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(54) 发明名称

结合PD-L1和LAG-3的结合分子

(57) 摘要

本公开内容涉及结合程序性死亡蛋白配体1 (PD-L1) 和淋巴细胞活化基因3 (LAG-3) 的抗体分子。所述抗体分子优选包括针对PD-L1的基于CDR的抗原结合位点,以及位于所述抗体分子的CH3结构域的两个或更多个结构性环中的LAG-3抗原结合位点。本公开内容的抗体分子获得例如在癌症治疗中的应用。

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1. 一种结合至程序性死亡蛋白配体1和淋巴细胞活化基因3的抗体分子,其中所述抗体分子包括:

(i) 针对程序性死亡蛋白配体1的基于互补决定区的抗原结合位点;和

(ii) 位于所述抗体分子的CH3结构域中的淋巴细胞活化基因3抗原结合位点,

其中,所述基于互补决定区的抗原结合位点包括SEQ ID NOs:86到91中列出的互补决定区,其中互补决定区序列根据ImMunoGeneTics编号方案确定;或者所述基于互补决定区的抗原结合位点包括SEQ ID NOs:136到141中列出的互补决定区,其中互补决定区序列根据Kabat编号方案确定;

其中所述淋巴细胞活化基因3结合位点包括所述CH3结构域的AB环中的氨基酸序列WDEPWGED (SEQ ID NO:1),所述CH3结构域的EF环中的PYDRWVWPDE (SEQ ID NO:3)以及位于所述CH3结构域的CD环中的SEQ ID NO: 2、8、13、18、23、28、33、38、43或48所示的氨基酸序列。

2. 根据权利要求1所述的抗体分子,其中:

(i) SEQ ID NO:1所示的氨基酸序列位于所述CH3结构域的残基11到18处;和/或

(ii) SEQ ID NO:3所示的氨基酸序列位于所述CH3结构域的残基92到101处;

其中所述氨基酸残基根据ImMunoGeneTics编号方案编号。

3. 根据权利要求1或2所述的抗体分子,其中所述淋巴细胞活化基因3抗原结合位点包括位于所述CH3结构域的CD环中的SEQ ID NO:2、28或38所示的氨基酸序列。

4. 根据权利要求1或2所述的抗体分子,其中所述淋巴细胞活化基因3抗原结合位点包括位于所述CH3结构域的CD环中的SEQ ID NO:2所示的氨基酸序列。

5. 根据权利要求1或2所述的抗体分子,其中SEQ ID NO:2、8、13、18、23、28、33、38、43或48所示的氨基酸序列位于所述抗体分子的CH3结构域的残基43到78处,其中所述残基根据ImMunoGeneTics编号方案编号。

6. 根据权利要求1或2所述的抗体分子,其中所述抗体分子是免疫球蛋白G分子。

7. 根据权利要求6所述的抗体分子,其中所述抗体分子是IgG1、IgG2、IgG3或IgG4分子。

8. 根据权利要求7所述的抗体分子,其中所述抗体分子是IgG1分子。

9. 根据权利要求1所述的抗体分子,其中所述抗体分子包括SEQ ID NO:5、10、15、20、25、30、35、40、45或50所示的CH3结构域。

10. 根据权利要求9所述的抗体分子,其中所述抗体分子包括SEQ ID NO:5、30或40所示的CH3结构域。

11. 根据权利要求10所述的抗体分子,其中所述抗体分子包括SEQ ID NO:5所示的CH3结构域。

12. 根据权利要求1所述的抗体分子,其中所述抗体分子包括CH2结构域,且所述CH2结构域具有SEQ ID NO:53或SEQ ID NO:54所示的序列。

13. 根据权利要求1所述的抗体分子,其中所述抗体分子包括SEQ ID NO:6、7、11、12、16、17、21、22、26、27、31、32、36、37、41、42、46、47、51或52所示的序列。

14. 根据权利要求13所述的抗体分子,其中所述抗体分子包括SEQ ID NO:6、7、31、32、41或42所示的序列。

15. 根据权利要求14所述的抗体分子,其中所述抗体分子包括SEQ ID NO:6或7所示的

序列。

16. 根据权利要求1所述的抗体分子,其中所述抗体分子包括SEQ ID Nos:92和93中列出的VH和/或VL结构域。

17. 根据权利要求1所述的抗体分子,其中所述抗体分子包括SEQ ID NOs:94到113中任一个所示的重链序列。

18. 根据权利要求17所述的抗体分子,其中所述抗体分子包括SEQ ID NO:94、95、104、105、108或109所示的重链序列。

19. 根据权利要求18所述的抗体分子,其中所述抗体分子包括SEQ ID NO:94或95所示的重链序列。

20. 根据权利要求1所述的抗体分子,其中所述抗体分子包括SEQ ID NO:116所示的轻链序列。

21. 根据权利要求9至20中任一项所述的抗体分子,其中所述抗体分子的所述CH3结构域还包括处在SEQ ID NO:5、10、15、20、25、30、35、40、45或50中显示的序列的紧邻C-末端的赖氨酸残基。

22. 根据权利要求21所述的抗体分子,其中所述抗体分子包括SEQ ID NO:135中列出的所述CH3结构域。

23. 根据权利要求1或2所述的抗体分子,其中所述抗体能够同时结合程序性死亡蛋白配体1和淋巴细胞活化基因3。

24. 根据权利要求23所述的抗体分子,其中所述程序性死亡蛋白配体1和淋巴细胞活化基因3存在于两个不同的细胞上。

25. 根据权利要求1或2所述的抗体分子,其中所述抗体分子缀合至免疫系统调节物、细胞毒性分子或可检测标记。

26. 根据权利要求1或2所述的抗体分子,其中所述抗体分子缀合至放射性同位素。

27. 根据权利要求25所述的抗体分子,其中所述免疫系统调节物或所述细胞毒性分子是细胞因子。

28. 一种结合至程序性死亡蛋白配体1和淋巴细胞活化基因3的抗体分子,其中所述抗体分子包括SEQ ID NO: 116中列出的轻链和SEQ ID NO: 94中列出的重链。

29. 一种结合至程序性死亡蛋白配体1和淋巴细胞活化基因3的抗体分子,其中所述抗体分子包括SEQ ID NO: 116中列出的轻链和SEQ ID NO: 94中列出的重链,以及其中所述重链中的CH3结构域序列具有SEQ ID NO: 135中列出的序列。

30. 一种核酸,其编码根据权利要求1到29中任一项所述的抗体分子。

31. 一种载体,其包括根据权利要求30所述的核酸。

32. 一种重组宿主细胞,其包括根据权利要求30所述的核酸或根据权利要求31所述的载体。

33. 一种生产根据权利要求1到29中任一项所述的抗体分子的方法,其包括在用于所述抗体分子的生产的条件下培养根据权利要求32所述的重组宿主细胞。

34. 根据权利要求33所述的方法,其还包括分离和/或纯化所述抗体分子。

35. 一种药物组合物,其包括根据权利要求1到29中任一项所述的抗体分子、以及药学可接受赋形剂。

36. 根据权利要求1到29中任一项所述的抗体分子在制备用于治疗癌症的药物中的用途。

37. 根据权利要求36所述的用途, 其中所述癌症选自由以下组成的组: 霍奇金淋巴瘤、非霍奇金淋巴瘤、卵巢癌、前列腺癌、结直肠癌、纤维肉瘤、肾细胞癌、黑素瘤、胰腺癌、乳腺癌、多形性胶质母细胞瘤、肺癌、头颈癌、胃癌、膀胱癌、宫颈癌、子宫癌、外阴癌、睾丸癌、阴茎癌、白血病、多发性骨髓瘤、鳞状细胞癌、食道癌、卡波西氏肉瘤和中枢神经系统CNS淋巴瘤、肝细胞癌、默克尔细胞癌、鼻咽癌和间皮瘤。

38. 根据权利要求36或37所述的用途, 其中所述治疗还包括向患者施用抗肿瘤疫苗。

39. 根据权利要求36或37所述的用途, 其中所述治疗还包括向患者施用化疗剂。

结合PD-L1和LAG-3的结合分子

[0001] 相关的申请

[0002] 本案与2016年6月20日提交的US62/352482相关,其全部内容通过引用以其整体合并于此。

发明领域

[0003] 本发明涉及结合到程序性死亡蛋白配体1(programmed death-ligand 1,PD-L1)和淋巴细胞活化基因3(LAG-3)的抗体分子。所述抗体分子优选包括针对PD-L1的基于互补决定区(CDR)的抗原结合位点,以及可以位于所述抗体分子的CH3结构域的两个或更多个结构性环中的LAG-3抗原结合位点。本发明的抗体分子获得例如在癌症治疗中的应用。

[0004] 发明背景

[0005] 淋巴细胞活化基因-3(LAG-3;CD223)是Ig超家族的成员,且与CD4在遗传上和结构上相关(虽然仅有20%的序列同一性)。如CD4一样,LAG-3结合到主要组织相容性复合体II类(MHC II类,MHC class II)分子,但具有比CD4更高的亲和性($K_D=60\text{nM}$)。LAG-3在活化的T细胞、NK细胞、浆细胞样树突细胞(pDCs)、B细胞、 $\gamma\delta$ T细胞上表达,参与免疫抑制,特别是通过在一定百分比的调节性T细胞(Treg)上持续强表达(Liang et al,2008)。

[0006] LAG-3基因位于人的12号染色体上,邻近CD4基因,横跨8个外显子。有五种可选的转录产物,其中,两种产生蛋白质产物:全长的跨膜蛋白,以及选择性剪接的可溶单体形式。全长转录产物编码分子量为70kDa的525个氨基酸的蛋白质,并具有功能活性,而可溶形式看起来不结合MHC II类分子,它的功能是未知的。人的全长LAG-3蛋白与食蟹猴(cynomolgus monkey,Macaca fascicularis)的LAG-3具有93%的序列同一性,与家鼠(house mouse,Mus musculus)LAG-3具有70%的序列同一性。

[0007] LAG-3为具有四个细胞外的Ig样结构域(D1-D4)的跨膜蛋白,以及负责LAG-3信号转导的细胞质部分。胞质结构域(cytoplasmic domain)具有与LAG-3相关蛋白(LAG-3-associated protein,LAP)相关的EP(谷氨酸/脯氨酸)基序,以及被认为是T细胞功能的LAG-3调节所需的KIEELE基序。关于EP基序的作用的报道表明,它可能负责LAG-3向T细胞表面膜的输送(Bae et al,2014),或可能在T细胞活化期间直接负责调节信号转导转录因子5(Signal transducers and activators of transcription,STAT5)的下游信号转导(Durham et al,2014),或可能两者皆有。

[0008] LAG-3对T细胞的免疫抑制机制被认为由活化的T细胞上LAG-3的交联驱动,在T细胞活化期间产生降低的钙通量(calcium flux)和IL-2释放(Huard et al,1997)。在抗原呈递细胞(Antigen Presenting Cell,APCs)上,LAG-3阳性调节性T细胞结合MHC II类分子导致降低的IL-12分泌和CD86的下调(Liang et al,2008),由不适当的激活导致T细胞的失效的“二级信号”,和/或通过APCs降低的抗原呈递。LAG-3敲除的小鼠模型是可行的,仅有轻度淋巴增生(lympho-hyperproliferation)(Workman et al,2003),表明LAG-3充当适度的免疫“刹车(brake)”。

[0009] 还已经提出LAG-3与II类MHC之间的这种抑制性相互作用发生在调节性T细胞

(regulatory T cells, Treg) 与 CD4 阳性 T 细胞之间 (Sega et al, 2014)。调节性 T 细胞通过抑制性细胞因子 (例如 IL-10 和转化生长因子 β (transforming growth factor- β , TGF β) 的释放、炎症性新陈代谢的操纵 (例如 CD73 分解代谢的腺苷)、调节 APC 成熟、或调节性 T 细胞与效应 T 细胞之间的直接相互作用抑制免疫应答。人类中有证据表明 MHC II 类阳性调节性 T 细胞比 MHC II 类阴性调节性 T 细胞更具抑制性 (Baecher-Allen et al, 2006), 并通过与效应 T 细胞上表达的 LAG-3 的直接相互作用主动抑制免疫应答。虽然 LAG-3 阴性调节性 T 细胞可以抑制常规的 T 细胞增殖, LAG-3 阴性 CD4 和 CD8 T 细胞却对 Treg 免疫抑制有抗性。这一过程被描述为通过称为胞啃作用 (trogocytosis) 的过程发生在人类 T 细胞之间 (Sega et al, 2014), 借此调节性 T 细胞不仅阻止 APC 成熟, 还获得 II 类 MHC 以抑制致敏的 (primed) LAG-3 阳性 CD4 T 细胞。

[0010] LAG-3 表达也是重复的抗原刺激的标记物 (marker)。在癌症中, T 细胞通常采取“衰竭的 (exhausted)”表型, 包括免疫抑制剂 (immune-suppressor) 例如程序性死亡蛋白 1 (PD-1)、细胞毒 T 淋巴细胞相关抗原 4 (CTLA-4)、T 细胞免疫球蛋白域和粘蛋白分子 3 (TIM-3) 和 LAG-3 的表达 (Wherry et al, 2011), 其中细胞一般不能适当地增殖和分泌响应抗原的趋化因子。这些免疫抑制剂的抑制降低了免疫阈值, 并 (重新) 允许 T 细胞的适当的抗癌反应。在临床前模型中, 已经使用对抗 LAG-3、CTLA-4 和 PD-1 的拮抗剂 (antagonist) 抗体证实了这一点, 其中观察到肿瘤负荷的降低。拮抗性抗体对 LAG-3 的抑制被认为重新激活了肿瘤微环境中的免疫应答, 其中, 在 CD4 阳性 T 细胞和 CD8 阳性 T 细胞上的 LAG-3 表达与衰竭的表型相关, 调节性 T 细胞上的 LAG-3 表达与潜在的免疫抑制能力相关。阻断 LAG-3 的抗体提高了 T 效应细胞的增殖、细胞因子产生、和细胞毒性, 并降低了调节性 T 细胞抑制物活性, 引起肿瘤生长的减少。

[0011] 在人类肿瘤中, 在来自人肾细胞癌和其他肿瘤例如黑素瘤和淋巴瘤的肿瘤浸润性淋巴细胞 (TILs) 上发现增加的 LAG-3 表达 (Demeure et al, 2001; Wolchock et al, 2013)。重要地, LAG-3 也与有慢性病毒感染 (Workman, 2005) 和癌症 (Workman et al, 2003) 的患者的 T 细胞功能障碍紧密相关。LAG-3 也被鉴定为多种人类癌症中肿瘤浸润性调节性 T 细胞的表面标记物 (Camisachi et al. 2010; Gandhi et al, 2006)。

[0012] 针对人 LAG-3 的单克隆抗体处于临床开发中, 以消除免疫抑制并潜在地增强癌症中的抗原呈递 (实体和血液系统恶性肿瘤 (solid and haematological malignancies))。

[0013] LAG-525 和 IMP-701 (诺华公司 (Novartis AG)) 是针对 LAG-3 的人抗体, 已分别进入肾癌 (肾细胞癌); 非小细胞肺癌 (Non-Small cell Lung Cancer, NSCLC); 鼻咽癌 (Nasopharyngeal Cancer); 结直肠癌 (Colorectal Cancer); 黑素瘤 (melanoma); 胃癌 (Gastric Cancer) 和胃食管接点的腺癌 (Adenocarcinoma of the Gastroesophageal Junction) 的 II 期和 I 期临床研究。

[0014] 抗 LAG-3 抗体百时美施贵宝公司-986016 (BMS-986016, Bristol-Myers Squibb Company) 目前处于卵巢癌 (Ovarian Cancer); NSCLC; 结直肠癌; 宫颈癌 (Cervical Cancer); 黑素瘤; 胃癌; 膀胱癌 (Bladder Cancer); 头颈癌鳞状细胞癌 (Head And Neck Cancer Squamous Cell Carcinoma); 肾细胞癌的 I 期临床测试中, 以及 NSCLC; 复发性慢性淋巴细胞性白血病 (CLL); 难治性慢性淋巴细胞性白血病 (Chronic Lymphocytic Leukemia, CLL); 黑素瘤; 非霍奇金淋巴瘤 (Non-Hodgkin Lymphoma); 霍奇金淋巴瘤; 弥散性

大B细胞淋巴瘤(Diffuse Large B-Cell Lymphoma);惰性淋巴瘤(Indolent Lymphoma);套细胞淋巴瘤(Mantle Cell Lymphoma);难治性多发性骨髓瘤(Refractory Multiple Myeloma);和复发性多发性骨髓瘤(Relapsed Multiple Myeloma)的II期研究中,作为单一治疗或作为组合治疗的部分。

[0015] 针对LAG-3的更多抗体也处于临床前的开发中。

[0016] 程序性死亡蛋白1(PD-1)和它的配体PD-L1(CD274,B7-H1)和PD-L2(B7-DC)传递抑制性信号,该抑制信号调节T细胞活化、耐受和免疫病理之间的平衡。PD-L1在所有免疫细胞和一些肿瘤细胞上瞬时表达。

[0017] PD-L1是I型跨膜蛋白,具有处于细胞外区域内的Ig-样结构域、跨膜结构域和短的胞质结构域。胞质结构域不具有已知的信号转导基序,表明在该配体与它的受体的相互作用上没有PD-L1的信号转导。它的分子量为40kDa(290个氨基酸),并且它由小鼠的染色体19上和人类的染色体9上的CD274基因编码。PD-L1是B7蛋白家族的成员,与B7.1和B7.2共享大约20%的氨基酸序列同一性。人类PD-L1与鼠类和食蟹猴的PD-L1直系同源体分别共享70%和93%的氨基酸同一性。

[0018] PD-L1以770nM的亲合性(K_D)结合它的受体PD-1。PD-1在活化的T细胞、B细胞和骨髓细胞上表达,调节细胞免疫应答的活化或抑制。PD-L1与PD-1的结合传递抑制性信号,降低细胞因子生产和T细胞的增殖。因此,细胞的PD-L1表达可以介导针对细胞毒性T淋巴细胞(cytotoxic T lymphocyte,CTL)杀伤的保护,并且细胞的PD-L1表达是在病毒感染期间阻抑慢性免疫应答的调节机制。癌症作为慢性和前炎症性疾病通过PD-L1表达的上调破坏这种免疫保护性途径,以逃避宿主免疫应答。在主动免疫应答的情境下,IFN γ 也上调PD-L1的表达。

[0019] PD-L1还通过与另一种蛋白质B7.1(也称为CD80)的相互作用来介导免疫抑制,阻断它通过CD28传递T细胞上的二级活化信号之一的能力。就肿瘤细胞上的PD-L1表达和它与B7.1的接合而言,在肿瘤免疫抗性方面这种特异性相互作用的关联性仍是不清楚的。

[0020] 已经显示了在各种各样的实体肿瘤(solid tumours)中的PD-L1表达。在跨越来自不同部位的19个肿瘤的一项研究中检查的654份样品中,89份(14%)是PD-L1阳性的(频率>5%)。最高的PD-L1阳性频率在头颈癌(17/54;31%)、子宫颈癌(10/34;29%)、原发性未知的癌症(cancer of unknown primary origin,CUP;8/29;28%)、多形性胶质母细胞瘤(GBM;5/20;25%)、膀胱癌(8/37;21%)、食道癌(16/80;20%)、三阴性(TN)乳腺癌(6/33,18%)和肝癌(6/41;15%)中观察到(Grosso et al,2013)。已经显示PD-L1的肿瘤相关表达赋予免疫抗性并潜在地保护肿瘤细胞免于T细胞介导的细胞凋亡。

[0021] 在鼠类体内研究中靶向PD-L1的治疗已经显示了极好的结果。在黑素瘤的B16鼠类模型中,使用抗PD-L1与GVAX或FVAX结合的疫苗接种策略治疗,在该研究结束时,对于存活(对照为30天,相对PD-L1治疗组52天)和无肿瘤动物百分比(5%)方面都产生了显著的效果(Curran et al,2010)。抗PD-L1治疗也已经用于研究P815鼠类乳腺错构瘤(mastoma)模型中免疫抑制的机制。被注射入小鼠中的P815细胞通常触发强烈的免疫应答,这导致它们的排斥。当PD-L1在P815细胞上表达时,这些细胞逃避免疫攻击,反过来,可以通过抗PD-L1抗体的给药来取消(Iwai et al,2002)。显然,在免疫原性的人类癌症中靶向PD-1/PD-L1轴线(Herbst et al,2014)通过抗癌免疫应答的刺激产生生存优势(Wolchok et al,2013;

Larkin et al,2015)。

[0022] 阿特朱单抗(atezolizumab,MPDL3280A,RG7466,TECENTRIQ)是结合PD-L1的人源化IgG1抗体。它在临床试验中作为单一试剂并且还与其他生物的/小分子的治疗相组合用于实体癌症的治疗,包括结直肠癌、乳腺癌、非小细胞肺癌、膀胱癌和肾细胞癌。使用阿特朱单抗治疗在NSCLC中产生23%、黑素瘤中为36%、膀胱癌中为33%、RCC中为14%、以及头颈癌中为13%的客观响应率(ORR)(Herbst et al,2014;Powles et al,2014)。

[0023] Avelumab(MSB0010718C)是一种结合PD-L1的全人的IgG1抗体,正在许多癌症,包括膀胱癌、胃癌、头颈癌、间皮瘤(mesothelioma)、非小细胞肺癌、卵巢癌、肾癌和默克尔(Merkel)细胞癌中进行临床测试。

[0024] 度伐鲁单抗(durvalumab,MEDI4736)是一种结合PD-L1的人类IgG1抗体,正在单独或与曲美母单抗(tremelimumab)组合在非小细胞肺癌、头颈部鳞状细胞癌(squamous cell carcinoma of the head and neck)、膀胱癌、胰腺癌的临床试验中进行测试,并与其他生物分子和小分子组合在另外的实体癌例如胃癌、黑素瘤和不可切除的肝细胞癌中进行测试。

[0025] 更多的抗PD-L1抗体已经在临床试验中测试,包括BMS-936559,其他的处于临床前的测试当中。

[0026] 然而,仅有少数抗LAG-3治疗当前处于临床测试中,都没有被批准用于治疗,因此仍然需要开发靶向LAG-3的另外的分子。虽然正在开发一些抗PD-L1治疗剂,但目前的数据显示,使用抗PD-L1单一治疗的整体治疗在不到50%的癌症患者中产生反应。因而,本领域仍然需要可以靶向LAG-3和/或PD-L1并且在癌症治疗中获得应用的另外的分子。

发明内容

[0027] 抗PD-1和抗PD-L1抗体主要涉及破坏免疫耐受和激活抗肿瘤免疫应答。在活化之后在T细胞上表达的、以及在衰竭的(exhausted)T细胞上结构性表达的LAG-3进一步将这些细胞维持在抑制状态。当与其他已建立的免疫抑制分子(即:PD-1、PD-L1)组合应用时,LAG-3的阻断也在鼠类肿瘤模型中已经显示了提供协同性改善的免疫应答(Woo et al,2012)。本发明人推测同时靶向这两种途径的疗法将直接解决促进和维持T细胞衰竭的机制。此外,本发明人期望靶向LAG-3可通过表达LAG-3的调节性T细胞对APC的作用抑制抗原呈递,并且发布的研究记录CD86的下调(Grosso et al,2013)。阻断这种相互作用预期维持抗原呈递,而阻断PD-L1信号转导预期会破坏耐受性,当两种途径同时被抑制时导致显著的抗肿瘤反应。

[0028] 尽管有来自临床前同基因小鼠肿瘤和病毒负载(viral load)模型的一些结果,关于抗LAG-3和抗PD-L1抗体组合的已发布的数据是有限的。在骨髓瘤的鼠类模型中,在低剂量全身照射后施用抗PD-L1和抗LAG-3阻断抗体的组合,将存活率提高至大于80%(Jing et al,2015)。没有观察到全身性或器官特异性自体免疫的证据。LAG-3和PD-1敲除小鼠显示了多个可移植肿瘤的显著提高的存活和清除(Woo et al,2012)。

[0029] 本发明人推测,结合至LAG-3和PD-L1二者的双特异性抗体相对于针对这些抗原的单克隆抗体的组合将具有许多优点,包括:

