 100 105

[3741] <210> 121

[3742] <211> 101

[3743] <212> PRT

[3744] <213> 人工序列

[3745] <220>

[3746] <223> 融合蛋白中的一种抗PD-1抗体的轻链可变区

[3747] <400> 121

[3748] Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly

[3749] 1 5 10 15

[3750] Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr

[3751] 20 25 30

[3752] Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile

[3753] 35 40 45

[3754] Tyr Thr Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly

[3755] 50 55 60

[3756] Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro

[3757] 65 70 75 80

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[3759] 85 90 95

[3760] Thr Phe Gly Gln Gly

[3761] 100

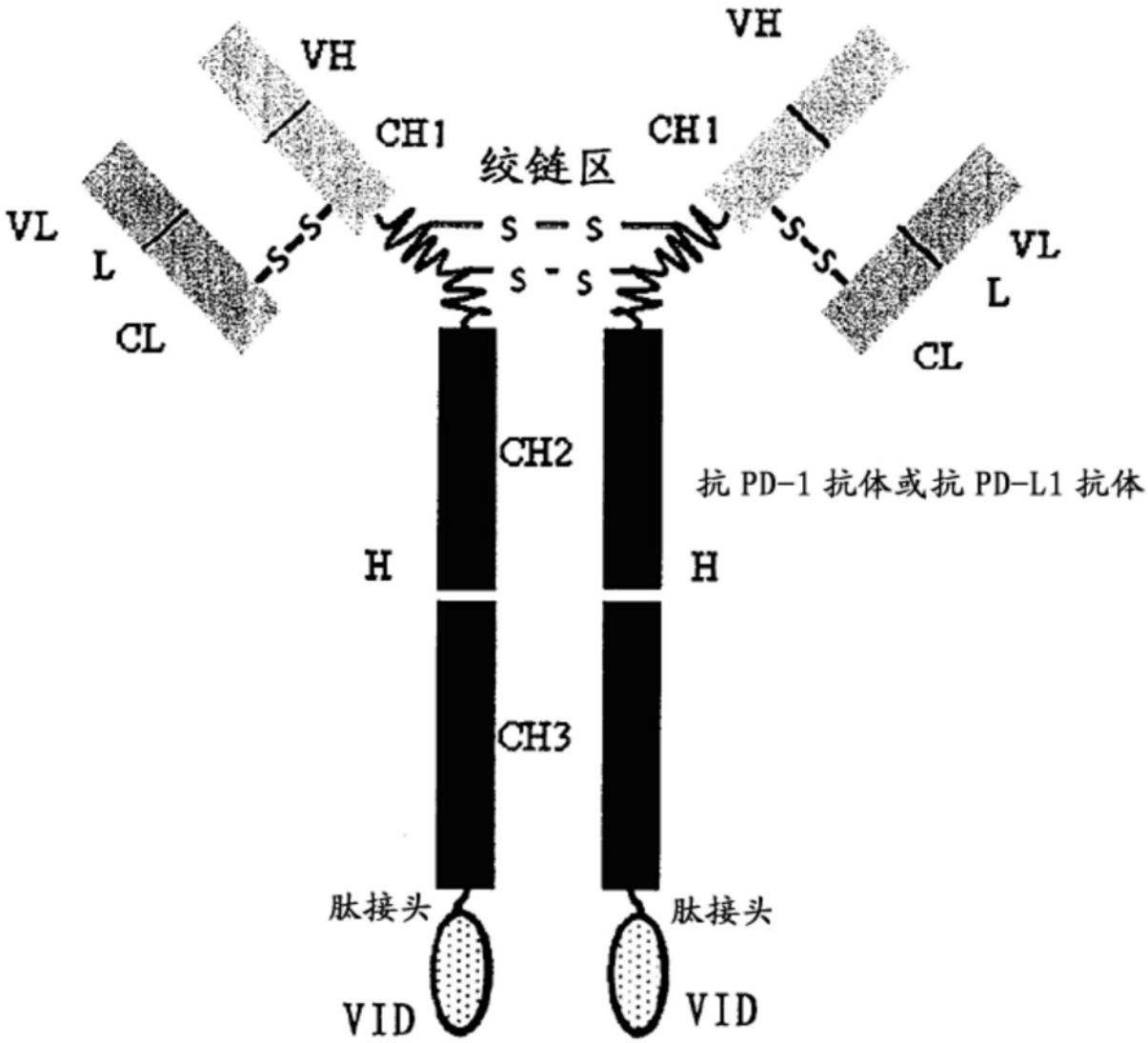
VH
CH1
VL
L
CL
绞链区
S—S
S-S
VH
CH1
VL
L
CL
CH2
抗 PD-1 抗体或抗 PD-L1 抗体
H
H
CH3
肽接头
肽接头
VID
VID