[0030] 1.直接治疗

[0031] 在淋巴结中,活化的T细胞表达LAG-3。抗LAG-3/PD-L1双特异性抗体的一部分靶向淋巴结中致敏的LAG-3-阳性T细胞,该细胞然后运输到肿瘤的位点,转运双特异性抗体。一旦处于肿瘤微环境之内,携带双特异性抗体的T细胞能够通过抗PD-L1部分立即接合并阻断肿瘤细胞上的PD-L1。因此,运输到肿瘤位点的所有T细胞将对LAG-3和PD-L1/PD-1信号转导都有抗性。

[0032] 2. 桥接

[0033] 致敏的CD8阳性T细胞在肿瘤微环境内遭遇肿瘤抗原,在此在不存在抑制信号的情况下它们通过杀死肿瘤细胞来反应。通过维持或延长T细胞与肿瘤细胞之间的这种接触,预期双特异性要优于单个单克隆治疗的结合。T细胞的活化中的信号强度是至关重要的,在癌症中呈递的抗原的情况下可能是关键(Engels et al,2013),结合至APC或癌细胞上的靶点的双特异性抗LAG-3/PD-L1抗体的存在,预期会增加T细胞能够成功识别抗原并变得活化的时间。

[0034] 3. 定位

[0035] 在炎症和进行中的免疫应答的区域中,由于局部的IFN- γ 释放,PD-L1表达显著提高。无论是对于目标癌细胞、肿瘤相关巨噬细胞(tumour-associated macrophages,TAM),还是T细胞群体的重复刺激,都是如此。拮抗PD-L1和LAG-3的双特异性抗体预计会定位并集中至肿瘤中最大PD-L1表达的区域,同时容许抗LAG-3部分的结合并阻止T细胞的LAG-3介导的抑制。

[0036] 在广泛的筛选和亲和成熟程序之后,本发明人得以鉴定出包括特异于分子的CH3结构域中的LAG-3的结合位点的十种特异性结合元件。这些分子显示为对人和食蟹猴LAG-3都具有高亲和力。预期对人LAG-3的高亲和力在人类患者中的例如含有表达LAG-3的肿瘤浸润性淋巴细胞(tumour-infiltrating lymphocytes,TILs)的癌症的治疗是有益的,而预期对食蟹猴LAG-3的高亲和力在食蟹猴疾病模型中特异性结合元件的性质的评估是有用的,该对食蟹猴LAG-3的高亲和力与对人LAG-3的亲和力是可比较的。这一点的理由是,所获得的结果在人类患者中该特异性结合元件的效果比在食蟹猴模型中测试对人和食蟹猴LAG-3的亲和力有更高变异性的分子时更有可能是预示性的。

[0037] 在T细胞活化试验中,该特异性结合元件还显示为具有高活性,预期在人类患者中通过增强LAG-3抑制的改进效力是有预示性的。

[0038] 本发明人进一步将这些在CH3结构域中包含特异于LAG-3的结合位点的特异性结合元件与包括针对PD-L1的基于CDR的抗原结合位点的抗体Fab结构域结合,来创建包括针对LAG-3和PD-L1两者的结合位点的双特异性抗体分子,预期其具有上文详述的优点。本发明人还制备了结合到鼠类LAG-3和鼠类PD-L1的这些抗体分子的替代鼠类版本,显示为能够在同基因小鼠癌症模型中显著抑制肿瘤生长。特别是,在测试的小鼠模型中,当给小鼠施用包括针对LAG-3和PD-L1的结合位点的抗体分子时,这些替代鼠类分子的使用证明对于肿瘤生长抑制有协同作用。基于肿瘤环境中小鼠LAG-3与PD-L1和人类LAG-3与PD-L1的类似作用机制,期望显示降低肿瘤负荷的效力的鼠类的研究转变为人类癌症患者中的临床治疗效益。基于这些结果,因而预期的是,本发明的抗体分子在人类患者的癌症的治疗中,特别是在抑制肿瘤生长方面,展示了比,例如结合LAG-3和PD-L1的两个独立的分子的施用优越的效果。

[0039] 因而,在第一个方面中,本发明提供了一种结合至PD-L1和LAG-3两者的抗体分子。具体地,这些抗体包括:

[0040] (i) 针对PD-L1的基于CDR的抗原结合位点;和

[0041] (ii) 位于或被工程化入该抗体分子的CH3结构域的两个或更多个结构性环中的LAG-3抗原结合位点。该LAG-3结合位点优选包括氨基酸序列WDEPWGED (SEQ ID NO:1) 和PYDRWVWPDE (SEQ ID NO:3)。

[0042] 抗体分子优选包括位于CH3结构域的AB环中的SEQ ID NO:1所示的氨基酸序列,以及位于CH3结构域的EF环中的SEQ ID NO:3所示的氨基酸序列。

[0043] 因而,在第一个方面中,本发明提供了一种结合程序性死亡蛋白配体1 (PD-L1) 和淋巴细胞活化基因3 (LAG-3) 的抗体分子。该抗体分子优选包括(i) 针对PD-L1的基于CDR的抗原结合位点;和(ii) 位于该抗体分子的CH3结构域中的LAG-3抗原结合位点。

[0044] LAG-3结合位点优选包括氨基酸序列WDEPWGED (SEQ ID NO:1) 和PYDRWVWPDE (SEQ ID NO:3)。氨基酸序列WDEPWGED优选位于CH3结构域的第一结构性环中,氨基酸序列PYDRWVWPDE优选位于CH3结构域的第二结构性环中。

[0045] 例如,LAG-3抗原结合位点可以位于抗体分子的CH3结构域的结构性环区中,其中结构性环区优选包括两个或更多个结构性环,并且其中LAG-3结合位点优选包括氨基酸序列WDEPWGED (SEQ ID NO:1) 和PYDRWVWPDE (SEQ ID NO:3)。

[0046] 作为进一步的实施例,LAG-3抗原结合位点可以工程化到抗体分子的CH3结构域的两个或更多个结构性环中,其中LAG-3结合位点优选包括氨基酸序列WDEPWGED (SEQ ID NO:1) 和PYDRWVWPDE (SEQ ID NO:3)。

[0047] 如上所述,LAG-3结合位点的序列优选位于抗体分子的CH3结构域的两个或更多个结构性环中。在优选的实施方式中,LAG-3抗原结合位点包括位于CH3结构域的AB环中的SEQ ID NO:1所示的氨基酸序列,以及位于CH3结构域的EF环中的SEQ ID NO:3所示的氨基酸序列。

[0048] SEQ ID NO:1所示的氨基酸序列优选位于CH3结构域的残基11到18处,和/或SEQ ID NO:3所示的氨基酸序列位于CH3结构域的残基92到101处;其中氨基酸残基根据免疫遗传学 (ImMunoGeneTics, IMGT) 编号方案编号。

[0049] 抗体分子的LAG-3抗原结合位点还可以包括以下序列之一,优选在抗体分子的CH3结构域的CD环中:

[0050] (i) SNGQPENNY (SEQ ID NOS 2、8和18);

[0051] (ii) SNGQPEDNY (SEQ ID NO:13);

[0052] (iii) SNGYPEIEF (SEQ ID NO:23);

[0053] (iv) SNGIPEWNY (SEQ ID NO:28);

[0054] (v) SNGYAEYNY (SEQ ID NO:33);

[0055] (vi) SNGYKEENY (SEQ ID NO:38);

[0056] (vii) SNGVPELNV (SEQ ID NO:43);或

[0057] (viii) SNGYQEDNY (SEQ ID NO:48)。

[0058] 优选地,抗体分子的LAG-3抗原结合位点还包括以下序列之一,优选在抗体分子的CH3结构域的CD环中:CH3结构域的CD环中的SEQ ID NO:2、28或38所示的氨基酸序列。更优

选地,抗体分子的LAG-3抗原结合位点还包括CH3结构域的CD环中的SEQ ID NO:2所示的氨基酸序列。

[0059] SEQ ID NO:2、8、13、18、23、28、33、38、43或48所示的氨基酸序列优选位于抗体分子的CH3结构域的残基43到78处,其中,残基根据IMGT编号方案编号。

[0060] LAG-3抗原结合位点的序列之外,抗体分子的CH3结构域的序列并未特别限制。优选地,CH3结构域是人免疫球蛋白G结构域,例如,人IgG1、IgG2、IgG3或IgG4 CH3结构域,最优选人IgG1 CH3结构域。人IgG1、IgG2、IgG3或IgG4 CH3结构域的序列是本领域已知的。

[0061] 在优选的实施方式中,抗体分子包括SEQ ID NO:5、10、15、20、25、30、35、40、45或50所示的CH3结构域,更优选SEQ ID NO:5、30或40所示的CH3结构域,最优选SEQ ID NO:5所示的CH3结构域。可选地,抗体分子可以包括CH3结构域,CH3结构域具有与SEQ ID NO:5、10、15、20、25、30、35、40、45或50,优选SEQ ID NO:5、30或40,更优选SEQ ID NO:5至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%的序列同一性的序列。

[0062] 抗体分子还可以包括CH2结构域。正如人IgG分子的情况一样,CH2结构域优选位于CH3结构域的N-末端。抗体分子的CH2结构域优选为人IgG1、IgG2、IgG3或IgG4的CH2结构域,更优选人IgG1的CH2结构域。人IgG结构域的序列是本领域已知的。在优选的实施方式中,抗体分子包括具有SEQ ID NO:53或SEQ ID NO:54所示的序列的IgG CH2结构域,或具有与SEQ ID NO:53或SEQ ID NO:54有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%的序列同一性的氨基酸序列的CH2结构域。

[0063] 在优选的实施方式中,抗体分子包括SEQ ID NO:6、7、11、12、16、17、21、22、26、27、31、32、36、37、41、42、46、47、51或52所示的序列,或与SEQ ID NO:6、7、11、12、16、17、21、22、26、27、31、32、36、37、41、42、46、47、51或52所示的序列有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%的序列同一性的序列。更优选地,抗体分子包括SEQ ID NO:6、7、31、32、41或42所示的序列,或与SEQ ID NO:6、7、31、32、41或42所示的序列有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%的序列同一性的序列。再更优选地,抗体分子包括SEQ ID NO:6或7所示的序列,或与SEQ ID NO:6或7所示的序列有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%的序列同一性的序列。

[0064] 在优选的实施方式中,抗体分子是人免疫球蛋白G分子,例如,人IgG1、IgG2、IgG3或IgG4分子,更优选人IgG1分子。人免疫球蛋白G分子的序列是本领域已知的,并且将如本文公开的CH3结构域或CH3结构域序列引入这样的分子中不会给技术人员呈现任何困难。

[0065] 抗体分子优选包括SEQ ID NOs:92和93所示的VH和/或VL结构域的CDR。确定给定VH或VL结构域中的CDR序列的方法是本领域已知的,包括Kabat和IMGT编号系统。更优选地,抗体分子优选包括SEQ ID NOs:86到91所示的互补决定区的一个或更多个、两个或更多个、三个或更多个、四个或更多个、五个或更多个、或全部六个。优选地,抗体分子分别包括SEQ ID NOs:92和93所示的VH和/或VL结构域。

[0066] 在优选的实施方式中,抗体分子包括SEQ ID NOs:94到113的任一个所示的重链序列,或具有与SEQ ID NOs:94到113的任一个有至少70%、至少75%、至少80%、至少85%、至

少90%、至少95%、至少96%、至少97%、至少98%或至少99%的序列同一性的氨基酸序列的重链,只要重链序列的VH结构域保持不变。更优选地,抗体分子包括SEQ ID NOs:94、95、104、105、108和109的任一个所示的重链序列,或具有与SEQ ID NOs:94、95、104、105、108和109的任一个有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%的序列同一性的氨基酸序列的重链,只要重链序列的VH结构域保持不变。再更优选地,抗体分子包括SEQ ID NO:94或95所示的重链序列,或具有与SEQ ID NOs:94或95有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%的序列同一性氨基酸序列的重链,只要重链序列的VH结构域保持不变。

[0067] 在进一步优选的实施方式中,抗体分子可以另外地或可选地包括SEQ ID NO:116所示的轻链序列,或具有与SEQ ID NO:116有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%或至少99%的序列同一性的氨基酸序列的轻链,只要轻链序列的VH结构域保持不变。

[0068] 抗体分子优选能够同时结合PD-L1和LAG-3。例如,PD-L1和LAG-3可以存在于两个不同的细胞上。不希望受到理论的限制,被认为这引起细胞之间的交联以及PD-L1和/或LAG-3的内在化,使得它们对于刺激是不可获得的。

[0069] 本发明人显示了一种抗体分子,所述抗体分子包括(i)针对PD-L1的基于CDR的抗原结合位点;和(ii)位于抗体分子的CH3结构域中的LAG-3抗原结合位点,根据本发明,FS18-7-9/84G09,惊人地介导表达PD-L1的细胞的补体依赖性细胞毒性、而不是表达LAG-3细胞的补体依赖性细胞毒性(complement dependent cytotoxicity,CDC),即使当样品中存在表达LAG-3和PD-L1的细胞的混合物时。预期这种性质是有用的,其中,如FS18-7-9/84G09的情况一样,抗体分子的基于CDR的抗原结合靶向肿瘤细胞,并且位于抗体分子的恒定域中的结合位点靶向免疫细胞,因为免疫细胞将免受由结合至抗体分子介导的CDC,而肿瘤细胞将经历CDC。

[0070] 因而,在进一步的实施方式中,本发明涉及一种结合至肿瘤抗原和免疫细胞抗原的抗体分子,其中所述抗体分子包括:

[0071] (i) 针对肿瘤抗原的基于CDR的抗原结合位点;和

[0072] (ii) 针对免疫细胞抗原的抗原结合位点,该免疫细胞抗原位于抗体分子的恒定域中,优选CH3或CH2结构域,更优选CH3结构域,

[0073] 其中当所述免疫细胞被抗体分子结合时,抗体分子不介导、或不介导显著的,包括所述免疫细胞抗原的免疫细胞的补体依赖性细胞毒性。

[0074] 优选地,当所述肿瘤细胞被抗体分子结合时,抗体分子还介导包括所述肿瘤抗原的肿瘤细胞的补体依赖性细胞毒性。

[0075] 用于测量抗体分子的CDC的方法在本领域中是已知的并在本文中描述。

[0076] 本发明人还显示了一种抗体分子,所述抗体分子包括(i)针对PD-L1的基于CDR的抗原结合位点;和(ii)位于抗体分子的CH3结构域中的LAG-3抗原结合位点,根据本发明,FS18-7-9/84G09,与表达PD-L1的细胞的抗体依赖性细胞的细胞毒性(antibody dependent cellular cytotoxicity,ADCC)相比,惊人地介导表达LAG-3的细胞的低的抗体依赖性细胞的细胞毒性(antibody dependent cellular cytotoxicity,ADCC)。再次预期这种性质是

有用的,其中,如FS18-7-9/84G09的情况一样,抗体分子的基于CDR的抗原结合靶向肿瘤细胞,并且位于抗体分子的恒定域中的结合位点靶向免疫细胞,因为免疫细胞将比被抗体结合的肿瘤细胞经历更低的ADCC。

[0077] 如本文解释的,降低或取消抗体分子的ADCC活性的突变是本领域已知的。一种这样的突变是本文描述的LALA突变。出人意料地发现的是,FS18-7-9/84G09对于表达LAG-3的细胞具有低ADCC活性。在不需要完全取消ADCC活性之处,这可能代表一种优势。

[0078] 因而,在进一步的实施方式中,本发明涉及一种结合至肿瘤抗原和免疫细胞抗原的抗体分子,其中所述抗体分子包括:

[0079] (i) 针对肿瘤抗原的基于CDR的抗原结合位点;和

[0080] (ii) 针对免疫细胞抗原的抗原结合位点,该免疫细胞抗原位于抗体分子的恒定域,优选CH3或CH2结构域,更优选CH3结构域,

[0081] 其中,与对于当所述肿瘤细胞被抗体分子结合时包括所述肿瘤抗原的肿瘤细胞的ADCC相比,抗体分子对于当所述免疫细胞被抗体分子结合时包括所述免疫细胞抗原的免疫细胞引起较低的ADCC。优选地,当所述免疫细胞被抗体分子结合时,抗体分子不介导、或不介导显著的,包括所述免疫细胞抗原的免疫细胞的ADCC。当所述免疫细胞被抗体分子结合时,抗体分子还可以不介导、或不介导显著的,包括所述免疫细胞抗原的免疫细胞的补体依赖性细胞毒性,和/或当所述肿瘤细胞被抗体分子结合时,抗体分子可以介导包括所述肿瘤抗原的肿瘤细胞的补体依赖性细胞毒性。

[0082] 用于测量抗体分子的ADCC的方法在本领域中是已知的并在本文中描述。

[0083] 不同的肿瘤抗原和免疫细胞抗原在本领域中是已知的。肿瘤抗原和免疫细胞抗原优选是细胞表面抗原。免疫细胞抗原优选是存在于肿瘤浸润性淋巴细胞上的抗原。

[0084] 针对所述免疫细胞抗原的抗原结合位点优选包括处在所述抗体分子的恒定域的一个或更多个结构性环中的一个或更多个修饰,例如,恒定域的AB、CD和/或EF环。例如,所述结合位点可以是本文描述的LAG-3结合位点。

[0085] 本发明的抗体分子可以缀合至免疫系统调节器、细胞毒性分子、放射性同位素或可检测标记(detectable label)。所述免疫系统调节器可以是细胞毒性分子是细胞因子。

[0086] 本发明还提供一种编码本发明的抗体分子的核酸,以及一种包含这样的核酸的载体。

[0087] 还提供了一种包含本发明的核酸或载体的重组宿主细胞。这样的重组宿主细胞可以用于产生抗体分子。因而,还提供的一种生产本发明的抗体分子的方法,所述方法包括在用于生产所述抗体分子的条件培养所述重组宿主细胞。所述方法还可以包括分离和/或纯化所述抗体分子的步骤。

[0088] 期望本发明的抗体分子应用于治疗应用,特别是人类中的治疗应用,例如癌症治疗。因而,还提供的一种包括根据本发明的抗体分子以及药学可接受赋形剂的药物组合物。

[0089] 本发明还提供了本发明的抗体分子,其用于治疗患者中的癌症的方法中。还提供的一种治疗患者的癌症的方法,其中,所述方法包括向所述患者施用治疗有效量的根据本发明的抗体分子。进一步提供的是根据本发明的抗体分子,其用于制造用于治疗患者的癌症的药物的用途。所述治疗还可以包括向所述患者施用抗肿瘤疫苗和/或化疗剂

(chemotherapeutic agent)。

[0090] 附图的简要说明

[0091] 附图1:A示出了在第二次亲和成熟之后鉴定的九种Fcab,FS18-7-32;FS18-7-33;FS18-7-36;FS18-7-58;FS18-7-62;FS18-7-65;FS18-7-78;FS18-7-88和FS18-7-95相对于亲本Fcab FS18-7-9的序列比对。B示出了这些Fcab的每一个与亲本Fcab FS18-7-9的序列同一性百分比。

[0092] 附图2示出了T细胞活化试验的结果。具体地,图2示出了用mAb² FS18-7-9/84G09(附图2A-C)、或FS18-7-62/84G09或FS18-7-78/84G09(附图2D-F)和对照抗体处理的细胞系的画面中,IL-2释放的代表性的标绘图,其是T细胞活化的指示。附图2A:使用LAG-3和PD-L1的试验需要两个靶点的抑制(FS18-7-9/84G09LALA,FS18-7-9/4420LALA+84G09,25F7+84G09LALA或25F7+S1LALA)以具有活化。附图2B:使用LAG-3的试验仅需要LAG-3的抑制(FS18-7-9/84G09LALA,FS18-7-9/4420LALA+84G09,25F7+84G09LALA,25F7+S1LALA,25F7,FS18-7-9/4420 LALA)以活化。附图2C:使用PD-L1的试验仅需要PD-L1的抑制(FS18-7-9/84G09LALA,FS18-7-9/4420LALA+84G09,25F7+84G09LALA,25F7+S1LALA,84G09LALA)以活化。附图2D:使用LAG-3和PD-L1的试验需要两个靶点的抑制(FS18-7-62/84G09LALA,FS18-7-78/84G09LALA,FS18-7-62/4420LALA+84G09,FS18-7-78/4420LALA+84G09,25F7+84G09LALA或25F7+S1LALA)以具有活化。附图E:仅使用LAG-3的试验需要LAG-3的抑制(FS18-7-62/84G09LALA,FS18-7-62/4420LALA,FS18-7-78/84G09LALA,FS18-7-78/4420LALA,FS18-7-62/4420LALA+84G09,FS18-7-78/4420LALA+84G09,25F7+84G09I_AI_A或25F7+S1LALA)以活化。附图2F:仅使用PD-L1的试验需要PD-L1的抑制(FS18-7-62/84G09LALA,FS18-7-78/84G09LALA,FS18-7-62/4420LALA+84G09,FS18-7-78/4420LALA+84G09,25F7+84G09LALA或25F7+S1LALA)以活化。

[0093] 附图3示出了,如IL-2释放所指示的,在cLAG-3+cPD-L1二者、和cLAG-3或cPD-L1单独功能性地显示食蟹猴交叉反应存在的情况下,FS18-7-9/84G09能够诱导T细胞活化。

[0094] 附图4示出了来自SEB化验的代表性的标绘图。LAG-3/PD-L1 mAb²以及LAG-3/4420 mAb²+84G09LALA的组合显示比单独的84G09LALA mAb更高的活化,而LAG-3/4420 mAb²或4420 mAb不显示显著的活化。

[0095] 附图5示出了在未建立的MC38同基因肿瘤模型中在第20天的终末肿瘤重量。LAG-3/PD-L1 mAb² (FS18-29/S1) 治疗的小鼠具有比用基准mAbs,C9B7W和S1的组合治疗的小鼠显著更小重量的终末肿瘤。

[0096] 附图6示出了未建立的MC38同基因肿瘤模型的生长曲线。LAG-3/PD-L1 mAb² (FS18-29/S1) 治疗的小鼠具有比用基准mAb,C9B7W与S1的组合治疗的小鼠、或用单独的S1治疗的小鼠更小的肿瘤。LAG-3/4420 mAb²和基准抗LAG-3 mAb对肿瘤生长具有很小的影响。

[0097] 附图7示出了在建立的MC38同基因肿瘤模型中在第24天的终末肿瘤重量。LAG-3/PD-L1 mAb² (FS18-29/S1) 在抑制肿瘤生长方面与基准抗体C9B7W与S1的组合是一样有效的。单独的FS18-29/4420对肿瘤生长没有值得注意的影响,且S1和C9B7W都对结果的肿瘤生长有轻微的影响。

[0098] 附图8示出了建立的MC38同基因肿瘤模型的肿瘤生长曲线。LAG-3/PD-L1 mAb²

(FS18-29/S1) 治疗的小鼠具有比用基准mAbs, C9B7W与S1的组合治疗的小鼠相似的肿瘤体积。用单独的S1或C9B7W治疗的小鼠显示了中间肿瘤体积, 而LAG-3/4420 mAb²治疗对肿瘤生长没有影响。

[0099] 附图9示出了在未建立的CT26同基因肿瘤模型中在第20天的终末肿瘤重量。LAG-3/PD-L1 mAb² (FS18-29/S1和FS18-35/S1) 比基准抗体C9B7W与S1的组合抑制肿瘤生长达到更大的程度。

[0100] 附图10示出了未建立的CT26同基因肿瘤模型的肿瘤生长曲线。在抑制肿瘤生长方面, 在FS18-35/S1对比IgG对照中展现了统计学上显著性差异。与IgG对照组相比, 基准抗体的组合没有观察到这种统计学上显著性差异。

[0101] 附图11示出了在未建立的MC38同基因肿瘤模型中在第22天的终末肿瘤重量, 用于比较mAb²中的LALA突变对肿瘤生长抑制的作用。在用有和没有LALA突变的mAb²治疗的小鼠之间, 末尾肿瘤重量中没有统计学上显著的差异。