图1

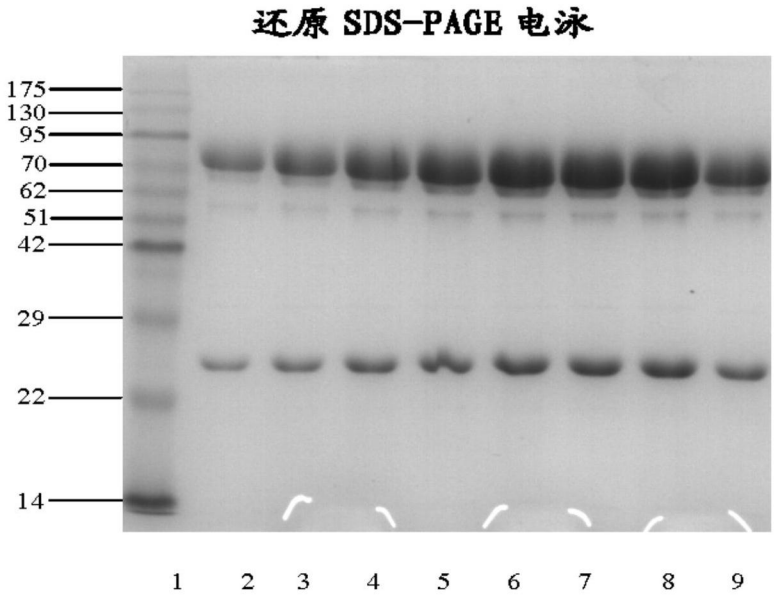
还原 SDS-PAGE 电泳
175
130
95
70
62
51
42
29
22
14
1 2 3 4 5 6 7 8 9

图2A

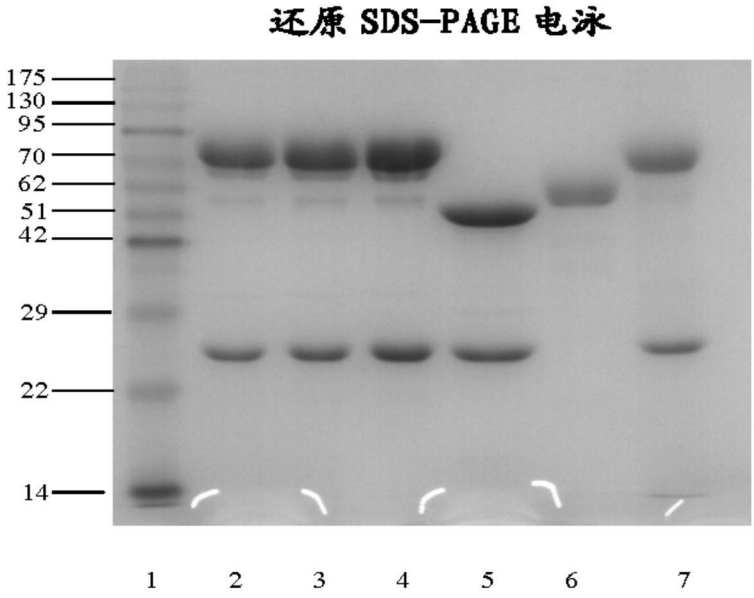
还原 SDS-PAGE 电泳
175
130
95
70
62
51
42
29
22
14
1 2 3 4 5 6 7