[0102] 附图12示出了未建立的MC38同基因肿瘤模型的肿瘤生长曲线, 用于比较有和没有LALA突变的mAb²对肿瘤生长抑制的作用。在用有和没有LALA突变的mAb²治疗的小鼠之间的肿瘤生长曲线没有统计学上显著性差异, 然而含有LALA突变的分子有提高肿瘤生长抑制的倾向。

[0103] 附图13示出了mab2治疗对T细胞LAG-3表达的作用。用mAb² FS18-29/S1、FS18-29/4420、S1、FS18-29/4420与S1、或对照抗体4420处理的CD8 (A)、CD4 (B) 和FoxP3 (C) 肿瘤浸润淋巴细胞 (TIL) 上的LAG-3表达在肿瘤接种后的第19天和第23天显示, 分别对应于最后一次mAb²/抗体给药后的第3天和第7天。在用mAb² FS18-29/S1的治疗后在第19天和第23天, LAG-3表达降低。给予FS18-29/4420与S1的组合的动物还显示LAG-3表达的降低, 但是效果延迟到直到第23天, 而单独施用的FS18-29/4420或S1引起很小到没有的LAG-3表达降低。

[0104] 附图14示出了, 使用乳酸脱氢酶 (LDH) 释放CDC试验的不同抗体/mAb²处理之后, 表达PD-L1和LAG-3的Raji细胞的裂解百分比。A和B分别示出了表达PD-L1和LAG-3的Raji细胞的CDC介导的裂解。将细胞与抗LAG-3抗体25F7、抗PD-L1抗体84G09、包括LALA突变的抗PD-L1抗体84G09、抗CD20抗体利妥昔单抗 (Rituximab)、mAb² FS18-7-9/84G09、包括LALA突变的mAb² FS18-7-9/84G09、或包括LALA突变的利妥昔单抗一起培养。在用幼兔补体处理后4小时测量LDH的释放, 表示为与总裂解相比的百分比。抗体/mAb²处理的浓度在X轴上指示。为所有曲线的斜率设置共享值, 以便能够在曲线之间进行比较。

[0105] 附图15示出了, 使用基于流式细胞术的CDC试验的各种处理之后死亡的表达PD-L1和LAG-3的Raji细胞的百分比。差异化荧光标记的表达PD-L1和LAG-3的细胞的混合物与对照抗体4420、抗CD20抗体利妥昔单抗 (RIT)、抗LAG-3抗体25F7与抗PD-L1抗体84G09的组合、或mAb² FS18-7-9/84G09一起培养。然后, 用婴儿兔补体处理细胞, 使用仅染色死细胞的染料进行染色。作为总细胞的百分比, 将两个细胞群体中死细胞的百分比评估为总细胞的百分比。在每种处理之后评估的细胞类型 (表达PD-L1或表达LAG-3, 通过差异化荧光标记物鉴定) 在附图15中指示, 位于相关处理的名称之后, 参见例如4420 PDL1, 这是指在用对照抗体4420处理之后表达PD-L1的Raji细胞的生存力的评估。抗体/mAb²处理的浓度在X轴上指示。

[0106] 附图16示出了, 使用乳酸脱氢酶 (LDH) 释放ADCC试验的不同处理之后表达PD-L1和LAG-3的Raji细胞的裂解 (细胞毒性) 百分比。细胞用抗CD20抗体利妥昔单抗、抗PD-L1抗体

84G09、mAb² FS18-7-9/84G09、包括LALA突变的利妥昔单抗、包括LALA突变的mAb² FS18-7-9/84G09、抗LAG-3抗体25F7、包括LALA突变的抗PD-L1抗体84G09、对照抗体4420、或包括LALA突变的对照抗体4420处理。然后，处理的细胞与原代NK细胞共孵育，测量特异性LDH释放，作为与靶细胞的总裂解相比的百分比。抗体/mAb²处理的浓度在X轴上指示。

[0107] 详细说明

[0108] 本发明涉及结合PD-L1和LAG-3两者的抗体分子。具体地，本发明的抗体分子包括针对PD-L1的基于CDR的抗原结合位点和位于所述抗体分子的恒定域中的LAG-3抗原结合位点。除非上下文另外需要，术语“PD-L1”和“LAG-3”可以指人类PD-L1和人类LAG-3、鼠类PD-L1和鼠类LAG-3和/或食蟹猴PD-L1和食蟹猴LAG-3。除非上下文另外需要，优选地，术语“PD-L1”和“LAG-3”是指人类PD-L1和人类LAG-3。

[0109] 术语“抗体分子”描述了一种免疫球蛋白，无论是天然的还是部分或完全合成地产生的。所述抗体分子可以是人的或人源化的。所述抗体分子优选是单克隆抗体分子。抗体的实施例是免疫球蛋白同种型，例如，免疫球蛋白G和它们的同种型子类，例如，IgG1、IgG2、IgG3和IgG4，以及其片段。

[0110] 如本文使用的，术语“抗体分子”因而包括抗体片段，只要所述片段包括针对PD-L1的基于CDR的抗原结合位点以及位于所述抗体分子的恒定域，例如，CH1、CH2或CH3结构域，优选CH3结构域的LAG-3抗原结合位点。除非上下文另外需要，本文使用的术语“抗体分子”因而等价于“抗体分子或其片段”。

[0111] 可以采用单克隆的和其他抗体并使用重组DNA技术的技术来产生保留原始抗体特异性的其他抗体或嵌合分子。这样的技术可以涉及将CDR、或可变区、和/或提供LAG-3抗原结合位点的恒定域序列导入不同的免疫球蛋白中。例如在EP-A-184187、GB 2188638A或EP-A-239400中描述了一个免疫球蛋白向另一个免疫球蛋白中的CDRs的导入。可以对相关的恒定域序列采用类似的技术。可选地，产生抗体分子的杂交瘤或其他细胞可以经历遗传突变或其他改变，这可能或可能不改变所产生的抗体的结合特异性。

[0112] 由于可以以许多方式修饰抗体，因此术语“抗体分子”应当被解释为覆盖抗体的抗体片段、衍生物、功能等效物和同源物，包含包括免疫球蛋白结合结构域的任何多肽，无论是天然的、完全合成的还是部分合成的。包括融合至另一个多肽的免疫球蛋白结合结构域或等效物的嵌合分子因而也被包括在内。EP-A-0120694和EP-A-0125023中描述了嵌合抗体的克隆和表达。

[0113] 包含CDR序列和CH3结构域两者的抗体片段的实施例是微抗体(minibody)，其包括连接到CH3结构域的单链抗体可变区片段(scFv) (Hu et al. (1996), Cancer Res., 56(13): 3055-61)。

[0114] 本发明的抗体分子结合到PD-L1和LAG-3。就此而言结合可以指特异性结合。术语“特异性”可以指情况，在该情况中抗体分子将不显示对除它的特异性结合配体(们)，此处是PD-L1和LAG-3，之外的分子的任何显著结合。术语“特异性”也可以用于所述抗体分子特异性于特定的表位之处，例如PD-L1和LAG-3上的表位，所述抗体分子将能够结合带有所述表位的各种抗原的情况下，该特定的表位被多种抗原所携带。

[0115] LAG-3与它最紧密相关的蛋白质CD4有40%的序列同一性。本发明人测试了FS18-7-9 Fcab，其包括用于结合CD4的SEQ ID NO:1到3所示的氨基酸序列。FS18-7-9 Fcab显示

不与CD4结合,表明这种分子特异性地结合LAG-3。因而,在优选的实施方式中,本发明的抗体分子的LAG-3结合位点不结合CD4,或不显示对CD4的任何显著结合。

[0116] 本发明的抗体分子优选地包含LAG-3抗原结合位点。所述LAG-3抗原结合位点位于所述抗体分子的恒定域中,例如,CH1、CH2、CH3或CH4结构域。优选地,所述LAG-3抗原结合位点位于所述抗体分子的CH3结构域中。所述LAG-3结合位点优选包括氨基酸序列WDEPWGED (SEQ ID NO:1) 和PYDRWWPDE (SEQ ID NO:3)。这些序列存在于所有先导抗LAG-3 Fcab克隆中,所述克隆如实施例中描述的由本发明人在广泛的筛选和表征程序之后鉴定。

[0117] SEQ ID NOs:1和2所示的氨基酸序列优选地位于所述抗体分子的恒定域的结构性环中。例如,在W02006/072620和W02009/132876中描述了将序列导入抗体恒定域的结构性环区中来创建新的抗原结合位点。

[0118] 抗体恒定域的结构性环包括AB、CD和EF环。在CH3结构域中,AB、CD和EF环位于CH3结构域的残基11-18、43-78和92-101,其中所述氨基酸残基编号根据免疫遗传学 (ImMunoGeneTics, IMGT) 编号方案。SEQ ID NO:1所示的氨基酸序列优选位于恒定域的AB环中。SEQ ID NO:3所示的氨基酸序列优选位于恒定域的EF环中。更优选地,SEQ ID NO:1所示的氨基酸序列位于CH3结构域的残基11到18处;和/或SEQ ID NO:3所示的氨基酸序列位于CH3结构域的残基92到101处,其中所述氨基酸序列编号是根据IMGT编号方案。

[0119] 另外,所述抗体分子优选包括在所述抗体分子的恒定域的结构性环中的SEQ ID NO:2、8、13、18、23、28、33、38、43或48中,更优选SEQ ID NO:2、28或38中,再更优选SEQ ID NO:2所示的氨基酸序列。所述结构性环优选是CD环,所述恒定域优选是CH3结构域。SEQ ID NO:2、8、13、18、23、28、33、38、43或48所示的氨基酸序列优选位于CH3结构域的残基43到78处,其中所述氨基酸残基编号根据IMGT编号方案。

[0120] 本发明的抗体分子还可以包括处在CH3结构域的位置36处的谷氨酸残基(E) 和/或处在位置85.2处的酪氨酸残基(Y),其中所述氨基酸残基编号根据IMGT编号方案。特别地,包含SEQ ID NO:8所示的CD结构性环区的抗体分子优选还包括处在CH3结构域的位置36处的谷氨酸残基(E)。类似地,包括SEQ ID NO:18所示的CD结构性环区的抗体分子优选地还包括处在所述CH3结构域的位置85.2处的酪氨酸残基(Y)。

[0121] 在优选的实施方式中,本发明的抗体分子包括CH3结构域,该CH3结构域包括、具有或由SEQ ID NO:5、10、15、20、25、30、35、40、45或50所示的序列组成,优选具有SEQ ID NO:5、30或40所示的序列的CH3结构域,更优选具有SEQ ID NO:5所示的序列的CH3结构域。

[0122] 本发明的抗体分子可以包括CH3结构域,该CH3结构域包括、具有或由SEQ ID NO:5、10、15、20、25、30、35、40、45或50所示的序列组成,其中该CH3结构域序列还包括处在SEQ ID NO:5、10、15、20、25、30、35、40、45或50中显示的序列的紧邻C-末端的赖氨酸残基。因而,例如,本发明的抗体分子可以包括CH3结构域,该CH3结构域包括、具有或由SEQ ID NO:5所示的序列组成,具有处在SEQ ID NO:5中显示的序列的C-末端的赖氨酸残基。这样的CH3结构域的序列则是如下的:GQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVPYDRWWPDEFSCSVMEALHNHYTQKSLSLSPGK (SEQ ID NO:135)

[0123] 此外,本发明的抗体分子可以包括免疫球蛋白G分子的CH2结构域,例如,IgG1、IgG2、IgG3或IgG4分子的CH2结构域。优选地,本发明的抗体分子包括IgG1分子的CH2结构域。该CH2结构域可以具有SEQ ID NO:53所示的序列。

[0124] 所述抗体分子的CH2结构域可以包括突变(mutation)以降低或取消CH2结构域与一种或多种Fc γ R受体,例如Fc γ RI、Fc γ RIIa、Fc γ RIIb、Fc γ RIII的结合,和/或与补体(complement)的结合。人IgG结构域的CH2结构域通常结合Fc γ 受体和补体,并且发明人假定与Fc γ 受体的结合降低将减少抗体依赖性细胞介导的细胞毒性(antibody-dependent cell-mediated cytotoxicity,ADCC),并且与补体的结合降低将减少所述抗体分子的补体依赖性细胞毒性(complement-dependent cytotoxicity,CDC)的活性。降低或取消CH2结构域与一种或多种Fc γ 受体和补体的结合的突变是已知的,包括Bruhns,et al.(2009)和Xu et al.(2000)中描述的“LALA突变”。因而,所述抗体分子可以包括CH2结构域,其中,CH2结构域包括该CH2结构域的位置4和处的丙氨酸残基,其中,所述编号为根据IMGT编号方案。例如,所述抗体分子包括IgG1 CH2结构域,其包括、具有或由SEQ ID NO:54所示的序列组成。

[0125] 本发明的抗体分子包括针对PD-L1的基于CDR的抗原结合位点。术语“基于CDR的抗原结合位点”是指包括六个CDR的残基的抗体分子可变区的抗原结合位点。针对PD-L1的抗体分子的制备和这样的抗体分子的CDR序列的测定完全在技术人员的能力范围之内,并且许多适合的技术是本领域已知的。

[0126] 优选地,本发明的抗体分子包括抗体84G09的HCDR3。已知HCDR3在确定抗体分子的特异性方面起到作用(Segal et al.,(1974),PNAS,71:4298-4302;Amit et al.,(1986),Science,233:747-753;Chothia et al.,(1987),J.Mol.Biol.,196:901-917;Chothia et al.,(1989),Nature,342:877-883;Caton et al.,(1990),J.Immunol.,144:1965-1968;Sharon et al.,(1990a),PNAS,87:4814-4817;Sharon et al.,(1990b),J.Immunol.,144:4863-4869;Kabat et al.,(1991b),J.Immunol.,147:1709-1719)。

[0127] 所述抗体分子还可以包括抗体84G09的HCDR1、HCDR2、LCDR1、LCDR2和/或LCDR3。本领域技术人员可以毫无困难地分别从SEQ ID NOs 92和93中所示的抗体84G09的VH和VL结构域序列确定CDR的序列。例如,CDR序列可以根据Kabat(Kabat,E.A.et al.,(1991))或IMGT编号方案来确定。

[0128] 根据IMGT编号方案,抗体84G09的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3的序列分别在SEQ ID NOs:86、87、88、89、90和91中示出。

[0129] 根据Kabat,抗体84G09的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3的序列分别在SEQ ID NOs:136、137、138、139、140和141中示出。

[0130] 所述抗体还可以包括抗体84G09的VH和/或VL结构域。抗体84G09的VH和VL结构域序列分别在SEQ ID NOs:92和93中显示。

[0131] 在优选的实施方式中,本发明的抗体分子包括(i)包括抗体84G09的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3序列的针对PD-L1的基于CDR的抗原结合位点,和(ii)位于所述抗体分子的CH3结构域中的LAG-3抗原结合位点,其中,所述LAG-3结合位点包括SEQ ID NOs:1和3所示的氨基酸序列,以及选自由SEQ ID NOs:2、8、13、18、23、28、33、38、43和48构成的组的氨基酸序列。

[0132] 更优选地,本发明的抗体分子包括(i)包括抗体84G09的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3序列的针对PD-L1的基于CDR的抗原结合位点,和(ii)位于所述抗体分子的CH3结构域中的LAG-3抗原结合位点,其中,所述LAG-3结合位点包括SEQ ID NOs:1和3所示的氨基酸序列,以及选自由SEQ ID NOs:2、28和38构成的组的氨基酸序列。

[0133] 再更优选地,本发明的抗体分子包括(i)包括抗体84G09的HCDR1、HCDR2、HCDR3、LCDR1、LCDR2和LCDR3序列的针对PD-L1的基于CDR的抗原结合位点,和(ii)位于所述抗体分子的CH3结构域中的LAG-3抗原结合位点,其中,所述LAG-3结合位点包括SEQ ID NOs:1、2和3所示的氨基酸序列。

[0134] 在优选的实施方式中,本发明的抗体分子包括分别包括、具有或由SEQ ID NOs:92和93所示的序列组成的VH结构域和VL结构域,以及包括、具有或由SEQ ID NO:5、10、15、20、25、30、35、40、45或50所示的序列组成的CH3结构域,优选包括、具有或由SEQ ID NO:5、30或40所示的序列组成的CH3,更优选包括、具有或由SEQ ID NO:5所示的序列组成的CH3结构域。

[0135] 在进一步优选的实施方式中,所述抗体分子包括重链以及轻链,所述重链包括、具有或由SEQ ID NOs:94到113所示的序列组成,所述轻链包括、具有或由SEQ ID NO:116所示的序列组成。更优选地,所述抗体分子包括重链以及轻链,所述重链包括、具有或由SEQ ID NOs:94、95、104、105、108和109所示的序列组成,所述轻链包括、具有或由SEQ ID NO:116所示的序列组成。最优选地,所述抗体分子包括重链以及轻链,所述重链包括、具有或由SEQ ID NO:94或95所示的序列组成,所述轻链包括、具有或由SEQ ID NO:116所示的序列组成。

[0136] 本发明的抗体分子还可以包括本文公开的结构性环、CH3结构域、CH2结构域、CH2和CH3结构域、轻链或重链序列的变体,只要所述轻链和重链序列的VL和VH结构域分别保持不变。可以通过序列改变、突变或筛选的方法来获得适合的变体。在优选的实施方式中,包括一种或多种变体序列的抗体分子保持了亲本抗体分子的一个或多个功能特征,例如,对LAG-3和PD-L1的结合特异性和/或结合亲和力。例如,包括一种或多种变体序列的抗体分子优选以与(亲本)抗体分子相同的或更高的亲和力结合至LAG-3和/或PD-L1。所述亲本抗体分子是不包括被合并到所述变体抗体分子中的氨基酸取代、删除和/或插入的抗体分子。

[0137] 例如,本发明的抗体分子可以包括结构性环、CH3结构域、CH2结构域、CH2和CH3结构域、轻链或重链序列,其具有与本文公开的结构性环、CH3结构域、CH2结构域、CH2和CH3结构域、轻链或重链序列具有至少70%、至少75%、至少80%、至少85%、至少90%、至少95%、至少96%、至少97%、至少98%、至少99%、至少99.1%、至少99.2%、至少99.3%、至少99.4%、至少99.5%、至少99.6%、至少99.7%、至少99.8%或至少99.9%的序列同一性,只要所述轻链和重链序列的VL和VH结构域分别保持不变。

[0138] 在优选的实施方式中,本发明的抗体分子包括CH3结构域序列,该CH3结构域序列与SEQ ID NO:4、5或135所示的CH3结构域序列具有至少97%、至少98%、至少99%、至少99.1%、至少99.2%、至少99.3%、至少99.4%、至少99.5%、至少99.6%、至少99.7%、至少99.8%或至少99.9%的序列同一性。

[0139] 在进一步优选的实施方式中,本发明的抗体分子包括CH3和CH2结构域序列,该CH3和CH2结构域序列与SEQ ID NO:6或7所示的CH2和CH3结构域序列具有至少97%、至少98%、至少99%、至少99.1%、至少99.2%、至少99.3%、至少99.4%、至少99.5%、至少99.6%、至少99.7%、至少99.8%或至少99.9%的序列同一性。

[0140] 序列同一性通常参考算法平均积分点(GAP)来定义(Wisconsin GCG package, Accelrys Inc, San Diego USA)。GAP使用内德勒曼(Needleman)和翁施(Wunsch)算法来比对两个完整的序列,最大化匹配的数量并最小化缺口的数量。一般地,使用默认的参数,缺

口创建罚分=12,及缺口延伸罚分=4。GAP的使用可以是优选的,但是可以使用其他算法,例如,贝尔实验室空时(BLAST)(其使用Altschul et al.(1990)J.Mol.Biol.215:405-410的方法),同源比较(FASTA)(其使用Pearson and Lipman(1988)PNAS USA 85:2444-2448的方法),或史密斯-华特曼(Smith-Waterman)算法(Smith and Waterman(1981)J.Mol Biol.147:195-197),或上文Altschul et al.(1990)的TBLASTN程序,一般采用默认参数。特别地,可以使用位置特异性迭代-Blast(psi-Blast)算法(Nucl.Acids Res.(1997) 25 3389-3402)。

[0141] 本发明的抗体分子还可以包括结构性环、CH3结构域、CH2结构域、CH2和CH3结构域、轻链或重链序列,其与本文公开的结构性环、CH3结构域、CH2结构域、CH2和CH3结构域、轻链或重链序列相比具有一个或多个氨基酸序列改变(氨基酸残基的添加、删除、取代和/或插入),优选20个改变或更少、15个改变或更少、10个改变或更少、5个改变或更少、4个改变或更少、3个改变或更少、2个改变或更少、或1个改变,只要所述轻链和重链序列的VL和VH结构域分别保持不变。特别地,可以在所述VH和VL结构域序列之外所述抗体分子的一个或多个框架区中进行改变。

[0142] 在优选的实施方式中,本发明的抗体分子可以包括CH3结构域序列,其与SEQ ID NO:4、5或135所示的CH3结构域序列相比具有一个或多个氨基酸序列改变(氨基酸残基的添加、删除、取代和/或插入),优选20个改变或更少、15个改变或更少、10个改变或更少、5个改变或更少、4个改变或更少、3个改变或更少、2个改变或更少、或1个改变。

[0143] 在进一步优选的实施方式中,本发明的抗体分子包括CH3和CH2结构域序列,其与SEQ ID NO:6或7所示的CH2和CH3结构域序列相比具有一个或多个氨基酸序列改变(氨基酸残基的添加、删除、取代和/或插入),优选20个改变或更少、15个改变或更少、10个改变或更少、5个改变或更少、4个改变或更少、3个改变或更少、2个改变或更少、或1个改变。

[0144] 还期待的是一种抗体分子,其与本发明的抗体分子竞争结合LAG-3和/或PD-L1,或其结合与本发明的抗体分子相同的LAG-3和/或PD-L1上的表位,其中,该抗体分子优选包括针对PD-L1的基于CDR的抗原结合位点和位于所述抗体分子的CH3结构域中的LAG-3抗原结合位点。测定两种抗体对抗原的竞争的方法在本领域中是已知的。例如,可以使用生物大分子相互作用分析仪(BIAcore)测定两种抗体对抗原的结合的竞争。用于绘制两种抗体结合的表位的方法在本领域中同样地是已知的。

[0145] 本发明的抗体分子优选以 1×10^{-9} M的亲和力(KD)或更大的亲和力结合LAG-3。例如,本发明的抗体分子可以以 8×10^{-10} M的亲和力(KD)或更大的亲和力结合LAG-3。

[0146] Fcab具有比单克隆抗体更小的结合界面,因为Fcab的结合位点与两个位于极为贴近的结合位点形成相当紧致的抗体片段。相比之下,典型的mAb的Fab臂(Fab arms)被柔性铰链区(flexible hinge region)分隔。当与典型的mAb的抗原结合位点相比时,Fcab的两个抗原结合位点也在空间上相互靠近。基于这种更小的结合界面和减小的两个结合位点的柔性,令人惊讶的是,抗LAG-3 Fcab能够以与单克隆抗体基准类似的亲和力和效价结合并抑制LAG-3。

[0147] 本发明的抗体分子优选以 1×10^{-9} M的亲和力(KD)或更大的亲和力结合PD-L1。

[0148] 可以通过例如表面等离子体共振(SPR)来测定抗体分子对同源抗原例如LAG-3或PD-L1的结合亲和力。可以通过流式细胞计(flow cytometry)来测定抗体分子对细胞表面

上表达的同源抗原例如LAG-3或PD-L1的结合亲和力。

[0149] 本发明的抗体分子优选能够结合细胞的表面上表达的LAG-3和PD-L1。该细胞优选为癌细胞。

[0150] 本发明的抗体分子优选能够同时结合细胞的表面上表达的LAG-3和PD-L1。在优选的实施方式中,本发明的抗体分子能够同时结合LAG-3和PD-L1,其中,所述LAG-3和PD-L1在单个细胞的表面上或在两个独立的细胞的表面上表达。

[0151] 本发明的抗体分子可以结合人类LAG-3、鼠类LAG-3和/或食蟹猴LAG-3。优选地,本发明的抗体分子结合人类LAG-3。最优选地,本发明的抗体分子结合人类LAG-3和人类PD-L1。

[0152] 本发明的抗体分子包括(i)针对PD-L1的基于CDR的抗原结合位点;和(ii)位于所述抗体分子的恒定域中的LAG-3抗原结合位点。不包括位于抗体分子的恒定域例如CH3结构域中的LAG-3抗原结合位点的抗体分子因而不形成本发明的部分。类似地,不包括针对PD-L1的基于CDR的抗原结合位点的分子不形成本发明的部分。

[0153] 本发明的抗体分子可以缀合到治疗试剂或可检测标记。在这种情况下,所述抗体分子可以被称为缀合物(conjugate)。例如,所述抗体分子可以与免疫系统调节器、细胞毒性分子、放射性同位素或可检测标记缀合。所述免疫系统调节器或细胞毒性分子可以是细胞因子。所述可检测标记可以是放射性同位素,例如,非治疗性放射性同位素(non-therapeutic radioisotope)。

[0154] 所述抗体分子可以通过肽键或接头(linker)的方式缀合到治疗试剂或可检测标记,即,在包括所述治疗试剂或可检测标记以及所述抗体分子或其多肽链组件(polypeptide chain component)的融合多肽(fusion polypeptide)之内。缀合的其他方式包括化学缀合,特别是使用双功能试剂的交联(例如,采用双试剂™(DOUBLE-REAGENTS™)交联试剂选择指南(Cross-linking Reagents Selection Guide),皮尔斯(Pierce))。

[0155] 所述抗体分子和所述治疗试剂或可检测标记因而可以直接相互连接,例如,通过任何适合的化学键或通过接头,例如肽接头(peptide linker)。

[0156] 所述肽接头可以是短的(2-20个,优选2-15个氨基酸的残基延伸)。肽接头序列的适合的实施例在本领域中是已知的。可以使用一个或多个不同的接头。所述接头的长度可以是约5个氨基酸。

[0157] 所述化学键可以是例如共价键或离子键。共价键的实施例包括肽键(酰胺键(amide bonds))和二硫键。例如,所述抗体分子与治疗或诊断试剂可以共价连接。例如,通过肽键(酰胺键)。因而,所述抗体分子和治疗或诊断试剂可以作为单链多肽产生(分泌)。

[0158] 本发明还提供了编码本发明的抗体分子的分离的核酸(isolated nucleic acids)。技术人员使用本领域公知的方法制备这样的核酸将没有困难。分离核酸可以用于表达本发明的抗体分子,例如,通过在细菌、酵母、昆虫或哺乳动物宿主细胞中的表达。优选的宿主细胞是哺乳动物细胞,例如,中国仓鼠卵细胞(CHO)、人胚肾细胞(HEK)或小鼠骨髓瘤细胞(NS0)细胞。所述核酸一般将以用于表达的重组载体(recombinant vector)的形式提供。

[0159] 例如,所述分离核酸可以包括SEQ ID NO:142、4、9、14、19、24、29、34、39、44或49所示的序列,它们分别编码FS18-7-9(CHO密码子优化的核苷酸序列)、FS18-7-9(HEK293表达

的核苷酸序列)、FS18-7-32、FS18-7-33、FS18-7-36、FS18-7-58、FS18-7-62、FS18-7-65、FS18-7-78、FS18-7-88和FS18-7-95的CH3结构域。

[0160] 包括这样的核酸和载体的体外的宿主细胞是本发明的部分,它们用于表达本发明的抗体分子的用途也是本发明的部分,所述抗体分子随后可以从细胞培养物中纯化,可选地配制到药物组合物中。因而本发明还提供了生产本发明的抗体分子的方法,其包括在用于生产所述抗体分子的条件下培养本发明的重组宿主细胞。如上所述培养适合的宿主细胞的方法在本领域中是公知的。所述方法还可以包括分离和/或纯化所述抗体分子。所述方法还可以包括将所述抗体分子,可选地与下文描述的药学可接受赋形剂或其他物质一起配制到药物组合物中。

[0161] 已知PD-L1在许多癌细胞上表达,而癌细胞上LAG-3的表达是更为有限的。两者都在免疫系统的细胞上表达。特别地,已知LAG-3在肿瘤环境内的衰竭的T细胞上表达。此外,本发明人已经示出了结合LAG-3和PD-L1两者的抗体分子的使用在同基因的小鼠癌症模型中抑制肿瘤生长是有效的,且示出了这样的分子比分别施用结合LAG-3和PD-L1的两种结合分子是更为有效的。

[0162] 因而,本发明的抗体分子可以用于治疗患者的癌症的方法中。患者优选是人类患者。

[0163] 使用本发明的抗体分子治疗的癌症的细胞可以在,例如,它们的细胞表面表达LAG-3。在一个实施例中,待治疗的癌症的细胞可以已经确定,例如,在它们的细胞表面表达LAG-3。例如,B细胞淋巴瘤已经显示了在它们的细胞表面表达LAG-3。用于测定细胞表面的抗原表达的方法在本领域中是已知的,并包括例如流式细胞术。

[0164] 下文的实施例4示出了本发明的抗体分子可以用于治疗小鼠中具有高水平LAG-3表达的免疫细胞,例如表达LAG-3的TIL的肿瘤。因而,另外地或可选地,使用本发明的抗体分子治疗的癌症的肿瘤可以包含LAG-3表达免疫细胞。LAG-3表达免疫细胞,例如,LAG-3表达TIL,存在于许多癌症的肿瘤细胞之间。在一个实施方式中,使用本发明的抗体分子治疗的癌症的肿瘤已经确定含有LAG-3表达免疫细胞。确定肿瘤中或肿瘤的外周部中LAG-3表达免疫细胞存在的方法在本领域中是已知的。

[0165] 下文的实施例4还示出了,本发明的抗体分子可以用于治疗在它们的细胞表面上表达PD-L1的肿瘤。因而,另外地或作为选择,使用本发明的抗体分子治疗的癌症的细胞可以例如在它们的细胞表面表达PD-L1。另外地或可选地,待治疗的癌症的肿瘤可以包括表达PD-L1的免疫细胞,例如TILs。待治疗的癌症的细胞可以已经确定,例如,在它们的细胞表面表达PD-L1。另外地或可选地,待治疗的癌症的肿瘤可以已经确定含有表达PD-L1的免疫细胞,例如TIL。

[0166] LAG-3和PD-L1的细胞表面表达预计容许抗体分子结合到所述免疫细胞和/或所述癌细胞的表面上表达的LAG-3和PD-L1。这被认为产生癌细胞和免疫细胞的直接治疗、桥接和定位。

[0167] 使用本发明的抗体分子治疗的癌症可以选自由以下组成的组:霍奇金淋巴瘤、非霍奇金淋巴瘤(例如弥散性大B细胞淋巴瘤、惰性非霍奇金淋巴瘤、套细胞淋巴瘤)、卵巢癌、前列腺癌、结直肠癌、纤维肉瘤、肾细胞癌、黑素瘤、胰腺癌、乳腺癌(breast cancer)、多形性胶质母细胞瘤(glioblastoma multiforme)、肺癌(例如非小细胞肺癌)、头颈部癌症(例

如头颈部鳞状细胞癌(head and neck squamous cell carcinoma)、胃癌(stomach cancer, gastric cancer)、膀胱癌、宫颈癌、子宫癌、外阴癌、睾丸癌(testicular cancer)、阴茎癌、白血病(例如慢性淋巴细胞性白血病、骨髓性白血病(myeloid leukemia)、急性类淋巴细胞白血病(acute lymphoblastoid leukaemia)、或慢性类淋巴细胞白血病(chronic lymphoblastoid leukaemia))、多发性骨髓瘤、扁平细胞癌、睾丸癌、食道癌(esophageal cancer)(例如胃食管交界部腺癌(adenocarcinoma of the gastroesophageal junction))、卡波西氏(Kaposi's)肉瘤和中枢神经系统(central nervous system, CNS)淋巴瘤、肝细胞癌、鼻咽癌(nasopharyngeal cancer)、默克尔(Merkel)细胞癌和间皮瘤(mesothelioma)。这些癌症的肿瘤已知或预计在它们的细胞表面表达PD-L1和/或含有表达PD-L1和/或LAG-3的免疫细胞,例如TIL。

[0168] 使用抗LAG-3抗体治疗肾细胞癌、肺癌(例如非小细胞肺癌)、鼻咽癌、结直肠癌、黑素瘤、胃癌(stomach cancer, gastric cancer)、食道癌(例如胃食管交界部腺癌)、卵巢癌、宫颈癌、膀胱癌、头颈部癌症(例如头颈部鳞状细胞癌)、白血病(例如慢性淋巴细胞性白血病)、霍奇金淋巴瘤、非霍奇金淋巴瘤(例如弥漫性大B细胞淋巴瘤、惰性非霍奇金淋巴瘤、套细胞淋巴瘤)和多发性骨髓瘤已经在临床试验中进行研究并显示了有前景的结果。因而,使用本发明的抗体分子治疗的癌症可以是肾细胞癌、肺癌(例如非小细胞肺癌)、鼻咽癌、结直肠癌、黑素瘤、胃癌(stomach cancer, gastric cancer)、食道癌(例如胃食管的接点的腺癌)、卵巢癌、宫颈癌、膀胱癌、头颈部癌症(例如头颈部鳞状细胞癌)、白血病(例如慢性淋巴细胞性白血病)、霍奇金淋巴瘤、非霍奇金淋巴瘤(例如弥漫性大B细胞淋巴瘤、惰性非霍奇金淋巴瘤、套细胞淋巴瘤)或多发性骨髓瘤。

[0169] 使用抗PD-L1抗体治疗黑素瘤、结直肠癌、乳腺癌、膀胱癌、肾细胞癌、膀胱癌、胃癌、头颈部癌症(例如头颈部的鳞状细胞癌)、间皮瘤、肺癌(例如,非小细胞肺癌)、卵巢癌、默克尔(Merkel)细胞癌、胰腺癌、黑素瘤和肝细胞癌已经在临床试验中进行研究并显示了有前景的结果。因而,使用本发明的抗体分子治疗的癌症可以是黑素瘤、结直肠癌、乳腺癌、膀胱癌、肾细胞癌、膀胱癌、胃癌、头颈部癌症(例如头颈部的鳞状细胞癌)、间皮瘤、肺癌(例如非小细胞肺癌)、卵巢癌、默克尔(Merkel)细胞癌、胰腺癌、黑素瘤或肝细胞癌。

[0170] 使用本发明的抗体分子以治疗的优选的癌症是肺癌(例如非小细胞肺癌)、膀胱癌、头颈部癌症(例如,头颈部鳞状细胞癌)、弥漫性大B细胞淋巴瘤、胃癌、胰腺癌和肝细胞癌。已知这些癌症的肿瘤包括LAG-3表达免疫细胞以及在它们的细胞表面表达PD-L1,或包含PD-L1表达免疫细胞。

[0171] 在应用涉及特定类型的癌症之处,例如,乳腺癌,这是指相关组织的恶性转化,在这种情况下为乳腺组织。源自不同组织例如卵巢组织的恶性转化的癌症,可能在身体的其他位置例如乳腺引起转移性病变,但不因此是本文所指的乳腺癌,而是卵巢癌。

[0172] 癌症可以为原发的或继发的癌症。因而,本发明的抗体分子可以供治疗患者的癌症的方法中使用,其中,所述癌症是原发肿瘤和/或肿瘤转移(tumour metastasis)。

[0173] 本发明的抗体分子被设计用于患者、优选人类患者的治疗的方法中。抗体分子通常将以药物组合物的形式施用,所述药物组合物可以包含除了所述抗体分子之外的至少一种成分,例如,药学可接受赋形剂。例如,除了活性成分之外,本发明的药物组合物可以包含药学可接受赋形剂、载体、缓冲剂、稳定剂或本领域技术人员公知的其他材料。这样的材料

应当是无毒的,并且不应干扰所述活性成分的效力。所述载体或其他材料的确切性质将取决于施用途径,其可以是注射,例如,静脉内的或皮下的。所述抗体分子可以静脉内地或皮下地施用。

[0174] 液体药物组合物一般包含液体载体,例如水、石油、动物或植物油、矿物油或合成油。可以包括生理盐溶液、葡萄糖或其他糖溶液或甘醇,例如乙二醇、丙二醇或聚乙二醇。

[0175] 对于静脉内注射或在患病位点(site of affliction)的注射,所述抗体分子或包含所述抗体分子的药物组合物优选为无热原的,并具有适合的pH值、等渗性和稳定性的肠外可接受水性溶液的形式。本领域相关技术人员完全能够使用例如等渗的运载体(isotonic vehicles),例如氯化钠注射液、林格(Ringer's)注射液、乳酸林格注射液来制备适合的溶液。根据需要可以采用防腐剂、稳定剂、缓冲剂、抗氧化剂和/或其他添加剂。制备药物制剂的许多方法是本领域技术人员已知的。参见,例如,Robinson ed., Sustained and Controlled Release Drug Delivery Systems, Marcel Dekker, Inc., New York, 1978。

[0176] 取决于待治疗的状况,包括根据本发明的抗体分子的组合物可以单独或与其他治疗组合同时地、依序地、或作为与其他治疗试剂的组合制剂施用。例如,本发明的抗体分子可以与现有的用于待治疗的疾病、例如上文所述癌症的治疗试剂组合施用。例如,本发明的抗体分子可以与第二抗癌治疗组合施用给患者,例如,化疗、抗肿瘤疫苗接种(anti-tumour vaccination)(也称为癌症免疫接种(cancer vaccination))、放疗、免疫治疗、溶瘤病毒(oncolytic virus)、嵌合抗原受体(chimeric antigen receptor, CAR) T细胞治疗、或激素治疗。

[0177] 预期的是,本发明的抗体分子可以作为抗癌治疗例如化疗、抗肿瘤疫苗接种或放疗中的佐剂。不希望受到理论的限制,与用化疗、抗肿瘤免疫接种或放疗单独实现的相比,被认为作为化疗、抗肿瘤疫苗接种或放疗的部分向患者施用抗体分子将触发针对癌症相关抗原LAG-3和PD-L1的更大的免疫应答。例如,抗LAG-3治疗在小鼠中治疗基于病毒的病理方面已经显示了良好的效果(Blackburn SD, et al., 2009)。

[0178] 因而治疗患者的癌症的方法可以包括向所述患者施用治疗有效量的与化疗剂、抗肿瘤疫苗、放射性核素、免疫治疗试剂、溶瘤病毒、CAR-T细胞或用于激素治疗的试剂组合的根据本发明的抗体分子。所述化疗剂、抗肿瘤疫苗、放射性核素、免疫治疗剂、溶瘤病毒、CAR-T细胞或用于激素治疗的试剂优选为用于讨论中的癌症的化疗剂、抗肿瘤疫苗、放射性核素、免疫治疗剂、溶瘤病毒、CAR-T细胞或用于激素治疗的试剂,即,已经显示在治疗讨论中的癌症中有效的化疗剂、抗肿瘤疫苗、放射性核素、免疫治疗剂、溶瘤病毒、CAR-T细胞或用于激素治疗的试剂。已经显示对讨论中的癌症有效的适合的化疗剂、抗肿瘤疫苗、放射性核素、免疫治疗剂、溶瘤病毒、CAR-T细胞或用于激素治疗的试剂的选择完全在有执业医师的能力范围之内。

[0179] 例如,在该方法包括与化疗剂组合向患者施用治疗有效量的根据本发明的抗体分子之处,所述化疗剂可以选自以下组成的组:紫杉烷(taxanes)、细胞毒抗生素、酪氨酸激酶抑制剂、聚腺苷二磷酸-核糖聚合酶(PARP)抑制剂、B_RAF酶抑制剂、烷化剂、铂类似物(platinum analogs)、核苷类似物(nucleoside analogs)、沙利度胺衍生物(thalidomide derivatives)、抗肿瘤化疗剂及其他。紫杉烷包括多西紫杉醇(docetaxel)、紫杉醇

(paclitaxel) 和白蛋白结合型紫杉醇 (nab-paclitaxel); 细胞毒抗生素包括放线菌素 (actinomycin)、博来霉素 (bleomycin)、蒽环类 (anthracyclines)、多柔比星 (doxorubicin) 和戊柔比星 (valrubicin); 酪氨酸激酶抑制剂包括埃罗替尼 (erlotinib)、吉非替尼 (gefitinib)、西替尼 (axitinib)、PLX3397、伊马替尼 (Imatinib)、可比替尼 (cobemitinib) 和曲美替尼 (trametinib); PARP 抑制剂包括皮拉帕尼 (piraparib); B-Raf 酶抑制剂包括威罗菲尼 (vemurafenib) 和达拉菲尼 (dabrafenib); 烷化剂包括达卡巴嗪 (dacarbazine)、环磷酰胺 (cyclophosphamide)、替莫唑胺 (temozolomide); 铂类似物包括顺羧酸铂 (carboplatin)、顺氯氨铂 (cisplatin) 和奥沙利铂 (oxaliplatin); 核苷类似物包括吉西他滨 (gemcitabine) 和阿扎胞苷 (azacitidine); 抗肿瘤药包括氟达拉滨 (fludarabine)。适用于本发明的其他化疗剂包括甲氨蝶呤 (methotrexate)、黛菲替尼 (defactinib)、恩替诺特 (entinostat)、培美曲塞 (pemetrexed)、卡培他滨 (capecitabine)、艾日布林 (eribulin)、伊立替康 (irinotecan)、氟尿嘧啶 (fluorouracil) 和长春碱 (vinblastine)。

[0180] 用于癌症的治疗的疫苗接种策略已经在临床中实现并在科学文献内详细讨论 (例如 Rosenberg, S. 2000 Development of Cancer Vaccines)。这主要涉及通过使用那些细胞作为免疫接种方法, 使用或不使用粒细胞巨噬细胞集落刺激因子 (GM-CSF) 促进免疫系统响应自体或异源癌细胞表达的各种细胞标记物。GM-CSF 激起抗原呈递中的强反应, 并且在与前述策略一起采用时特别有用。

[0181] 施用可以是“治疗有效量”, 这足以显示对患者的益处。这样的益处可以至少是至少一种症状的改善。因而特定疾病的“治疗”是指至少一种症状的改善。施用的实际用量、施用的速率和时程将取决于要治疗的疾病的性质和严重程度、治疗的具体患者、个体患者的临床状况、失调的原因、组合物的递送位点、抗体分子的类型、施用的方法、施用的安排、以及医师已知的其他因素。治疗的处方, 例如, 剂量的判定等, 在全科医师和其他医师的责任能力之内, 并且可以取决于治疗的疾病的症状和/或发展的严重程度。抗体分子的适当的剂量在本领域中是公知的 (Ledermann et al. (1991) Int. J. Cancer 47:659-664; 和 Bagshawe et al. (1991) Antibody, Immunoconjugates and Radiopharmaceuticals 4:915-922)。根据施用的抗体分子的情况, 可以使用本文或医师手册 (Physician's Desk Reference, 2003) 中指定的具体剂量。抗体分子的治疗有效量或适合的剂量可以通过比较它的体外活性和动物模型中的体内活性来确定。将小鼠和其他测试动物中的有效剂量外推至人类的方法是已知的。确切的剂量将取决于许多因素, 包括要治疗的区域的大小和位置, 以及所述抗体分子的确切性质。听从医师的处理, 治疗可以每日地、每周两次地、每周或每月间隔地重复。可以在手术之前和/或之后给予治疗, 可以在外科治疗的解剖位置直接施用或施加。

[0182] 包括以下实验例的本公开内容所给出的本发明的进一步的方面和实施方式对于本领域技术人员而言将是明显的。

[0183] 本说明书中提及的所有文献通过引用以其整体合并在本文中。

[0184] 本文中使用的“和/或”被视为具有或不具有另一个的两个指定特征或组件中的每一个的具体公开。例如, “A 和/或 B”将被视为 (i) A, (ii) B 和 (iii) A 和 B 中的每一个的具体公开内容, 正如每一个在本文中单独列出一样。

[0185] 除非上下文另有指示, 否则上述特征的描述和定义不限于本发明的任何特定方面

或实施方式,并且同样适用于所描述的所有方面和实施方式。

[0186] 现在将通过实施例并参考上文描述的附图来说明本发明的某些方面和实施方式。

实施例

[0187] 实施例1-Fcab分子的选择和表征

[0188] 1.1抗人LAG-3 Fcab的初始选择和亲和成熟

[0189] 1.1.1初始选择

[0190] 展示人IgG1的CH3结构域(IMGT编号1.4-130)的初始噬菌体文库(Naïve phage libraries)使用重组Fc-标签化的人LAG-3(LAG-3 Fc)抗原(R&D systems,2319-L3-050)进行选择,所述CH3结构域在AB(残基14-18)和EF(残基92-101)环内随机化。使用蛋白A(Life Technologies,10002D)或蛋白G(Life Technologies,10004D)珠子(beads)上捕获的抗原对文库进行三轮选择。通过酶联免疫吸附测定(ELISA)筛选输出结果,阳性结合者进行亚克隆(sub-cloned),并使用易选毕赤酵母表达试剂盒(EasySelect Pichia Expression Kit)(Life Technologies,K1740-01)在巴斯德毕赤氏酵母(Pichia pastoris)中表达为可溶Fcab(含有截短的铰链)。然后在Biacore 3000(GE Healthcare)上筛选Fcab与重组人LAG-3 Fc结合。简单地,使用胺偶联(GE Healthcare,BR-1000-50)将LAG-3 Fc(R&D systems,2319-L3-050)以7200U的密度偶联在CM5芯片(chip)(GE Healthcare,BR-100012)上。Fcab在HBS-P(GE Healthcare,BR100368)缓冲液中稀释,并以250nM、500nM和1000nM注射3分钟,然后容许在缓冲液中解离5分钟。使用BIAevaluation 3.2软件分析参考减去的数据(LAG-3 Fc流动池2-空白流动池)以鉴定结合。然后测试Fcab对HEK细胞表达的人LAG-3的结合(LAG-3克隆到pcDNA5FRT载体[Life Technologies,V6010-20]中[方法参见章节1.4.5])。简单地,在含有10%胎牛血清(FBS)(Life Technologies,10270-1-6)、100μg/ml潮霉素(Hygromycin)B(Melford Laboratories Ltd,Z2475)、15μg/mL杀稻瘟菌素(Blasticidin)(Melford Laboratories Ltd,B1105)和1μg/1mL脱氧土霉素(Doxycyclin)(Sigma,D9891)的细胞培养基(DMEM)中生长的、过量表达人LAG-3的HEK 293细胞使用细胞解离缓冲液(Life Technologies,13151-014)从组织培养烧瓶上剥离,并且以 2×10^5 个细胞/孔(well)接种在V形底96孔平板中。Fcab与细胞在5μM细胞在100μl体积中4℃下孵育1小时。洗涤平板,二抗(抗人Fc-488,Jackson ImmunoResearch,109-546-098)在磷酸盐缓冲液(PBS)中以1:1000稀释,并向细胞中添加100μl,在4℃下孵育30分钟。洗涤平板,并且细胞在含有1μg/mL苯基吡啶(DAPI)(Biotium,40043)的100μl PBS中重悬浮。在DB流式细胞仪[FACSCanto] II细胞计(BD Biosciences)上读取该平板,使用FlowJoX分析数据。然后Fcab通过使用脂质体(lipofectamine)(Life Technologies,11668-019)转染到Flp-In T-Rex 293细胞(Life Technologies,R780-07)中,在哺乳动物细胞中表达。测试LAG-3结合Fcab对A375细胞(美国型培养菌种集[ATCC],CRL-1619)上人II类MHC与重组LAG-3 Fc(使用实施例1.6中的方法)的结合的抑制。从三轮噬菌体选择中鉴定出54个独特的Fcab序列,通过BIAcore分析确定这些Fcab中的12个结合LAG-3 Fc,和/或结合表达LAG-3的细胞。所选Fcab中的三个还能够抑制LAG-3与II类MHC的相互作用,选择用于亲和成熟。这三个Fcab称为FS18-3、FS18-7和FS18-21。

[0191] 1.1.2亲合成熟

[0192] 首次亲和成熟

[0193] 通过对使用上述的初始选择过程鉴定的三个Fcab的每一个的AB环中的五个残基(残基14-18),以及EF环中的五个(残基92-94和97-98)或八个(残基92-94和97-101)残基进行随机化构建六个噬菌体展示亲和成熟文库。