图2B

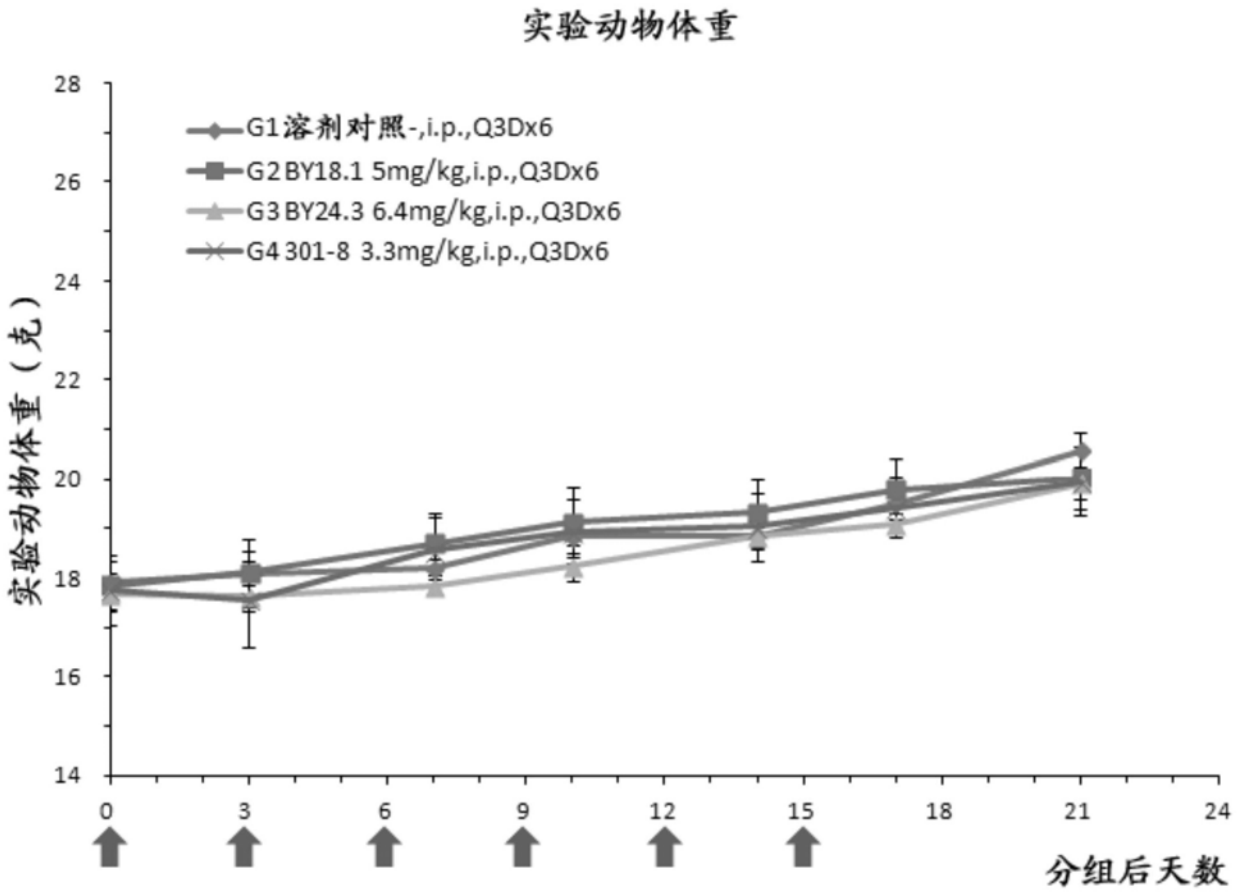
实验动物体重
G1溶剂对照-,i.p.,Q3Dx6
G2 BY18.1 5mg/kg,i.p.,Q3Dx6
G3 BY24.3 6.4mg/kg,i.p.,Q3Dx6
G4 301-8 3.3mg/kg,i.p.,Q3Dx6
实验动物体重（克）
28
26
24
22
20
18
16
14
0
3
6
9
12
15
18
21
24
分组后天数