[0194] 使用重组人LAG-3 Fc(R&D systems,2319-L3-050)和表达人LAG-3的HEK细胞(如上所述)选择所述亲和成熟文库。通过噬菌体ELISA筛选输出,阳性结合者进行亚克隆,在HEK Expi293细胞中表达为可溶Fcab(含有截短的铰链)(Fcab克隆到蛋白质截短试验5[pTT5]载体[National Research Council of Canada]中,使用ExpiFectamine 293转染试剂盒[Life Technologies,A14524]转染到Expi293F细胞[Life technologies,A14527]中)。然后筛选HEK表达的可溶Fcab以结合细胞表达的人LAG-3、结合细胞表达的食蟹猴LAG-3(实施例1.4.3的方法),以及阻断II类MHC结合重组LAG-3 Fc的能力(实施例1.6中的方法)。进一步测试阻断性Fcab以确定它们是否能够在T细胞活化试验中逆转LAG-3诱导的IL-2分泌抑制(实施例2.1中的方法)。使用这些筛选方法从六个亲和成熟文库中鉴定出61个独特的抗LAG-3 Fcab。来自FS18-7系的亲和成熟的Fcab显示了具有与食蟹猴LAG-3的最高水平的交叉反应性。选择具有与食蟹猴LAG-3 Fc的最强结合以及T细胞活性试验中活性最高的Fcab的来自该谱系的三个Fcab(称为FS18-7-7、FS18-7-9和FS18-7-11)进一步地亲和力和成熟。这三个Fcab还显示为阻断LAG-3 Fc与表达II类MHC的细胞的相互作用。

[0195] 第二次亲和成熟

[0196] 来自第一次亲和成熟的三个Fcab(FS18-7-7、FS18-7-9和FS18-7-11)的库(pool)用于创建进一步地亲和成熟文库。CD环很难使用来自ELLA Biotech的随机化引物随机化。CD环中的部分氨基酸位置(残基45.1-78)使用除半胱氨酸之外的、氨基酸的等摩尔分布随机化。还在整个CH3结构域序列上进行易错PCR以引入可能增强结合的其他突变。

[0197] 在噬菌体中产生亲和成熟文库,并执行针对生物素化重组LAG-3 avi-Fc(BPS Bioscience,71147)和HEK hLAG-3的选择,以及通过噬菌体ELISA筛选以结合重组LAG-3 Fc(R&D systems,2319-L3-050)。86个独特的Fcab(含有截短的铰链)在HEK293F细胞中表达。还如上所述筛选选定的Fcab在T细胞活化试验中的活性。在第二次亲和成熟期间,在T细胞活化试验中鉴定的具有最高活性的九个Fcab(FS18-7-32;FS18-7-33;FS18-7-36;FS18-7-58;FS18-7-62;FS18-7-65;FS18-7-78;FS18-7-88和FS18-7-95)以及亲本Fcab克隆FS18-7-9然后进一步如下表征。这九个Fcab与亲本Fcab克隆FS18-7-9的序列比对在附图1A中显示。附图1B详述了九个Fcab克隆的每一个与亲本Fcab克隆FS18-7-9的序列同一性百分比。源自另两个亲本Fcab克隆FS18-7-7和FS18-7-11的亲和成熟的Fcab不是像来自FS18-7-9的亲和成熟的Fcab那么有前景的候选物,因此没有进一步继续。

[0198] 1.2特异于小鼠LAG-3的替代Fcab的选择

[0199] 使用上述的初始选择方案选出的Fcab FS18-7用于产生噬菌体文库以针对小鼠LAG-3进行选择。执行两轮亲和成熟,并且显示了高亲和力、特异性结合小鼠LAG-3的Fcab克隆FS18-7-108-29和FS18-7-108-35在亲和成熟后被选出。确认了FS18-7-108-29和FS18-7-108-35在T细胞活化试验中抑制小鼠LAG-3的能力。使用八位组(Octet)(Forteo Bio)的表位绘图显示抗小鼠LAG-3 Fcab与抗人LAG-3 Fcab(在如上述第二次亲和成熟后选出的)竞争结合人LAG-3。抗人LAG-3和抗小鼠LAG-3 Fcab之间存在4到8个残基的差异。因而预期的

是,抗小鼠LAG-3 Fcab代表了抗人LAG-3 Fcab在小鼠中的结合与功能的适合的替代物。

[0200] 1.3模拟mAb²的构建和表达

[0201] 制备包含上文1.1和1.2中鉴定的前导抗人LAG-3和抗小鼠LAG-3 Fcab的“模拟”mAb²,以容许mAb²形式中的这些Fcab的表征。从抗LAG-3 Fcab和抗异硫氰酸荧光素(FITC)抗体4420(详情参见SEQ ID NO:83、SEQ ID NO:84和SEQ ID NO:85)(Bedzyk,W.D.,et al.1989 and Bedzyk,W.D.,et al.1990)制备这些模拟mAb²。在重链的CH2结构域中具有(SEQ ID NO:63、65、67、69、71、73、75、77、79和81)和不具有(SEQ ID NO:64、66、68、70、72、74、76、78、80和82)LALA突变下制备模拟mAb²(详见下文章节1.5),并且该模拟mAb²还包括抗FITC mAb 4420(SEQ ID NO:85)的轻链。通过HEK293-6E细胞中的瞬时表达产生模拟mAb²,使用mAb Select SuRe蛋白A柱纯化。

[0202] 1.4 Fcab对LAG-3的结合亲和力

[0203] 1.4.1通过表面等离子共振(SPR)测定的Fcab对人LAG-3的亲和力

[0204] 使用BIAcore T200(GE Healthcare)测量模拟mAb²形式中的抗人LAG-3 Fcab对人LAG-3的亲和力。CM5传感器芯片(GE Healthcare,BR1005-30)的流动池4上以人LAG-3-Fc(R&D Systems,2319-L3-050)固定,并且使用胺偶联试剂盒(GE Healthcare,BR-1000-50)将流动池3用缓冲液固定用于参考。LAG-3-Fc在pH为5的乙酸钠(ForteoBio,18-1069)中稀释到5μg/ml,以10μl/分钟的流动速度注射12秒,随后通过注射乙醇胺420秒将表面钝化。固定水平是158 RU。模拟mAb²(或对照抗人LAG-3 mAb,25F7)在HBS-P缓冲液(GE Healthcare,BR-1003-68)中以自4μg/ml起的2倍稀释度系列进行稀释。对照mAb/模拟mAb²以30μl/分钟以240秒的缔合时间、30μl/分钟的300秒解离时间注射。使用25mM NaOH对表面以100μl/分钟再生30秒。数据减去双重参考并使用BIAevaluation 3.2软件分析以计算动力学常数。模拟mAb²形式中的Fcab具有0.8-1.1nM范围内的人LAG-3的亲和力(表1),其类似于基准抗人LAG-3 mAb 25F7的亲和力。这是令人惊讶的,因为Fcab具有比单克隆抗体更小的结合界面,由于Fcab的结合位点形成相对紧致的抗体片段,其中两个结合位点紧密接近。相比之下,典型的mAb的Fab臂被柔性的铰链区分隔。基于这种更小的结合界面和Fc区中两个结合位点的相关降低的柔性,出乎意料的是,抗LAG-3 Fcab能够以与基准抗体25F7类似的亲和力和效价结合并抑制LAG-3。

[0205] 表1:模拟mAb²形式的LAG-3特异性Fcab对人LAG-3的结合亲和力

[0206]	模拟 mAb ² 形式的抗人 LAG-3 Fcab 和 基准抗人 LAG-3 mAb, 25F7	K _D (M)
	FS18-7-9	8.3×10^{-10}
	FS18-7-62	9.5×10^{-10}
	FS18-7-78	8.4×10^{-10}
	FS18-7-32	8.6×10^{-10}
	FS18-7-36	8.9×10^{-10}
	FS18-7-65	1.1×10^{-9}
	25F7	3.2×10^{-10}

[0207] 1.4.2 SPR测定的特异于小鼠LAG-3的替代Fcab对小鼠LAG-3的结合亲和力

[0208] 使用Biacore 3000 (GE Healthcare) 测量特异于小鼠LAG-3的替代Fcab对小鼠LAG-3的亲合力。使用胺偶联(胺偶联试剂盒,GE Healthcare,BR-1000-50)将在10mM pH为5.0的乙酸钠(ForteBio,18-1069)中稀释的mLAG-3 Fc(R&D Systems,3328-L3-050)直接包被在CM5芯片(GE Healthcare,BR-1000-12)上。用小鼠Fc(SinoBiological,51094-MNAH)包被流动池1,以及mLAG-3 Fc以950RU包被流动池2。Fcab在HBS-P缓冲液(GE Healthcare,BR-1003-68)中稀释,并且以不同浓度(自100nM起的四倍稀释度)以20 μ l/分钟注射3分钟,然后容许该Fcab在缓冲液中解离12分钟。通过以30 μ l/分钟注射10mM pH为2.5的甘氨酸30秒来再生芯片。数据减去双重参考,使用BIAevaluation 3.2软件分析以计算动力学常数。以单位数纳摩尔亲合力结合小鼠LAG-3的被测替代Fcab在表2中示出。

[0209] 表2:替代LAG-3特异性Fcab对小鼠LAG-3的结合亲合力(K_D)

[0210]	特异于小鼠LAG-3的替代Fcab	亲合力 K_D (nM)
	FS18-7-108-29	1.5
	FS18-7-108-35	2.1

[0211] 1.4.3通过流式细胞术测定的Fcab对细胞上表达的人LAG-3的结合亲合力

[0212] 产生过量表达LAG-3的细胞系

[0213] 使用伦蒂-X慢病毒包装系统(Lenti-X HTX Packaging System)(Clontech,Cat.No 631249),使用慢病毒转导方法产生过量表达人、食蟹猴或小鼠LAG-3的D011.10细胞(National Jewish Health)。含有小鼠LAG-3 cDNA(SEQ ID NO:96)、人LAG-3 cDNA(SEQ ID NO:95)或食蟹猴LAG-3 cDNA(SEQ ID NO:97)的伦蒂-X表达载体(pLVX)(Clontech,Cat.No 631253)使用伦蒂-X慢病毒包装组合共转染到Lenti-X 293T细胞系(Clontech,Cat.No 632180)中来产生病毒。用伦蒂-X慢病毒包装系统产生的慢病毒载体转导D011.10细胞系。

[0214] 模拟mAb²形式中的抗人LAG-3 Fcab对表达人LAG-3的细胞(用人LAG-3转染的D011.10细胞系)的亲合力使用流式细胞术进行测量。mAb2和对照mAb稀释物(2 $\times$ 终浓度)在1 $\times$ 杜氏磷酸盐缓冲液(DPBS)(Gibco,14190-094)中一式三份制备。在PBS+2%牛血清蛋白(BSA)(Sigma,A7906)中制备D011.10:LAG-3细胞悬浮液,以4 $\times 10^6$ 个细胞/ml的50 μ l/孔接种到V形底96孔平板(Costar,3897)中。将50 μ l的mAb²或对照mAb(抗人LAG-3 mAb,25F7)稀释物添加到含有细胞的反应孔中(最终体积100 μ l),并在4 $^{\circ}$ C孵育1小时。洗涤平板,然后添加100 μ l/孔的在PBS+2%BSA中1:1000稀释的二抗(抗人Fc-488抗体,Jackson ImmunoResearch,109-546-098),并在暗处在4 $^{\circ}$ C下孵育30分钟。洗涤平板,并在含有1mg/ml的DAPI(Biotium,40043)的PBS中重悬浮。使用坎托II(Canto II)流式细胞计(BD Biosciences)读取平板。排除死细胞,测量FITC通道(488nm/530/30)中的荧光。在绘制医学图表(GraphPad Prism)软件中使用log(激动剂) vs response拟合数据。所有测试的模拟mAb²形式的Fcab和基准抗人LAG-3 mAb,25F7以类似的亲合力(EC_{50})结合人LAG-3,在1.2-2.1nM的范围内,如表3所示。

[0215] 表3:流式细胞术测定的、模拟mAb²形式的抗人LAG-3 Fcab对表达人LAG-3的D011.10细胞的结合亲合力

[0216]

模拟 mAb ² 形式的抗人 LAG-3 Fcab 和基准抗人 LAG-3 mAb, 25F7	EC ₅₀ (nM)
FS18-7-9	1.2
FS18-7-32	1.6
FS18-7-33	1.5
FS18-7-36	1.5
FS18-7-62	2.1
FS18-7-65	1.6
FS18-7-78	1.7
25F7	2.1

[0217] 1.4.4通过流式细胞术测定的Fcab对细胞上表达的食蟹猴LAG-3的结合亲和力

[0218] 使用流式细胞术测量模拟mAb²形式的抗人LAG-3 Fcab对表达食蟹猴LAG-3的细胞(用食蟹猴LAG-3转染的D011.10细胞系)的亲和力。mAb²和对照mAb稀释物(2×终浓度)在1×DPBS(Gibco,14190-094)中一式三份制备。在PBS+2%BSA(Sigma,A7906)中制备D011.10:LAG-3细胞悬浮液,以4×10⁶个细胞/ml的50μl/孔接种到V形底96孔平板(Costar,3897)中。50μl的mAb²或对照mAb(抗人LAG-3 mAb,25F7)稀释物添加到含有细胞的反应孔中(最终体积100μl),在4℃孵育1小时。洗涤平板,然后添加100μl/孔的在PBS+2%BSA中1:1000稀释的二抗(抗人Fc-488抗体,Jackson ImmunoResearch,109-546-098),在暗处在4℃下孵育30分钟。洗涤平板,并在含有1mg/ml的DAPI(Biotium,40043)的PBS中重悬浮。使用Canto II流式细胞计(BD Biosciences)读取平板。排除死细胞,并测量FITC通道(488nm/530/30)中的荧光。在GraphPad Prism软件中使用log(激动剂)vs response拟合数据。模拟mAb²形式的测试的Fcab以0.5-0.6nM的亲和力结合食蟹猴LAG-3表明,在食蟹猴中的毒物学研究预计对人类中所见的效果是预示性的(参见表4)。基准抗人LAG-3 mAb,25F7,以15倍的更弱的亲和力(EC₅₀)结合食蟹猴LAG-3(表4)。

[0219] 表4:通过流式细胞术,抗LAG-3 Fcab对表达食蟹猴LAG-3的D011.10细胞的结合亲和力

[0220]

模拟 mAb ² 形式的抗人 LAG-3 Fcab 和基准抗人 LAG-3 mAb, 25F7	EC ₅₀ (nM)
FS18-7-9	0.6
FS18-7-62	0.5
FS18-7-78	0.5
25F7	9.0

[0221] 1.4.5通过流式细胞术测定的,替代抗小鼠LAG-3 Fcab和抗人LAG-3 Fcab对细胞上表达的小鼠LAG-3的结合亲和力

[0222] 产生过量表达mLAG-3的HEK细胞

[0223] 使用核酸内切酶(KpnI)(纽英伦[NEB],R0142)和NotI(NEB,R0146)限制性酶切,将小鼠LAG-3序列(SEQ ID NO:96)亚克隆到pcDNA5FRT载体(Life Technologies,V6010-20)中。然后使用脂质体(Lipofectamine)2000(Life Technologies,11668-019)将载体转化到

四环素诱导性启动子(Flp-In T-REx) 293HEK细胞系(Life Technologies,R780-07)中。转化的Flp-In T-REx 293细胞在含有10%FBS((Life Technologies,10270-1-6)、100μg/mL潮霉素B(Melford Laboratories Ltd,Z2475)、15μg/ml杀稻瘟菌素(Melford Laboratories Ltd,B1105)的DMEM(Life Technologies,61965-026)中生长3-4周,直到显现稳定转化的细胞的集落。这些集落在存在1μg/ml的细胞脱氧土霉素(Sigma,D9891)的情况下扩增,使用PE结合的抗小鼠LAG-3(克隆C9B7W,BD Biosciences,552380)测试小鼠LAG-3表达。

[0224] 使用流式细胞术测量替代抗小鼠LAG-3 Fcab(含有截短的铰链;SEQ ID NO:58)对细胞表达的小鼠LAG-3的亲和力。在含有10%FBS(Life Technologies,10270-1-6)、100μg/ml潮霉素B(Melford Laboratories Ltd,Z2475)、15μg/ml杀稻瘟菌素(Melford Laboratories Ltd,B1105)和1μg/ml脱氧土霉素(Sigma,D9891)的DMEM中生长的、表达mLAG-3的HEK细胞使用细胞解离缓冲液(Life Technologies,13151-014)从组织培养烧瓶上剥离,以 2×10^5 个细胞/孔接种在V形底96孔平板(Costar,3897)中。平板在4℃下在1500rpm离心3分钟来沉淀细胞。Fcab(或对照mAb)的稀释系列与细胞在100μl体积中在4℃下孵育1小时。洗涤平板,且二抗(用于Fcab的抗人Fc-488,Jackson ImmunoResearch,109-546-098,或用于C9B7W的抗大鼠IgG(H+L)、荧光基团488(Alexa Fluor 488)结合物,ThermoFisher,A-11006)在PBS中1:1000稀释,并将100μl在4℃下向细胞中添加30分钟(平板保持在暗处)。随后洗涤平板,且细胞重悬浮在含有1μg/ml DAPI(Biotium,40043)的100μl PBS中。使用Canto II流式细胞计(BD Biosciences)读取平板。排除死细胞,测量FITC通道(488nm/530/30)中的荧光。在GraphPad Prism软件中使用log((激动剂)vs response拟合数据。所测试的Fcab以相似的亲和力结合小鼠LAG-3(参见表5)。基准LAG-3 mAb C9B7W(2B Scientific,BE0174-50MG)以比Fcab弱17倍的亲和力(EC_{50})结合小鼠LAG-3(表5)。

[0225] 表5:通过流式细胞术的、替代抗小鼠LAG-3 Fcab对表达小鼠LAG-3的HEK细胞的结合亲和力

[0226]	抗小鼠 LAG-3 Fcab 和基准抗小鼠 LAG-3 mAb, C9B7W	EC_{50} (nM)
	FS18-7-108-29	4.5
	FS18-7-108-35	4.5
	C9B7W	79

[0227] 使用流式细胞术测量模拟mAb²形式的抗人LAG-3 Fcab FS18-7-9对细胞表达的小鼠LAG-3的亲和力。在含有10%FBS(Life Technologies,10270-1-6)、100μg/ml潮霉素B(Melford Laboratories Ltd,Z2475)、15μg/ml杀稻瘟菌素(Melford Laboratories Ltd,B1105)和1μg/ml脱氧土霉素(Sigma,D9891)的DMEM中生长的、表达mLAG-3的HEK细胞使用细胞解离缓冲液(Life Technologies,13151-014)从组织培养烧瓶上剥离。通过在4℃下1500rpm离心3分钟沉淀细胞来采集细胞,重悬浮在1×DPBS中,然后以 1.2×10^5 个细胞/孔的30μl接种到V形底96孔平板(Costar,3897)中。添加1:1体积的mAb²(或对照mAb)稀释物系列,与细胞在4℃下孵育1小时。洗涤平板,二抗(抗人Fc-488,Jackson ImmunoResearch,109-546-098)在PBS中1:1000稀释,并将60μl在4℃下向细胞中添加30分钟(平板保持在暗

处)。随后洗涤平板,细胞重悬浮在含有1 μ g/ml DAPI (Biotium,40043)的60 μ l PBS中。使用Canto II流式细胞计(BD Biosciences)读取平板。排除死细胞,测量FITC通道(488nm/530/30)中的荧光。在GraphPad Prism软件中使用log(激动剂)vs response拟合数据。与替代抗小鼠LAG-3 Fcab FS18-7-9-108的2.6nM的EC₅₀相比,模拟mAb²形式的抗人LAG-3 Fcab FS18-7-9以19nM的EC₅₀结合小鼠LAG-3(表6)。人mAb,25F7不显示任何可检测的对小鼠LAG-3的结合,表明了人LAG-3 Fcab、FS18-7-9具有与25F7不同的LAG-3上的结合表位。

[0228] 表6:通过流式细胞术的、人抗LAG-3 Fcab FS18-7-9对表达小鼠LAG-3的HEK细胞的结合亲和力和

[0229]	抗人 LAG-3 Fcab、抗小鼠 LAG-3 Fcab 和基准抗人 LAG-3 mAb, 25F7	EC ₅₀ (nM)
	FS18-7-108-29	2.6
	FS18-7-9	19
	25F7	不结合

[0230] 1.5 Fcab对Fc受体的结合亲和力

[0231] 已知在人IgG1的CH2结构域中的LALA突变的导入减少Fc低受体结合(Bruhns,P., et al.(2009)and Xu,D.et al.(2000))。使用BIAcore确认LALA突变降低了Fcab(模拟mAb²形式)对Fc γ 受体的结合亲和力。使用模拟mAb²形式的Fcab在Biacore T200仪(GE Healthcare)上执行人Fc γ R结合试验。(R&D Systems,1257-FC,1330-CD,1875-CD,4325-FC)使用胺偶联(胺偶联试剂盒,GE Healthcare,BR-1000-50)将人Fc γ Rs固定在S系列CM5芯片(GE Healthcare,BR-1005-30)上至表面密度为Fc为RI 370 RU,Fc γ RIII(高亲和力人Fc γ R)264RU,Fc4 RU和Fc4 RU(低亲和力人Fc亲和)500 RU。对于每个固定的芯片,流动池保持空白用于背景扣除。使用浓度为5 μ g/ml的pH为5的乙酸钠(ForteBio,18-1069)固定Fc度0度1,并且在15秒周期中以10 μ l/分钟的流动速度注射,直到达到需要的固定水平。

[0232] 对于高亲和力Fc γ RI和Fc γ RIII,200 μ g/mL的mAbs或模拟mAb²以30 μ l/分钟的流动速度流经芯片3分钟,随后解离5分钟。运行缓冲液是HBS-P(0.01M HEPES pH 7.4,0.15M NaCl,0.005%v/v表面活性剂P20,GE Healthcare,BR-1003-68)。对于低亲和力的Fc γ RIIa和Fc γ RIIb,模拟mAb²的浓度提高到500 μ g/ml。

[0233] 阳性对照是野生型IgG1同种型mAb,其与对照LALA IgG1 mAb和对不相关靶点的单克隆IgG2和IgG4同种型mAbs比较。通过以100 μ l/分钟的流动速度注射10mM氢氧化钠(VWR,28244.262)30分钟来再生流动池。通过双重参考空白流动池(没有固定的Fc γ R)并减去来自测试mAb²的缓冲循环,使用BiaEvaluation软件版本3.2 RC1进行数据分析。结果在表7中显示。

[0234] 表7:通过SPR的、模拟mAb²形式的抗人LAG-3 Fcab(如上文详述的包含LALA突变)与人Fc γ 受体的结合反应(binding response)

mAb/模拟 mAb ²	缔合末尾(end of association)的结合反应 (RU)			
	FcγRI	FcγRIII	FcγRIIa	FcγRIIb
FS18-7-9	1.4	6.6	-9.8	-8.5
FS18-7-62	-0.9	0.7	-10	-8.5
[0235] FS18-7-78	-0.3	4.0	-10.7	-9.2
模拟 mAb LALA	2	8.0	-12.7	-9.6
IgG2	0	1.9	9.7	7.4
IgG4	9	3.1	4.3	15.1
模拟 mAb IgG1	26	44	13	17.7

[0236] 与没有LALA突变的对照抗体(模拟mAb IgG)相比,测试的所有模拟mAb²(都包含上文阐述的LALA突变)显示了对测试的Fcγ受体显著降低的结合,表明LALA突变降低了这些模拟mAb²的Fcγ受体结合,因而预计降低mAb²的ADCC活性。

[0237] 1.6阻断II类MHC与LAG-3的结合

[0238] 通过测量LAG-3 Fc与表达人II类MHC的黑素瘤细胞系的A375细胞的结合研究了Fcab(含有截短的铰链;SEQ ID NO:58)阻断重组人或小鼠LAG-3 Fc与人II类MHC之间的相互作用的能力。使用细胞解离缓冲液(Life Technologies,13151-014)将在含有10%FBS(Life Technologies,10270-106)的DMEM(Life Technologies,61965-026)中生长的A375(ATCC,CRL-1619)细胞从细胞培养烧瓶上剥离,并以 2×10^5 个细胞/孔接种到V形底96孔平板(Costar,3897)中。平板在4℃下在1500rpm离心3分钟来沉淀细胞。相关浓度的Fcab或对照mAb在含有10%FBS的100μl DMEM中与1μg/ml的LAG-3 Fc(人LAG-3-Fc R&D Systems,2319-L3-050或小鼠LAG-3 Fc R&D Systems,3328-L3-050)在4℃下孵育1小时。LAG-3/Fcab混合物添加到A375细胞,并在4℃下孵育1小时。洗涤细胞。二抗(Alexa Fluor 488结合的山羊抗人Fc F(ab')₂,Jackson ImmunoResearch,109-546-098或山羊抗小鼠IgG(H+L)488结合物,Life Technologies,A-1101)以1:1000在PBS稀释,并将100μl在4℃下向细胞中添加30分钟(平板保持在暗处)。在PBS中洗涤细胞一次,重悬浮在100μl PBS+1μl/ml DAPI(Biotium,40043)中。平板在BD FACSCanto II细胞计(BD Biosciences)上读取,使用FlowJo软件分析数据。

[0239] 两种抗小鼠LAG-3 Fcab都能抑制人II类MHC与小鼠LAG-3的相互作用,而对照抗小鼠LAG-3 mAb(C9B7W,2B Scientific,BE0174-50MG)则不能(参见表8)。

[0240] 表8:替代抗小鼠LAG-3 Fcab抑制小鼠LAG-3与II类MHC的结合

替代抗小鼠 LAG-3 Fcab 和对照抗小鼠 LAG-3 mAb C9B7W	IC ₅₀ (nM)
[0241] FS18-7-108-29	0.6
FS18-7-108-35	0.7
C9B7W	不阻断

[0242] 测试的抗人LAG-3 Fcab也能以与对照抗人LAG-3 mAb(25F7)相似的效价抑制人II类MHC与人LAG-3的相互作用。

[0243] 表9:抗人LAG-3 Fcab抑制人LAG-3与II类MHC的结合

[0244]	抗人 LAG-3 Fcab 和对照抗人 LAG-3 mAb	IC ₅₀ (nM)
	25F7	
	FS18-7-108-33	2.6
	FS18-7-108-78	2.4
	25F7	3.6

[0245] 实施例2:mAb和mAb²分子的制备和表征

[0246] 2.1 mAb 84G09的制备

[0247] 2.1.1 DNA构建体产生

[0248] 编码84G09的可变重链和轻链区的DNA插入物为用于哺乳动物表达的优化的密码子,并且由DNA2.0(Menlo Park,CA,USA)合成。pJ-Amp-high宿主载体中提供的该插入物通过EcoRI和NheI限制消化亚克隆至表达载体pFS-hHC2.1-G1m17(z)LALA(含有LALA突变的IgG重链)或pFS-hHC2.1-G1m17(z)(没有LALA突变的IgG重链)以及pFShK1.0(IgG kappa轻链)中。

[0249] 通过菌落PCR和随后由第三方(GATC Biotech)进行的核苷酸测序分析验证克隆的保真度。

[0250] 2.1.2细胞维持

[0251] HEK293-6E细胞(NRCC)在补充有4mM的GlutaMAX-1(Invitrogen,35050-038)、0.1%的Pluronic F-68(Invitrogen A13835-01)和25μg/ml的遗传霉素(geneticin)(Invitrogen,10131-027)的预温热F17培养基(Invitrogen,A13835-01)中传代培养。细胞在37℃、140rpm、5%CO₂下孵育,并在三个然后四天的方案中以0.3×10⁶个细胞/ml进行传代培养。

[0252] 2.1.3瞬时转染

[0253] HEK293-6E细胞使用1mg/ml的PEIpro(Polyplus,PPLU115)瞬时转染。转染之前24小时,细胞以0.8×10⁶个细胞/mL播种到培养基中。对于每200ml细胞培养物,通过混合10ml温热的Opti-MEMI(Invitrogen,11058-021)、100μg编码重链的无内毒素DNA以及100μg编码轻链的无内毒素DNA来制备DNA混合物。通过混合10ml温热的Opti-MEMI和200μl PEIpro并旋涡来制备PEI混合物。DNA混合物快速添加到涡旋的PEI混合物中,通过持续1秒脉冲3次的涡旋混合,在室温下孵育3分钟,一滴一滴地添加到细胞中。转染后48小时,向每个烧瓶中添加20ml具有0.5%Tryptone N1(TekniScience Inc.,19553)的F17加增补剂。

[0254] 转染后6天,通过4500rpm离心40分钟收获细胞。然后用0.22μm聚醚砜过滤装置(Millipore,SCGPU01RE,SCGPU02RE,SCGPU05RE,SCGPU11RE)过滤上清液,并储存在+4℃等待纯化。

[0255] 2.1.4蛋白A层析

[0256] 在AKTAexplorer或AKTExpress上使用预先包装的5ml HiTrap MabSelect SuRe柱(GE Healthcare,11-0034-95)纯化澄清的上清液。简单地,用pH7.0的50mM Tris-HCl、250mM NaCl平衡柱子,用5ml/min相同的缓冲液洗涤未结合的物质。用10mM pH 3.0的甲酸钠5ml/min洗脱产物。根据厂商的建议,使用用pH7.4 PBS预平衡的PD-10柱(GE Healthcare,17-0851-01)立即将洗脱的样品缓冲液交换到PBS pH 7.4中。

[0257] 2.1.5通过光谱测定法测量产物浓度

[0258] 使用具有DropPlate 96 D+ (PerkinElmer, CLS135136) 的LabChip DS (PerkinElmer, 133089) 测量每种纯化产物在280nm处的吸光度。使用VectorNTI Advance v11.5.4软件(Thermofisher Scientific, A13784) 计算的消光系数(A280为1mg/ml) 计算产物浓度。

[0259] 2.1.6产物浓缩

[0260] 必要时, 使用Amicon Ultra-4离心过滤器单元30K (Millipore, UFC803024) 浓缩纯化的级分。通过在3000rpm下离心10分钟使Ultracel再生纤维素膜与PBS pH 7.4平衡后, 将样品加载至4ml单元并以3000rpm离心直至达到所需的蛋白质浓度。

[0261] 2.1.6滤器消毒

[0262] 使用预湿的Millex-GV PVDF注射过滤器(Millipore, SLGV013SL) 过滤最终样品。

[0263] 2.2人LAG-3/PD-L1 mAb²的制备

[0264] 在人IgG1的未修饰CH3结构域的序列中存在的XhoIBamHI位点内, 通过人LAG-3特异性Fab FS18-7-9、FS18-7-32、FS18-7-33、FS18-7-36、FS18-7-58、FS18-7-62、FS18-7-65、FS18-7-78、FS18-7-88和S18-7-95的CH3结构域替换单克隆抗体84G09的CH3结构域(有和没有LALA突变), 制备mAb²分子FS18-7-9/84G09 (SEQ ID NOs: 94和95)、FS18-7-32/84G09 (SEQ ID NOs: 96和97)、FS18-7-33/84G09 (SEQ ID NOs: 98和99)、FS18-7-36/84G09 (SEQ ID NOs: 100和101)、FS18-7-58/84G09 (SEQ ID NOs: 102和103)、FS18-7-62/84G09 (SEQ ID NOs: 104和105)、FS18-7-65/84G09 (SEQ ID NOs: 106和107)、FS18-7-78/84G09 (SEQ ID NOs: 108和109)、FS18-7-88/84G09 (SEQ ID NOs: 110和111) 以及FS18-7-95/84g09 (SEQ ID NOs: 112和113) 的重链。如上文的章节2.1中对mAb 84G09描述的, mAb²的重链与与84G09的轻链 (SEQ ID NO: 116) 共转染。然后如上文的章节2.1对mAb 84G09描述的, 表达和纯化mAb²。

[0265] 2.3人LAG-3/模拟mAb²的制备

[0266] 使用mAb 4420的重链 (SEQ ID NOs: 83和84; 有和没有LALA突变) 以及轻链 (SEQ ID NO: 85), 如上文章节2.1对mAb 84G09描述的, 制备抗FITC mAb (有和没有LALA突变)。

[0267] 在人IgG1的未修饰CH3结构域的序列中存在的XhoIBamHI位点内, 通过人LAG-3特异性Fab FS18-7-9、FS18-7-32、FS18-7-33、FS18-7-36、FS18-7-58、FS18-7-62、FS18-7-65、FS18-7-78、FS18-7-88和S18-7-95的CH3结构域替换单克隆抗体4420的CH3结构域(有和没有LALA突变), 制备mAb²分子FS18-7-9/4420 (SEQ ID NOs: 63和64)、FS18-7-32/4420 (SEQ ID NOs: 65和66)、FS18-7-33/4420 (SEQ ID NOs: 67和68)、FS18-7-36/4420 (SEQ ID NOs: 69和70)、FS18-7-58/4420 (SEQ ID NOs: 71和72)、FS18-7-62/4420 (SEQ ID NOs: 73和74)、FS18-7-65/4420 (SEQ ID NOs: 75和76)、FS18-7-78/4420 (SEQ ID NOs: 77和78)、FS18-7-88/4420 (SEQ ID NOs: 79和80) 以及FS18-7-95/4420 (SEQ ID NOs: 81和82)。如上文的章节2.1中对mAb 84G09描述的, mAb²的重链与4420的轻链共转染。然后如上文的章节2.1对mAb 84G09描述的, 表达和纯化蛋白。

[0268] 2.4小鼠LAG-3/PD-L1 mAb²的制备

[0269] 如上文章节2.1对mAb 84G09描述的, 使用mAb S1的重链 (SEQ ID NOs: 122和123) 以及轻链 (SEQ ID NO: 119), 制备小鼠抗PD-L1 mAb (有和没有LALA突变)。

[0270] 通过在人IgG1的未修饰CH3结构域的序列中存在的XhoI和BamHI位点内, 用小鼠

LAG-3特异性Fcabs FS18-7-108-29和FS18-7-108-35的CH3结构域替换单克隆抗体S1的CH3结构域(有和没有LALA突变),制备mAb²分子FS18-7-108-29/S1(SEQ ID NOs:117和118)和FS18-7-108-35/S1(SEQ ID NOs:120和121)的重链。如上文的章节2.1中对mAb 84G09描述的,mAb²的重链与S1的轻链共转染。然后如上文的章节2.1对mAb 84G09描述的,表达和纯化蛋白。

[0271] 2.5 mAb²对人LAG-3和人PD-L1的结合亲和性和动力学

[0272] 根据厂家对BIAcore T200仪的说明,通过胺偶联(GE Healthcare,BR-1000-50)将蛋白L(Thermo,21189)固定在Series S CM5芯片(GE Healthcare,BR-1005-30)的流动池1和2上,表面密度为2000 RU。对于LAG-3结合,mAb²样品(均含有LALA突变)仅在流动池2上捕获,以从0.5nM开始以2倍稀释系列的4个浓度的人LAG-3 Fc(R&D Systems,2319-L3)以30μl/分钟的流动速度流经流动池1和2。缔合时间为3分钟,解离时间为6分钟。运行缓冲液是HBS-P(GE Healthcare,BR-1003-68)。通过以100μl/分钟的流速注入10mM氢氧化钠(NaOH)20秒来再生两个流动池。通过对空白流动池的双重参考来分析数据。

[0273] 对于PD-L1结合,从40nM开始的PD-L1 Fc(R&D Systems,156-B7)两倍稀释度系列的四个浓度流经同一蛋白L芯片上捕获的mAb²。所有其他条件与LAG-3结合的相同(参见上文)。

[0274] 结合动力学与1:1 Langmuir模型拟合以产生结合缔合(k_a)和解离(k_d)速率。通过将每个样品的解离速率除以缔合速率来计算平衡结合常数(K_D)。数据分析使用BiaEvaluation软件版本3.2进行。结果在表10和11中示出。

[0275] 表10:通过SPR测定的,mAb²对人LAG-3的结合亲和力和动力学

[0276]

mAb ²	K_D (pM)	k_a (1/Ms) x10 ⁶	k_d (1/s) x10 ⁻⁴
84G09LALA	不结合	-	-
FS18-7-09/84G09LALA	56	6.3	3.5
FS18-7-32/84G09LALA	49	5.6	2.8
FS18-7-33/84G09LALA	43	4.2	1.8
FS18-7-36/84G09LALA	38	4.4	1.7
FS18-7-62/84G09LALA	36	5.4	2.0
FS18-7-65/84G09LALA	39	5.9	2.3
FS18-7-78/84G09LALA	29	4.8	1.4

[0277] 表11:通过SPR测定的,mAb²对人PD-L1的结合亲和力和动力学

[0278]

mAb ²	K_D (nM)	k_a (1/Ms) x10 ⁵	k_d (1/s) x10 ⁻⁴
84G09LALA	1.2	3.8	4.6
FS18-7-09/84G09LALA	1.0	3.8	3.9
FS18-7-32/84G09LALA	1.0	3.4	3.2
FS18-7-33/84G09LALA	1.1	3.7	4.2
FS18-7-36/84G09LALA	3.5	1.6	5.6
FS18-7-62/84G09LALA	1.3	1.7	2.2
FS18-7-65/84G09LALA	1.1	1.3	1.4
FS18-7-78/84G09LALA	1.0	1.0	1.0

[0279] 对于所有测试的mAb², 对人PD-L1和人LAG-3的结合亲和力是相当的。人PD-L1的mAb²结合亲和力与84G09相当, 表明将LAG-3结合位点引入CH3结构域不影响PD-L1结合。

[0280] 2.6 mAb²与人类LAG-3和人PD-L1的同时结合

[0281] 通过SPR测试mAb² (FS18-7-09/84G09、FS18-7-32/84G09、FS18-7-33/84G09、FS18-7-36/84G09、FS18-7-62/84G09、FS18-7-65/84G09和FS18-7-78/84G09, 全部具有LALA突变) 同时结合LAG-3和PD-L1的能力。按照厂家的说明, 将人PD-L1Fc (R&D Systems, 156-B7) 以150 RU的表面密度固定在Series S CM5芯片 (GE Healthcare, BR-1005-30) 的流动池2上。流动池1进行活化和钝化, 不固定任何蛋白质用于背景扣除。对每种样品, 10μg/ml的mAb²以10μl/分钟的流速流经流动池1和2持续3分钟。随后, 40nM的LAG-3Fc (R&D Systems, 2319-L3) 以10μl/分钟的流速流经流动池1和2持续3分钟。对于每个结合步骤, 跟踪解离3分钟。在每个循环之后用100μl/分钟流速的25mM NaOH 15秒注射将传感器芯片再生。

[0282] 所有测试的mAb²都能够同时地结合LAG-3和PD-L1。亲本抗PD-L1 mAb 84G09仅结合PD-L1。

[0283] 2.7. 替代mAb²对鼠类LAG-3和鼠类PD-L1的同时结合

[0284] 在BIAcore 3000 (GE Healthcare) 上通过SPR测试两种替代小鼠mAb² (FS18-7-108-29/S1和FS18-7-108-35/S1, 都含有LALA突变) 同时结合鼠类LAG-3和鼠类PD-L1的能力。按照厂家的说明, 将鼠类PD-L1Fc (R&D Systems, 1019-B7-100) 以830 RU的表面密度固定在CM5芯片的流动池4上。流动池3上固定820 RU的人-Fc (R&D system, 110-HG) 用于背景扣除。对每种样品, 50nM的mAb²以20μl/分钟的流速流经流动池1和2持续150秒。随后, 50nM的鼠类LAG-3Fc (R&D Systems, 3328-L3-050) 以20μl/分钟的流速流经流动池3和4持续150秒。对于每个结合步骤, 跟踪解离3分钟。在每个循环后用2×10μl的50mM NaOH再生传感器芯片。测试的两种mAb²都能够同时结合鼠类LAG-3和鼠类PD-L1, 因而是人类LAG-3/PD-L1 mAb²的适合的替代物。

[0285] 2.8包括LALA突变的mAb²结合人Fc γ 受体

[0286] 根据厂家对BIAcore3000仪的说明, 将人Fc γ 受体固定在CM5芯片上, Fc γ RI (R&D Systems, 1257-FC) 和Fc γ RIIa (R&D Systems, 4325-FC) 的表面密度大约200 RU, Fc γ RIIa (R&D Systems, 1330-CD) 和Fc γ RIIb/c (R&D Systems, 1875-CD) 大约500 RU。对于Fc γ RI和Fc γ RIIa, 100μg/ml的mAb或mAb²以10μl/分钟的流速流经芯片持续3分钟, 跟踪解离5分钟。运行缓冲液是PBS (Lonza, BE17-516F) +0.05% (v/v) P20表面活性剂 (GE Healthcare, BR-1000-54)。阳性对照是野生型IgG1 4420-mAb。针对不相关的靶点的单克隆的IgG2和IgG4 mAb (20H4和MOR7490) 和小鼠IgG1 (Sigma, P5305) 被列入作为参考点。由于结合复合物的快速的离解速率, 不需要再生。对于Fc γ RIIa和Fc γ RIIb/c测试, mAb²的浓度提高到500μg/ml以补偿对这两种受体的较弱的结合。结果在表12中示出。

[0287] 表12: 通过SPR测定的, 抗LAG-3/PD-L1 mAb²对人Fc γ 受体的结合反应

mAb/mAb ²	缔合末尾时的结合反应 (RU)			
	FcγRI	FcγRIII	FcγRIIa	FcγRIIb/c
FS18-7-9/84G09LALA	<1	<5	<1	<2
FS18-7-33/84G09LALA	<1	<5	<1	<2
FS18-7-62/84G09LALA	<1	<5	<1	<2
[0288] FS18-7-78/84G09LALA	<1	<5	<1	<2
84G09 mAb LALA	<1	<5	<1	<2
IgG2	<1	<5	9	<2
IgG4	8	<5	8	9
4420 mAb IgG1	30	28	29	18
小鼠 IgG1	<1	<5	7	<2

[0289] 如所预期的,导入mAb或mAb²的LALA变体降低了这些分子结合人Fc γ 受体的能力。

[0290] 2.9 mAb²与表达人类和食蟹猴LAG-3的细胞的结合

[0291] 使用KpnI (NEB,R0142) 和NotI (NEB,R0146) 限制性酶切,将人类LAG-3序列 (SEQ ID NO:126) 或食蟹猴LAG-3序列 (SEQ ID NO:128) 亚克隆到pcDNA5FRT载体 (Life Technologies,V6010-20) 中。然后使用脂质体 (Lipofectamine) 2000 (Life Technologies, 11668-019) 将载体转化到Flp-In T-REx293 HEK细胞系 (Life Technologies,R780-07) 中。转化的Flp-In T-REx293细胞在含有10%FBS (Life Technologies,,10270-1-6)、100μg/mL 潮霉素B (Melford Laboratories Ltd,Z2475)、15μg/ml 杀稻瘟菌素 (Melford Laboratories Ltd,B1105) 的DMEM (Life Technologies,61965-026) 中生长3-4周,直到显现稳定转化的细胞的集落。这些集落在存在1μg/ml 脱氧土霉素 (Sigma,D9891) 的情况下扩增,通过流式细胞术确认LAG-3表达的测试。

[0292] 使用流式细胞术测定mAb² (都含有LALA突变) 对细胞表达的人类或食蟹猴LAG-3的亲性和性。在含有10%FBS (Life Technologies,10270-1-6)、100μg/ml 潮霉素B (Melford Laboratories Ltd,Z2475)、15μg/ml 杀稻瘟菌素 (Melford Laboratories Ltd,B1105) 和1μg/ml 脱氧土霉素 (Sigma,D9891) 的DMEM中生长的、表达人类或食蟹猴LAG-3的HEK细胞使用细胞解离缓冲液 (Life Technologies,13151-014) 从组织培养烧瓶上剥离,以2×10⁵个细胞/孔接种在V形底96孔平板 (Costar,3897) 中。平板在4℃下在1500rpm离心3分钟来沉淀细胞。mAb² (或对照mAb) 的稀释系列与细胞在100μl 体积中在4℃下孵育1小时。洗涤平板,二抗 (抗人Fc-488,Jackson ImmunoResearch,109-546-098) 在PBS中1:1000稀释,并将100μl 在4℃下向细胞中添加30分钟 (平板保持在暗处)。洗涤平板,并且细胞在含有1μg/mL 苯基吲哚 (DAPI) (Biotium,40043) 的100μl PBS中重悬浮。使用Canto II流式细胞计 (BD Biosciences) 读取平板。排除死细胞,测量FITC通道 (488nm/530/30) 中的荧光。在GraphPad Prism软件中使用log (激动剂) vs response拟合数据。平板在BD FACSCanto II细胞计 (BD Biosciences) 上读取,使用FlowJo分析数据。结果在表13中示出。

[0293] 表13:流式细胞术测定的、抗LAG-3/PD-L1 mAb²对表达人类或食蟹猴LAG-3的HEK细胞的结合亲和力

	人类 LAG-3		食蟹猴 LAG-3	
	EC ₅₀ (nM)	95%置信区间	EC ₅₀ (nM)	95%置信区间
[0294] FS18-7-09/84G09LALA	3.179	2.311 至 4.372	29.9	22.16 至 40.35
FS18-7-62/84G09LALA	4.079	2.736 至 6.083	26.37	15.80 至 44.02
FS18-7-78/84G09LALA	2.526	1.474 至 4.329	24.75	19.31 至 31.73
25F7	4.192	2.791 至 6.297	156.5	107.3 至 228.2

[0295] 结果确认mAb²结合HEK细胞上表达的人类和食蟹猴LAG-3。关于计算的EC₅₀值,当与对照抗LAG-3抗体25F7比较时,测试的mAb²显示了与人LAG-3更好或相等的结合,并且与食蟹猴LAG-3至少好两倍的结合。没有观察到与HEK细胞系的表面上表达的其他蛋白质的交叉反应性。

[0296] 2.10 mAb²与表达人类和食蟹猴PD-L1的细胞的结合

[0297] 使用KpnI (NEB, R0142) 和NotI (NEB, R0146) 限制性酶切,将人类PD-L1序列 (SEQ ID NO:129) 或食蟹猴PD-L1序列 (SEQ ID NO:131) 亚克隆到pcDNA5FRT载体 (Life Technologies, V6010-20) 中。然后使用脂质体 (Lipofectamine) 2000 (Life Technologies, 11668-019) 将载体转化到四环素诱导性启动子 (Flp-In T-REx) 293HEK细胞系 (Life Technologies, R780-07) 中。转化的Flp-In T-REx 293细胞在含有10%FBS (Life Technologies, 10270-1-6)、100μg/mL潮霉素B (Melford Laboratories Ltd, Z2475)、15μg/mL杀稻瘟菌素 (Melford Laboratories Ltd, B1105) 的DMEM (Life Technologies, 61965-026) 中生长3-4周,直到显现稳定转化的细胞的集落。这些集落在存在1μg/mL脱氧土霉素 (Sigma, D9891) 的情况下扩增,LAG-3表达通过流式细胞术确认。

[0298] 使用流式细胞术测定mAb² (都含有LALA突变) 结合细胞表达的人类或食蟹猴PD-L1或对亲本 (未转化的细胞) 的亲合性。在含有10%FBS (Life Technologies, 10270-1-6)、100μg/mL潮霉素B (Melford Laboratories Ltd, Z2475)、15μg/mL杀稻瘟菌素 (Melford Laboratories Ltd, B1105) 和1μg/mL脱氧土霉素 (Sigma, D9891) 的DMEM中生长的、表达人类或食蟹猴PD-L1的HEK细胞使用细胞解离缓冲液 (Life Technologies, 13151-014) 从组织培养烧瓶上剥离,以2×10⁵个细胞/孔接种在V形底96孔平板 (Costar, 3897) 中。平板在4℃下在1500rpm离心3分钟来沉淀细胞。mAb² (或对照mAb) 的稀释系列与细胞在100μl体积中在4℃下孵育1小时。洗涤平板,二抗 (抗人Fc-488, Jackson ImmunoResearch, 109-546-098) 在PBS中1:1000稀释,并将100μl在4℃下向细胞中添加30分钟 (平板保持在暗处)。洗涤平板,并且细胞在含有1μg/mL苯基吡啶 (DAPI) (Biotium, 40043) 的100μl PBS中重悬浮。使用Canto II流式细胞计 (BD Biosciences) 读取平板。排除死细胞,测量FITC通道 (488nm/530/30) 中的荧光。在GraphPad Prism软件中使用log (激动剂) vs response拟合数据。平板在BD FACSCanto II细胞计 (BD Biosciences) 上读取,使用FlowJo分析数据。结果在表14中示出。