图3

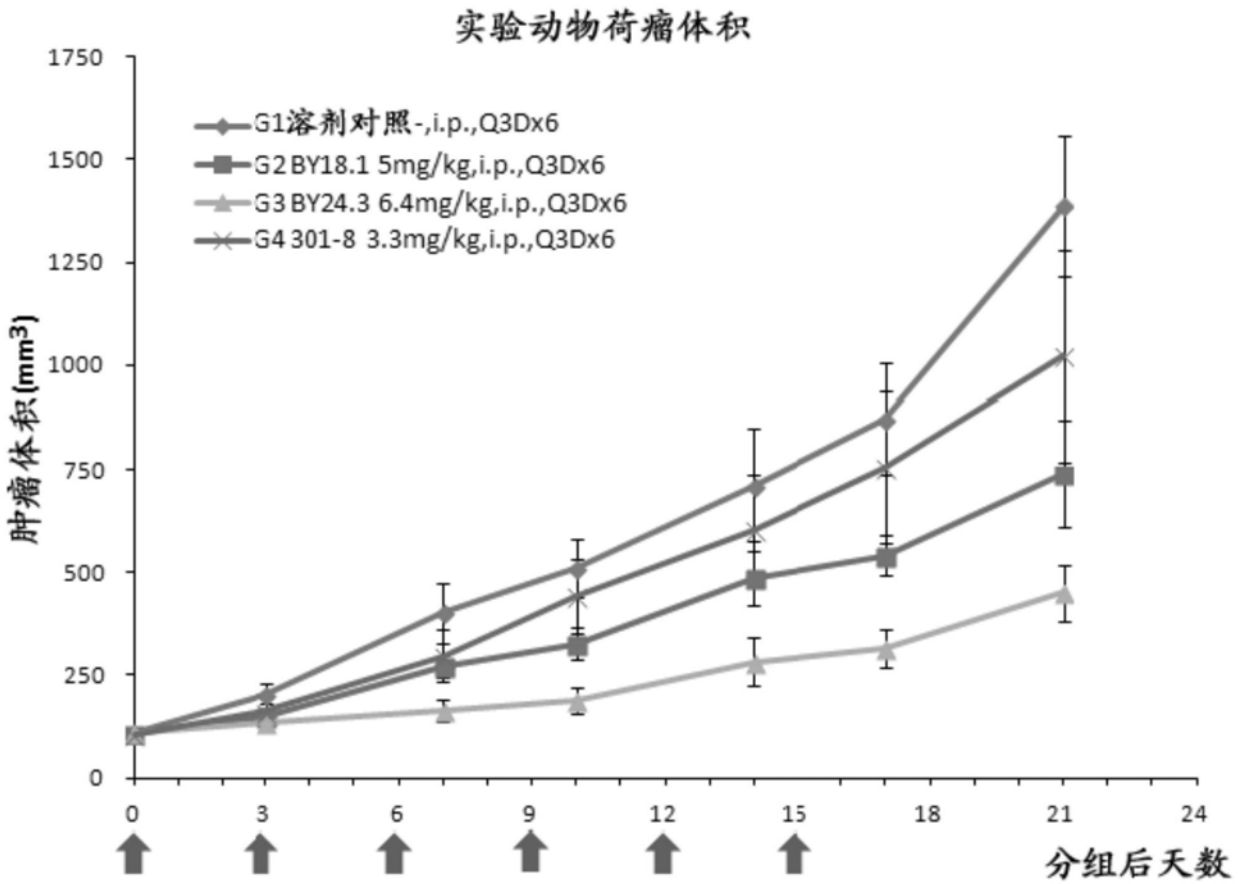
实验动物荷瘤体积
G1溶剂对照-,i.p.,Q3Dx6
G2 BY18.1 5mg/kg,i.p.,Q3Dx6
G3 BY24.3 6.4mg/kg,i.p.,Q3Dx6
G4 301-8 3.3mg/kg,i.p.,Q3Dx6
肿瘤体积(mm3)
1750
1500
1250
1000
750
500
250
0
0
3
6
9
12
15
18
21
24
分组后天数

图4