[0299] 表14:流式细胞术测定的、抗LAG-3/PD-L1 mAb²对表达人类或食蟹猴PD-L1的HEK细胞的结合亲和力

	人类 PD-L1 HEK		食蟹猴 PD-L1	
	EC ₅₀ (nM)	95%置信区间	EC ₅₀ (nM)	95%置信区间
84G09	3.107	2.230 至 4.331	1.641	1.244 至 2.164
FS18-7-09/84G09	3.19	2.208 至 4.610	1.674	1.393 至 2.012
FS18-7-09/84G09	3.51	2.570 至 4.794	1.814	1.503 至 2.189
FS18-7-33/84G09	3.448	2.436 至 4.881	1.895	1.566 至 2.292
[0300] FS18-7-32/84G09	3.816	2.749 至 5.298	1.984	1.644 至 2.393
FS18-7-58/84G09	3.775	2.957 至 4.820	1.861	1.541 至 2.247
FS18-7-33/84G09	3.225	2.214 至 4.700	1.733	1.397 至 2.150
FS18-7-65/84G09	3.999	2.782 至 5.750	1.845	1.455 至 2.339
FS18-7-36/84G09	3.907	2.844 至 5.367	1.999	1.580 至 2.528
FS18-7-88/84G09	3.492	2.541 至 4.800	1.814	1.464 至 2.247
FS18-7-58/84G09	3.907	2.998 至 5.093	2.033	1.622 至 2.550
84G09 (亲本)	3.051	2.181 至 4.267	1.959	1.515 至 2.533

[0301] 所有测试的LAG-3/PD-L1 mAb²以与84G09 mAb接近的EC₅₀结合人类PD-L1和食蟹猴PD-L1,表明PD-L1结合亲和力不受到mAb²的CH3结构域中LAG-3结合位点引入的影响。

[0302] 2.11替代小鼠mAb²与表达小鼠LAG-3或小鼠PD-L1的细胞的结合

[0303] 使用KpnI (NEB, R0142) 和NotI (NEB, R0146) 限制性酶切,将鼠类LAG-3序列 (SEQ ID NO:127) 或鼠类PD-L1序列 (SEQ ID NO:130) 亚克隆到pcDNA5FRT载体 (Life Technologies, V6010-20) 中。然后使用脂质体 (Lipofectamine) 2000 (Life Technologies, 11668-019) 将载体转化到四环素诱导性启动子 (Flp-In T-REx) 293HEK细胞系 (Life Technologies, R780-07) 中。转化的Flp-In T-REx 293细胞在含有10%FBS (Life Technologies, 10270-1-6)、100μg/mL潮霉素B (Melford Laboratories Ltd, Z2475)、15μg/ml杀稻瘟菌素 (Melford Laboratories Ltd, B1105) 的DMEM (Life Technologies, 61965-026) 中生长3-4周,直到显现稳定转化的细胞的集落。这些集落在存在1μg/ml脱氧土霉素 (Sigma, D9891) 的情况下扩增,LAG-3或PD-L1表达通过流式细胞术确认。

[0304] 使用流式细胞术测定mAb² (都含有LALA突变) 结合细胞表达的鼠类LAG-3或鼠类PD-L1的亲和性。在含有10%FBS (Life Technologies, 10270-1-6)、100μg/ml潮霉素B (Melford Laboratories Ltd, Z2475)、15μg/ml杀稻瘟菌素 (Melford Laboratories Ltd, B1105) 和1μg/ml脱氧土霉素 (Sigma, D9891) 的DMEM中生长的、表达鼠类LAG-3或鼠类PD-L1的HEK细胞使用细胞解离缓冲液 (Life Technologies, 13151-014) 从组织培养烧瓶上剥离,以2×10⁵个细胞/孔接种在V形底96孔平板 (Costar, 3897) 中。平板在4℃下在1500rpm离心3分钟来沉淀细胞。mAb² (或对照mAb) 的稀释系列与细胞在60μl体积中在4℃下孵育1小时。洗涤平板,且二抗 (用于mAb²的抗人Fc-488, Jackson ImmunoResearch, 109-546-098, 或用于抗LAG-3对照C9B7W的抗大鼠IgG (H+L)、荧光基团488 (Alexa Fluor 488) 结合物, ThermoFisher, A-11006) 在PBS中1:1000稀释,并将50μl在4℃下向细胞中添加30分钟 (平板保持在暗处)。洗涤平板,然后将细胞重悬浮在50μl FACS Cell Fix (BD Bioscience,

340181)中15分钟,任何洗涤并重悬浮在含有1 μ g/ml DAPI (Biotium,40043)的100 μ l PBS中。使用Canto II流式细胞计(BD Biosciences)读取平板。排除死细胞,测量FITC通道(488nm/530/30)中的荧光。在GraphPad Prism软件中使用log(激动剂)vs response拟合数据。平板在BD FACSCanto II细胞计(BD Biosciences)上读取,使用FlowJo分析数据。结果在表15中显示。

[0305] 表15:流式细胞术测定的、替代抗小鼠LAG-3/PD-L1 mAb²对表达鼠类LAG-3或鼠类PD-L1的HEK细胞的结合亲和力

	鼠类 LAG-3 HEK		鼠类 PD-L1 HEK	
	EC50 (nM)	95%置信区间	EC50 (nM)	95%置信区间
[0306] C9B7W	27	12.27 至 58.04	N/A	-
FS18-7-108-29/S1	2.27	1.064 至 4.857	11.9	7.627 至 18.68
FS18-7-108-29/4420	2.29	1.256 至 4.164	N/A	-
FS18-7-108-35/S1	3.84	2.126 至 6.926	12.3	8.873 至 17.16
FS18-7-108-35/4420	2.38	0.7819 至 7.239	N/A	-

[0307] 替代mAb²能够结合表达鼠类LAG-3的细胞和表达鼠类PD-L1的细胞。替代mAb²对表达鼠类LAG-3的细胞的结合亲和力与抗人LAG-3/PD-L1 mAb²与人LAG-3的亲和力大约相同(2.3-3.8nM相比2.5-4.2nM),替代mAb²对表达鼠类PD-L1的细胞的结合亲和力在抗人LAG-3/PD-L1 mAb²对人类PD-L1的亲力的3倍之内(11.9-12.3nM相比3.1-4.0nM),表明这些mAb²是用于小鼠体内研究的对于抗人LAG-3/PD-L1 mAb²的适合的替代。

[0308] 实施例3:T细胞活化试验和SEB试验中mAb²分子的活性

[0309] 3.1 T细胞活化试验

[0310] 基于D011.10 OVA T-淋巴细胞和LK35.2 B-淋巴细胞杂交瘤细胞系的IL-2释放试验用于mAb²的功能筛选。IL-2释放是T细胞活化的标记物。表达内源的鼠类PD-1的T细胞用空载体(pLVX)或人LAG-3构建体转染。B细胞用空载体(pLVX)或人PD-L1构建体转染。

[0311] 将这四种细胞系的三种组合并排用于测试mAb²的T细胞活化:

[0312] • D011.10 pLVX+LK35.2 hPD-L1用于抗PD-L1活性;

[0313] • D011.10 hLAG-3+LK35.2 pLVX用于抗LAG-3活性;

[0314] • D011.10 hLAG-3+LK35.2 hPD-L1用于同时的抗LAG-3/抗PD-L1活性。

[0315] 所有mAb²(都含有LALA突变)在这项T细胞活化试验中测试两次。在功能性T细胞活化试验中使用过量表达食蟹猴靶点(cPD-L1和cLAG-3)的细胞测试了与食蟹猴LAG-3和PD-L1的交叉反应性。

[0316] 过量表达LAG-3的T细胞系的产生

[0317] 使用伦蒂-X慢病毒包装系统(Lenti-X HTX Packaging System)(Clontech, Cat.No 631249),使用慢病毒转导方法产生过量表达人、食蟹猴或小鼠LAG-3的D011.10细胞(National Jewish Health)。含有小鼠LAG-3 cDNA(SEQ ID NO:127)、人LAG-3 cDNA(SEQ ID NO:126)或食蟹猴LAG-3 cDNA(SEQ ID NO:128)的伦蒂-X表达载体(pLVX)(Clontech, Cat.No 631253)使用伦蒂-X慢病毒包装组合共转染到Lenti-X 293T细胞系(Clontech,

Cat.No 632180) 中来产生病毒。用伦蒂-X慢病毒包装系统产生的慢病毒载体转导D011.10细胞系。

[0318] 过量表达PD-L1的抗原呈递细胞的产生

[0319] 使用伦蒂-X慢病毒包装系统 (Lenti-X HTX Packaging System) (Clontech, Cat.No 631249), 使用慢病毒转导方法产生过量表达人、食蟹猴或小鼠PD-L1的LK35.2 B细胞淋巴瘤 (ATCC, HB-98)。含有小鼠PD-L1 cDNA (SEQ ID NO:130)、人PD-L1 cDNA (SEQ ID NO:129) 或食蟹猴PD-L1 cDNA (SEQ ID NO:131) 的伦蒂-X表达载体 (pLVX) (Clontech, Cat.No 631253) 使用伦蒂-X慢病毒包装组合共转染到Lenti-X 293T细胞系 (Clontech, Cat.No 632180) 中来产生病毒。用伦蒂-X慢病毒包装系统产生的慢病毒载体转导LK35.2细胞系。

[0320] 培养基和肽

[0321] 细胞培养基: DMEM (Gibco, 61965-026) 10% FBS (Gibco, 10270-106), 1mM 丙酮酸钠 (Gibco, 11360-070), 1μg/ml 嘌呤霉素 (Gibco, A11138-03)

[0322] 实验培养基: 没有嘌呤霉素的完全D011.10培养基。

[0323] OVA肽 (分子量=1773.9 Da): H- ISQAVHAAHAEINEAGR-OH (Pepscan)

[0324] 细胞:

[0325] • D011.10 hLAG-3: 用慢病毒载体转导以过量表达人LAG-3的D011.10T细胞杂交瘤;

[0326] • D011.10 pLVX: 用空的慢病毒载体转导的D011.10T细胞杂交瘤;

[0327] • D011.10 cLAG-3: 用慢病毒载体转导以过量表达食蟹猴LAG-3的D011.10 T细胞杂交瘤;

[0328] • LK 35.2 hPD-L1: 用含有hPD-L1的慢病毒载体转导以过量表达人类PD-L1的B细胞杂交瘤;

[0329] • LK 35.2 PLVX: 用空的慢病毒 (pLVX) 载体转导的B细胞杂交瘤;

[0330] • LK 35.2 cPD-L1: 用慢病毒载体转导以过量表达食蟹猴PD-L1的B细胞杂交瘤;

[0331] 0.3×10^6 个细胞/mL的D011.10细胞 (D011.10 pLVX细胞或者D011.10hLAG-3细胞)) 以1:1的比例与 $3 \times$ 终浓度的抗体混合。抗体和D011.10细胞在37℃、5% CO₂下孵育1小时。LK 35.2细胞 (pLVX和PD-L1-pLVX两者) 以 3×10^5 个细胞/mL实验培养基与1.5μM的OVA肽孵育30分钟。以1:2的比例按以下组合将LK35.2细胞+OVA添加到D011.10细胞/处理混合物中:

[0332] 人类功能筛选

[0333] D011.10 pLVX+LK35.2 hPD-L1,

[0334] D011.10 hLAG-3+LK35.2 pLVX,

[0335] D011.10 hLAG-3+LK35.2 hPD-L1;

[0336] 食蟹猴交叉反应性筛选

[0337] D011.10 pLVX+LK35.2 cPD-L1,

[0338] D011.10 cLAG-3+LK35.2 pLVX,

[0339] D011.10 cLAG-3+LK35.2 cPD-L1;

[0340] 细胞在37℃、5% CO₂下孵育24小时。采集上清液, 根据厂家的说明书用小鼠IL-2

ELISA试剂盒 (eBioscience, 88-7024-88 or R&D systems, SM2000) 进行分析。使用带有 BioTek Gen5软件的平板读取器在450 nm下读取平板。从450nm的光吸收值中减去570nm的光吸收值 (校正)。用于计算细胞因子浓度的标准曲线基于四参数逻辑曲线拟合 (BioTek Gen5软件)。在GraphPadPrism中, 将鼠白介素-2 (mouse interleukin-2, mIL-2) 的浓度相对于Fcab或基准mAb的log浓度作图, 并使用log (agonist) vs response方程将产生的曲线拟合。表16示出了按照对照 (84G09+25F7) 的百分比计算的、mAb²和对照mAb的EC₅₀值和最大IL-2释放。附图2A-F示出了用FS18-7-9/84G09、FS18-7-62/84G09或FS18-7-78/84G09和对照处理的细胞系面板的IL-2释放的代表性的图。在存在两个靶点 (D011.10 hLAG-3+LK35.2 hPD-L1) 的T细胞活化试验中, 仅当LAG-3和PD-L1都被抑制时诱导了IL-2释放, 例如, 当使用mAb²或LAG-3与PD-L1抗体的组合时。因而, 所述mAb²具有相对于单独的单个试剂的益处。在仅LAG-3 (D011.10 hLAG-3+LK35.2 pvlx) 或PD-L1 (D011.10 pvlx+LK35.2 PD-L1) 的试验中, 在抑制这些靶点方面mAb²显示了与单一试剂类似的活性, 表明所述mAb²是能够在存在LAG-3、PD-L1或LAG-3+PD-L1的情况下能引起T细胞活性的唯一的单一分子。

[0341] 表16: 九种mAb²的EC₅₀和最大IL2释放 (计算为与对照-84G09+25F7相比的IL2释放百分比)

[0342]

mAb ² /对照mAbs	平均	SD	平均	SD
	EC ₅₀		计算为对照% (84G09+25F7) 的最大 IL2 释放	
FS18-7-09/84G09LALA	0.75	0.20	65.89	24.04
FS18-7-33/84G09LALA	0.82	0.35	63.95	36.56
FS18-7-78/84G09LALA	0.82	0.38	64.39	39.28
FS18-7-62/84G09LALA	0.65	0.02	58.97	18.13
FS18-7-65/84G09LALA	0.81	0.20	70.25	2.22
FS18-7-95/84G09LALA	1.10	-	79.77	-
FS18-7-32/84G09LALA	1.19	0.00	82.94	14.67
FS18-7-36/84G09LALA	1.05	0.32	71.56	8.83
FS18-7-58/84G09LALA	1.16	0.21	79.40	0.10
84G09LALA + 25F7	1.32	0.25	100.00	

[0343] mAb²之一 (含有LALA突变的FS18-7-9/84G09) 在D011.1-/LK35.2 T细胞活化试验中测试食蟹猴功能性交叉反应性。附图3A-C示出了三项基于细胞的分析中的面板中的结果。FS18-7-9/84G09能够在cLAG-3+cPD-L1两者以及单独的cLAG-3或cPD-L1存在的情况下诱导T细胞活化, 表明所述mAb²是功能性地食蟹猴交叉反应性的, 因而适用于基于灵长类的安全性研究。

[0344] 3.2葡萄球菌肠毒素B试验

[0345] 在基于人-PBMC的葡萄球菌肠毒素B试验 (SEB试验) 中测试三种mAb² (全部含有

LALA突变)。葡萄球菌肠毒素B是一种超级抗原,并结合抗原呈递细胞(antigen presenting cell,APC)上呈递的II类MHC分子、T细胞受体(T cell receptor,TCR)的 $\alpha\beta$ 链,引起T细胞的非特异性活化和细胞因子释放。不需要抗原存在以见到T细胞活化。SEB试验利用具有生理水平的检查点抑制剂的刺激的人类细胞(stimulated human,PBMC),可以用于确认在人类系统中T细胞活化被mAb²增强。使用来自四个不同供体的细胞在SEB系统中测试了三种mAb²。

[0346] 扩增的T细胞的产生

[0347] 通过Ficoll梯度分离从白细胞分离PMBC。根据厂家的说明,使用人类CD4⁺ T细胞分离试剂盒(Miltenyi Biotec Ltd,130-096-533)分离CD4⁺ T细胞。通过旋涡重悬浮入T-活化剂CD3/CD28免疫磁珠(Dynabeads)(Life technologies,11131D)。将珠子转移到无菌的15ml试管中,添加具有10%FBS(Life Technologies,10270106))和1×青霉素链霉素(Penicillin Streptomycin,Life Technologies,15140122)的10ml RPMI(Life Technologies,61870044)来洗涤Dynabeads。丢弃上清液。在具有10%FBS和1×青霉素链霉素溶液的RPMI和50 IU/ml重组人IL2(Peprotech,200-02-50ug)中的 1.0×10^6 个细胞/ml的CD4⁺ T细胞与3:1珠子与细胞比率的所需量转移至T75烧瓶(Greiner Bio-one,690195)并在37°C+5%CO₂下孵育。3天后,轻轻地重悬浮细胞并计数。根据需要,通过加入新鲜培养基(RPMI-10%FBS+青霉素链霉素溶液1×+50IU/ml rhuIL2)将细胞密度维持在 $0.8-1 \times 10^6$ 个细胞/ml之间。在第7天或第8天,取出CD3/28珠子并将CD4⁺ T细胞以 1×10^6 个细胞/ml新鲜培养基RPMI-10%FBS+青霉素链霉素溶液1×与降低的10IU/ml rhuIL2静置过夜。冷冻保存细胞待用。

[0348] MoIDC的产生

[0349] 按照厂家的说明,使用人Pan单核细胞分离试剂盒(Miltenyi Biotec Ltd,130-096-537)从人PBMC分离未接触的单核细胞。按照厂家的说明,使用人Mo-DC分化培养基(Miltenyi Biotec Ltd,130-094-812)将单核细胞分化为iDC。

[0350] SEB试验

[0351] 在实验前一天解冻扩增的T细胞,用AIM培养基(Gibco,12055-091)洗涤,并在AIM培养基中以 1×10^6 个细胞/ml在37°C、5%CO₂下孵育过夜。在DPBS(Gibco,14190-169)中制备2 μ M浓度的每种抗体/混合物,并在培养基(30 μ l+270 μ l)中1:10稀释,得到200nM。在96孔板中,以1:10(30 μ l+270 μ l实验培养基;2×最终浓度)进行连续稀释。解冻MoIDC,用AIM培养基洗涤,并以1:10的比例与来自相同供体的T细胞(5ml 2×10^5 个细胞/ml的iDC与 2×10^6 个细胞/ml的5ml T细胞混合)混合。将20 μ l浓度为0.1 μ g/ml的SEB(Sigma,S4881)加入到10ml细胞中。在圆底96孔板中,将100 μ l细胞/SEB混合物加入到100 μ l抗体稀释液中,得到每孔的200 μ l AIM培养基中0.1ng/ml SEB、 10^4 个iDC细胞与 10^5 个T细胞的比例,最终抗体浓度为100、10、1、0.1、0.01、0.001nM。细胞在37°C、5%CO₂下孵育3天。收集上清液并立即用人IFN γ ELISA试剂盒(R&D Systems,PDIF50)测定或在-20°C下冷冻用于进一步分析。根据试剂盒制造商的说明书,使用用PBA(DPBS,2%BSA(Sigma,A7906-100G))1:30稀释的上清液进行分析。在GraphPad Prism软件中,将人IFN γ 的浓度相对于mAb²或mAb的log浓度作图,并使用log(agonist)vs response方程将产生的曲线拟合。表17示出了使用来自四种不同细胞供体(供体A至D)的细胞的SEB试验中的EC₅₀值和IFN γ 释放的跨度。图4示出了具有单一供体的SEB分析的代表性标绘图。在所有六项试验中,LAG-3/PD-L1 mAb²和LAG-3/FITC mAb²+

84G09LALA的组合显示出比单独的84G09LALA mAb更大的活化,而当试验LAG-3/FITC mAb²或4420 mAb时,它们没有表现出显著的活化。因此,SEB试验的结果在更具生理性的系统中证实了D011.10/LK35.2试验的结果。

[0352] 表17. 基于4种不同的细胞供体的六项SEB试验对六种mAb²计算的EC₅₀值。

[0353]

试验 1 供体 A				
	EC ₅₀ (nM)	95%置信区间	SPAN	95%置信区间
FS18-7-09/84G09LALA	0.1551	0.08521 至 0.2824	12280	10802 至 13758
FS18-7-62/84G09LALA	0.1424	0.08665 至 0.2340	12120	10897 至 13342
FS18-7-78/84G09LALA	0.2774	0.1220 至 0.6310	14156	11970 至 16341
84G09 LALA	0.1884	0.08960 至 0.3962	10077	8612 至 11542
FS18-7-09/4420LALA	-	-	1010	384.8 至 1635
FS18-7-62/4420LALA	-	-	416.1	-443.1 至 1275
FS18-7-78/4420LALA	-	-	411	-1103 至 1925
84G09 LALA + FS18-7-09/4420LAL	0.2455	0.1030 至 0.5850	11836	9888 至 13785
84G09 LALA + FS18-7-62/4420LAL	0.1601	0.05399 至 0.4750	11448	8958 至 13937
84G09 LALA + FS18-7-78/4420LAL	0.1774	0.06863 至 0.4587	12250	9955 至 14544

[0354]

4420 LALA	-	-	218.6	-35.91 至 473.1
试验 1 供体B				
	EC ₅₀ (nM)	95%置信区间	SPAN	95%置信区间
FS18-7-09/84G09LALA	0.07316	0.02255 至 0.2374	11825	8919 至 14730
FS18-7-62/84G09LALA	0.03236	0.007146 至 0.1465	12170	8419 至 15921
FS18-7-78/84G09LALA	0.09718	0.03128 至 0.3019	15198	11594 至 18802
84G09 LALA	0.08562	0.03403 至 0.2154	12343	9957 至 14730
FS18-7-09/4420LALA	-	-	1337	-195.8 至 2870
FS18-7-62/4420LALA	-	-	2508	-2118 至 7133
FS18-7-78/4420LALA	-	-	1425	-58.52 至 2908
84G09 LALA + FS18-7-09/4420LAL	0.2861	0.1005 至 0.8143	16037	12890 至 19184
84G09 LALA + FS18-7-62/4420LAL	0.1431	0.02857 至 0.7172	13907	9358 至 18455
84G09 LALA + FS18-7-78/4420LAL	0.3775	0.08929 至 1.596	14418	10502 至 18334
4420 LALA	-	-	2293	1028 至 3558
试验 2 供体 A				
	EC ₅₀ (nM)	95%置信区间	SPAN	95%置信区间
FS18-7-09/84G09LALA	0.2761	0.1654 至 0.4611	20727	18729 至 22724
FS18-7-33/84G09LALA	0.1934	0.07990 至 0.4681	171 03	14156 至 20049
FS18-7-78/84G09LALA	0.2384	0.1596 至 0.3560	19822	18311 至 21333
84G09 LALA	0.3788	0.1166 至 1.230	11745	9138 至 14352
FS18-7-09/4420LALA	-	-	1991	-1927 至 5909
FS18-7-33/4420LALA	-	-	~ 1.053e+006	(非常宽)
FS18-7-78/4420LALA	-	-	~ 72657	(非常宽)

[0355]

84G09 LALA + FS18-7-09/4420LALA	0.5202	0.2624 至 1.031	23346	20230 至 26462
84G09 LALA + FS18-7-33/4420LALA	0.2881	0.1529 至 0.5428	22529	19853 至 25205
84G09 LALA + FS18-7-78/4420LALA	0.4335	0.2089 至 0.8996	20955	18038 至 23873
试验 2 供体 B				
	EC ₅₀ (nM)	95%置信区间	SPAN	95%置信区间
FS18-7-09/84G09LALA	0.139	0.04157 至 0.4646	21572	16269 至 26874
FS18-7-33/84G09LALA	0.07278	0.01615 至 0.3280	19554	13408 至 25699
FS18-7-78/84G09LALA	0.1356	0.03552 至 0.5178	22319	16212 至 28426
84G09 LALA	0.1959	0.03365 至 1.140	12077	7938 至 16216
FS18-7-09/4420LALA	-	-	1272	-963.4 至 3507
FS18-7-33/4420LALA	-	-	2272	-190.8 至 4735
FS18-7-78/4420LALA	-	-	1960	-1287 至 5207
84G09 LALA + FS18-7-09/4420LALA	0.2889	0.07772 至 1.074	23661	17835 至 29488
84G09 LALA + FS18-7-33/4420LALA	0.3	0.06936 至 1.298	26145	18971 至 33320
84G09 LALA + FS18-7-78/4420LALA	0.271	0.03980 至 1.845	25489	16292 至 34686
试验 1 供体 C				
	EC ₅₀ (nM)	95%置信区间	SPAN	95%置信区间
FS18-7-09/84G09LALA	0.06739	0.01933 至 0.2349	2987	15107 至 27710
84G09 LALA	0.08347	0.0331 至 0.2105	1509	11046 至 17414
84G09 LALA + FS18-7-09/4420LALA	0.1618	0.06635 至 0.3944	1744	13346 至 20704

试验 1 供体 D					
[0356]		EC ₅₀ (nM)	95%置信区间	SPAN	95%置信区间
	FS18-7-09/84G09LALA	0.04373	0.01797 至 0.1064	1850	15995 至 23799
	84G09 LALA	0.07043	0.03483 至 0.1424	1045	10996 至 15405
	84G09 LALA +				
	FS18-7-09/4420LALA	0.1351	0.08359 至 0.2182	968	15318 至 19403

[0357] 实施例4:mAb²分子在鼠类肿瘤模型中的体内活性

[0358] 4.1 mAb²分子在MC38未建立的肿瘤模型中的活性

[0359] 这项实验中使用MC38同基因肿瘤模型,因为已知MC38肿瘤在它们的细胞表面表达PD-L1并且是高度免疫原性的导致肿瘤环境和肿瘤外周部中免疫细胞上提高的LAG-3表达。

[0360] 称为FS18-29/S1、含有LALA突变的替代小鼠mAb² FS18-7-108-29/S1 (SEQ ID NO: 117和119) 使用MC38同基因小鼠肿瘤生长模型测试体内活性。mAb²抑制肿瘤生长的能力与LAG-3/模拟mAb²的抑制肿瘤生长的能力比较,称为FS18-29/4420的含有LALA突变 (SEQ ID NO:132和85) 的FS18-7-108-29/4420,基准抗LAG-3 mAb C9B7W (2B scientific;产品号BE0174-50MG),含有LALA突变 (SEQ ID NO:122和119) 的基准抗PD-L1mAb S1比较,以及与mAbs C9B7W和S1的组合比较。

[0361] 年龄8-10周、每个重量20-25g的C57BL/6雌性小鼠 (Charles River) 在研究开始之前休息一周。所有动物进行微芯片化并给予独特的标识符。每组有10只小鼠。MC38结肠癌细胞系最初被扩增、保存 (S. Rosenberg, NIH), 然后使用IMPACT I 方案,通过IDEXX BioResearch针对病原体预筛选,并显示其是不含病原体的。解冻来自-150℃存储的MC38细胞,并添加到T175组织培养烧瓶中具有10%FCS (Gibco,10270-106) 的20ml DMEM (Gibco, 61965-026) 中。使用异氟烷 (Abbott Laboratories) 麻醉小鼠,每只动物接受左肋皮下注射的 2×10^6 个细胞。肿瘤细胞接种后的7-8天,将此时没有肿瘤的小鼠从研究中去除。

[0362] 在注射之前24小时之内,通过SEC-HPLC性能分析对所有mAb²分子和对照抗体进行分析,并检查杂质。以PBS中10mg/kg的终浓度制备抗体,在组合研究与第二抗体组合。在肿瘤接种后第8、11和14天通过腹膜内 (IP) 注射向小鼠施用mAb²分子和对照抗体。进行肿瘤的精确测量,在所讨论的当天执行任何药物给药,并对小鼠进行密切观察以用于试验的剩余部分。使用卡尺进行肿瘤体积测量,以确定肿瘤的最长轴和最短轴。以下公式用于计算肿瘤体积:

[0363] $L \times (S^2) / 2$

[0364] 其中L=最长轴;S=最短轴

[0365] 在第20天当肿瘤负荷被认为接近限制时停止试验。人道地处死所有小鼠,切下肿瘤并称重。

[0366] 结果在图5和6中示出。LAG-3/PD-L1 mAb² (FS18-29/S1) 治疗的小鼠具有比用基准mAbs C9B7W和S1的组合治疗的小鼠重量显著更小的终末肿瘤。特别地,使用GraphPad Prism软件包内的双尾学生t检验进行终末肿瘤重量的统计分析,证明FS18-29/S1施用与基

准抗体C9B7W和S1组合施用之间有统计学显著的差异($p=0.0125$),表明与由单独分子提供的LAG-3和PD-L1抑制相比,由相同分子提供的LAG-3和PD-L1抑制产生对终末肿瘤重量的协同作用。

[0367] 替代 mAb^2 FS18-29/S1对肿瘤生长也有显著影响,阻止8个生长的MC38肿瘤中的6个建立,并减缓其余2个肿瘤的生长。组合施用基准抗LAG-3和PD-L1抗体减慢7只动物的肿瘤生长,没有动物没有肿瘤。

[0368] 单独的FS18-29/4420对肿瘤生长没有显著影响,表明对于最大功效, mAb^2 需要抗PD-L1 Fab。单独的基准抗小鼠LAG-3抗体对所产生的肿瘤生长几乎没有或没有影响,而基准抗小鼠PD-L1阻止该群组中7个肿瘤中的1个的建立,并且具有减缓肿瘤生长的一些总体效果。

[0369] 同基因小鼠模型被接受作为用于测试抑制治疗靶点的抗肿瘤效果的合适的鼠系统,已经广泛用于验证人类治疗剂的开发。

[0370] 4.2 mAb^2 分子在MC38建立的肿瘤模型中的活性

[0371] 称为FS18-29/S1、含有LALA突变的替代小鼠 mAb^2 FS18-7-108-29/S1 (SEQ ID NO: 117和119)在MC38同基因小鼠肿瘤生长模型中测试体内活性。 mAb^2 抑制肿瘤生长的能力与LAG-3/模拟 mAb^2 抑制肿瘤生长的能力比较,称为FS18-29/4420的含有LALA突变 (SEQ ID NO: 132和85)的FS18-7-108-29/4420,基准抗LAG-3 mAb C9B7W,含有LALA突变 (SEQ ID NO: 122和119)的基准抗PD-L1 mAb S1比较,以及与C9B7W和S1的组合比较。

[0372] 年龄8-10周、每个重量20-25g的C57BL/6雌性小鼠(Charles River)在研究开始之前休息一周。所有动物进行微芯片化并给予唯一的标识符。每组10有只小鼠。MC38结肠癌细胞系最初被扩增、保存(S. Rosenberg, NIH),然后使用IMPACT I方案,通过IDEXX Bioresearch针对病原体预筛选,并显示其是不含病原体的。解冻来自 -150°C 存储的MC38细胞(大约 $3-5 \times 10^6$ 个),并添加到T175组织培养烧瓶中具有10%FCS(Gibco, 10270-106)的20mlDMEM(Gibco, 61965-026)中。使用异氟烷(Abbott Laboratories)麻醉小鼠,将100 μl 中的 2×10^6 个细胞皮下注射到每只小鼠的左肋中。在肿瘤细胞接种后7-8天,常规监测小鼠的健康和适合于开始研究的肿瘤生长。当大多数小鼠表现出5-10mm直径的肿瘤时,将它们分类并随机分组回到研究队列中。此时从研究中除去任何没有适当大小的肿瘤的小鼠。

[0373] 在注射之前24小时之内,通过SEC-HPLC性能分析对所有 mAb^2 分子和对照抗体进行分析,并检查混杂质。以PBS中10mg/kg的终浓度制备抗体,在组合研究与第二抗体组合。在肿瘤接种后第15、18和21天通过IP注射液向小鼠施用 mAb^2 分子和对照抗体。每周麻醉三次下,以盲法对动物进行健康筛查,在此期间进行肿瘤的精确测量。使用卡尺进行肿瘤体积测量,以确定肿瘤的最长轴和最短轴。用于计算肿瘤体积的公式如上文章4.1中所列。

[0374] 在第24天当肿瘤负荷被认为接近限制时停止试验。人道地处死所有小鼠,切下肿瘤并称量。结果在图7和8中示出。

[0375] 在小鼠的同基因肿瘤模型中有效控制或抑制肿瘤生长最好通过早期时间点的治疗干预(起始肿瘤体积小于 40mm^3)来实现。干预进行得越晚,越难以观察到对肿瘤生长的积极效果,而这可能更类似于人类临床环境中的情况。

[0376] 当在C57BL/6小鼠的早期时间点给予时,FS18-29/S1在抑制肿瘤生长和阻止免疫感受态小鼠中MC38结肠癌的建立方面都具有积极作用。当在稍晚的时间点(起始肿瘤体积

为50-125mm³)施用,FS18-29/S1与基准抗体的组合一样仅在抑制肿瘤生长方面有效。单独的FS18-29/4420对肿瘤生长没有值得注意的影响,S1和C9B7W都对产生肿瘤生长有轻微的影响。

[0377] 4.3 mAb²分子在CT26未建立的肿瘤模型中的活性

[0378] CT26同基因肿瘤模型用于该项实验,因为已知CT26肿瘤在它们的细胞表面表达PD-L1并且是高度免疫原性的导致肿瘤环境和肿瘤外周部中免疫细胞上提高的LAG-3表达。

[0379] 称为FS18-29/S1的含有LALA突变(SEQ ID NO:117和119)的替代小鼠mAb² FS18-7-108-29/S1,以及称为FS18-35/S1的含有LALA突变的(SEQ ID NO:120和119)FS18-7-108-35/S1在CT26同基因小鼠肿瘤生长模型中测试体内活性。抑制肿瘤生长的mAb²的能力与LAG-3/模拟mAb²的抑制肿瘤生长的能力比较,称为FS18-29/4420的含有LALA突变(SEQ ID NO:132和85)的FS18-7-108-29/4420,和称为FS18-35/4420含有LALA突变(SEQ ID NO:133和85)的FS 18-7-108-35/4420比较,基准LAG-3 mAb C9B7W,含有LALA突变(SEQ ID NO:122和119)的基准PD-L1 mAb S1比较以及与C9B7W和S1的组合比较。

[0380] 年龄8-10周、每个重量20-25g的BALB/c雌性小鼠(Charles River)在研究开始之前休息一周。所有动物进行微芯片化并给予唯一的标识符。每组有10只小鼠。CT26结肠癌细胞系(ATCC,CRL-2638)最初被扩增、保存,然后使用IMPACT I方案,通过IDEXX BioResearch针对病原体预筛选,并显示其是不含病原体的。解冻来自-150℃存储的CT26细胞(大约3-5×10⁶个),并添加到T175组织培养烧瓶中具有10%FCS(Gibco,10270-106)的20ml DMEM(Gibco,61965-026)中。在肿瘤细胞接种后7-8天,常规监测小鼠的健康和适合于研究的开始的肿瘤生长。当大多数小鼠表现出直径3-5mm³的肿瘤时,将它们分类并随机分组回到研究队列中。此时从研究中除去任何没有肿瘤的小鼠。

[0381] 在注射的24小时之内,通过SEC-HPLC性能分析对所有mAb²分子和对照抗体进行分析,并检查杂质。以PBS中10mg/kg的终浓度制备抗体,在组合研究与第二抗体组合。在肿瘤接种后第8、11和14天小鼠施用mAb²分子和对照抗体。对动物进行健康筛选,在此期间进行肿瘤的精确测量。使用卡尺进行肿瘤体积测量,以确定肿瘤的最长轴和最短轴。用于计算肿瘤体积的公式如上文章节4.1中所列。

[0382] 在第20天当肿瘤负荷被认为接近限制时停止试验。人道地处死所有小鼠,切下肿瘤并称重。结果在图9和10中示出。

[0383] 使用GraphPad Prism软件包内的双尾学生t检验执行终末肿瘤重量的统计分析。使用来自统计计算的R项目的统计模型包statmod(Elso et al.,2004和Baldwin et al.,2007)的比较生长曲线函数来确定肿瘤生长曲线的统计分析。

[0384] 在抑制肿瘤生长方面,在FS18-35/S1 mAb²与IgG对照(正常生长)之间有已证明的统计学上显著的差异。对于基准抗体的组合或FS18-29/S1 mAb²对比IgG对照组,或对比该试验中的任何其他组,没有观察到这种统计学上显著的差异。

[0385] CT26肿瘤模型是一种侵略性的、快速生长的肿瘤模型,其本身倾向于使小鼠发生肠转移,并且因此具有非常有限的治疗窗口。

[0386] 令人惊讶的是,与IgG对照组相比,基准LAG-3和PD-L1抗体的组合没有显著抑制肿瘤生长。然而,与IgG对照相比,FS18-35/S1治疗组确实显示了生长的显著抑制。虽然与IgG对照相比,FS18-29/S1它确实抑制肿瘤生长,但它不是统计学上显著的。该试验显示了第二

种肿瘤模型,其中小鼠反应性LAG-3/PD-L1 mAb²已经证明在减缓肿瘤生长方面具有至少与基准单克隆抗体组合的施用相同程度的积极效果。

[0387] 4.4在MC38未建立的肿瘤模型中LALA突变对肿瘤生长抑制的影响

[0388] 测试两种mAb² (FS18-7-108-29/S1 LALA和FS18-7-108-29/S1) 来检验在Fc区中有和没有LALA突变的这些mAb²在抗肿瘤活性方面的潜在的差异。具有(SEQ ID NO:117和119)和没有LALA突变(SEQ ID NO:118和119)的称为FS18-29/S1的替代小鼠mAb² FS18-7-108-29/S1使用MC38同基因小鼠肿瘤生长模型测试体内活性。抑制肿瘤生长的mAb²的能力与LAG-3/模拟mAb²的抑制肿瘤生长能力比较,称为FS18-29/4420LALA和FS18-29/4420的有(SEQ ID NO:132和85)和没有LALA突变(SEQ ID NO:134和85)的FS18-7-108-29/4420比较,以及有和没有LALA突变的LAG-3/模拟mAb²与有(SEQ ID NO:122和119)和没有LALA突变(SEQ ID NO:123和119)的基准PD-L1 mAb S1的组合比较。

[0389] 年龄8-10周、每个重量20-25g的C57BL/6雌性小鼠(Charles River)在研究开始之前休息一周。所有动物进行微芯片化并给予唯一的标识符。每组有10只小鼠。MC38结肠癌细胞系最初被扩增、保存(S.Rosenberg,NIH),然后使用IMPACT I方案,通过IDEXX Bioresearch对进行病原体预筛选,并显示其是不含病原体的。解冻来自-150℃存储中MC38细胞(大约 $3-5 \times 10^6$ 个)并添加到T175组织培养烧瓶中具有10%FCS(Gibco,10270-106)的20ml DMEM(Gibco,61965-026)中。使用异氟烷(Abbott Laboratories)麻醉小鼠,将100μl中的 2×10^6 个细胞皮下注射到每只小鼠的左肋中。允许小鼠在观察下恢复,接种日期记为第0天。在肿瘤细胞接种后7-8天,常规监测小鼠的健康和适合于研究的开始的肿瘤生长。此时从研究中除去任何没有肿瘤的小鼠。

[0390] 在注射之前24小时之内,通过SEC-HPLC性能分析对所有mAb²分子和对照抗体进行分析,并检查杂质。以PBS中10mg/kg的终浓度制备抗体,在组合研究与第二抗体组合。在肿瘤接种后第8、11和14天通过IP注射向小鼠施用mAb²分子和对照抗体。每周麻醉三次下,以盲法对动物进行健康筛查,在此期间进行肿瘤的精确测量。使用卡尺进行肿瘤体积测量,以确定肿瘤的最长轴和最短轴。用于计算肿瘤体积的公式如上文章节4.1中所列。

[0391] 人道地处死所有小鼠,切下肿瘤并称重。结果在图11和12中示出。

[0392] 这项试验确认了,在MC38结肠癌模型中,存在或缺乏取消ADCC活性的LALA突变对于肿瘤生长没有统计学上显著的作用,然而包括LALA突变的那些mAb²倾向于产生提高的肿瘤生长抑制。尽管如此,证明了包括该突变以潜在地抑制针对表达LAG-3或PD-L1的T细胞的ADCC活性的理论,因为LALA突变对于LAG-3/PD-L1 mAb²的抗肿瘤活性没有不利影响。有一些证据表明,包含LALA突变仅对PD-L1抗体是至关重要的。

[0393] 这项试验还检查了LAG-3/PD-L1 mAb²相对于单独抗体的施用(LAG-3LALA+PD-L1 LALA)是否具有提高的效力。在这种情况下,在这两个组之间没有显著差异。两个组都抑制MC38结肠癌模型中的生长。

[0394] 4.5结论

[0395] 总而言之,从以上结果清楚的是,当包括针对LAG-3和PD-L1两者的结合位点的mAb²在测试的小鼠模型中被施用给小鼠时,对于肿瘤生长抑制有协同作用。基于这些结果,预期的是,本发明的抗体分子将在治疗人类患者的癌症中将比分别结合LAG-3和PD-L1的两个独立的分子的施用显示优越的效果。

[0396] 实施例5:mAb²治疗对T细胞LAG-3表达的影响

[0397] 在表达卵白蛋白的MC38同基因小鼠肿瘤生长模型(MC38.OVA)中测试称为FS18-29/S1的含有LALA突变(SEQ ID NOs:117和119)的替代小鼠mAb² FS18-7-108-29/S1引起降低的肿瘤负荷的机制。FS18-29/S1的作用与LAG-3/模拟mAb²,称为FS18-29/4420的含有LALA突变(SEQ ID NOs:132和85)的FS18-7-108-29/4420,含有LALA突变(SEQ ID NOs:122和119)的基准PD-L1 mAb S1的作用比较,以及与FS18-29/4420和S1的组合的作用比较。

[0398] 在植入当天,在对数期生长期(log phase growth)收获培养的MC38.OVA细胞(汇合-75%)并以 1×10^7 个细胞/mL的浓度重悬于PBS中。通过首先用异氟烷麻醉每只动物,然后将 1×10^6 个MC38.OVA细胞(0.1mL悬浮液)皮下植入每只试验动物的左肋来引发肿瘤。肿瘤细胞植入后的十一天,使用确定性随机化方法将动物随机分入个体肿瘤体积为32到62.5mm³的五组。在肿瘤接种后第12、14和16天以10mg/kg的抗体或mAb²对动物给药,并在肿瘤接种后第19和23天从每组的3只动物中采集肿瘤。GentleMACS™分离器用于使肿瘤与细胞离解,随后通过70μm细胞过滤器筛分以获得单细胞悬浮液。将96孔板上的 1×10^6 个细胞/孔重悬于具有1:3000的生存力染色和Fc阻断(抗CD16/32抗体)的FACS缓冲液中。使用包括针对CD43、CD8a、CD4、FoxP3和LAG-3的标记抗体的Master Mix对用于FACS分析的细胞进行染色。对于FoxP3细胞内染色,在用FoxP3抗体染色之前将细胞固定并透性化(permeabilized)。样品在补偿矩阵并计算至少500,000个事件的Canto II流式细胞仪上运行。

[0399] 在这个实验中,在已经施用了抗体/mAb²的第三剂之后,当观察到对照和mAb²治疗之间肿瘤的生长方的分离时,但在可能偏离结果的肿瘤尺寸之间存在很大差异之前,检查TIL的LAG-3表达。在这个时间点上,在用mAb²FS18-29/S1或用FS18-29/4420和S1的组合治疗的动物中,发现TIL上的LAG-3表达显著降低。特别地,如图13所示,在用FS18-29/S1治疗之后的肿瘤接种后第19天和第23天,分别对应于最后一次抗体/mAb²给药之后第3天和第7天,CD8、CD4和FoxP3肿瘤浸润淋巴细胞(TIL)上的LAG-3表达降低。LAG-3表达的降低在第23天是更为显著的,但是在第19天仍是明显的。给予FS18-29/4420与S1的组合的动物还显示TIL上LAG-3表达的降低,但是效果延迟到直到第23天,而单独施用的FS18-29/4420或S1的治疗对TIL上的LAG-3表达影响很小至没有影响。

[0400] 这些结果显示,LAG-3和PD-L1的双重抑制对通过TIL的LAG-3表达的降低是必需的,因为在用针对LAG-3或PD-L1的单一试剂治疗的动物中没有见到这种现象。不希望受理论的限制,认为双重抗LAG-3和抗PD-L1治疗引起TIL上LAG-3表达的降低,从而减少了LAG-3的抑制效果并允许TIL克服衰竭。一旦TIL变为活化的,它们能识别由肿瘤所表达的新抗原,并针对新抗原产生反应。因而认为这是用抗LAG-3/PD-L1 mAb²治疗引起肿瘤负荷降低的机制。

[0401] 实施例6:的抗体依赖性细胞毒性和mAb²的补体依赖性细胞毒性活性

[0402] IgG1抗体通常通过分子的恒定区内的守恒的(conserved)相互作用位点展现效应因子功能(effector functions)。这些包括抗体依赖性细胞毒性(ADCC),所述抗体依赖性细胞毒性由与单核细胞/巨噬细胞、树突细胞、NK细胞、嗜中性细胞和其他粒细胞上表达的FcγR的结合所介导,以及补体依赖性细胞毒性(CDC),所述补体依赖性细胞毒性由与C1q补体成分的结合引发的补体级联的诱导所介导。由于LAG-3主要在活化的T细胞上表达,PD-L1

在这些细胞上表达但还以高水平在肿瘤细胞上表达,因此研究了mAb² FS18-7-9/84G09 (SEQ ID NOs:94和116)诱导ADCC和CDC的能力。

[0403] 具体地,测试了表达LAG-3或PD-L1的细胞的FS18-7-9/84G09治疗随后与NK细胞或补体孵育是否诱导相应的靶细胞的裂解。此外,由于FS18-7-9/84G09是一种双特异性抗体,因此还测试了所述特异性之一的靶点衔接是否影响针对表达其他特异性的靶点的细胞的效应因子功能。

[0404] 理解mAb² FS18-7-9/84G09的效应因子功能对于许多原因是有用的,包括确定降低效应因子功能的突变,例如LALA突变,是否应包括在分子中以保护参与肿瘤杀伤的表达LAG-3的效应T细胞免于FS18-7-9/84G09介导的ADCC和/或CDC。

[0405] 6.1研究设计

[0406] 重组表达LAG-3或PD-L1的Raji细胞用于所有试验中,使用它们的CD20内源表达作为使用利妥昔单抗(Rituximab)的通用版本进行靶向的对照,来展现添加的补体和NK细胞制品独立于目标蛋白质的重组表达的功能活性。在这些实验之前确认靶点表达。

[0407] 为了确定针对LAG-3或PD-L1表达细胞的基础CDC活性,使用LDH释放测定该活性,由底物向荧光染料的转化来测量(Promega的CytoTox-ONE™)。为了测量包括LAG-3表达细胞和PD-L1表达细胞二者的细胞混合物中哪些靶细胞正在被裂解,通过在与mAb²/抗体孵育之后差异化荧光标记的靶细胞的流式细胞术,使用从活细胞中排出的荧光染料来检测死细胞,测量差异CDC。

[0408] 为了确定对LAG-3或PD-L1表达细胞的ADCC活性,使用从冷冻的PBMC分离的NK细胞以及比色法测量的LHD释放(Promega的CytoTox 96)来测量该活性。对于所有这些研究,不同的同种型和Fc结构的利妥昔单抗用作对照。测量ADCC差异的可靠方法是未知的,因此不测量差异ADCC活性。

[0409] 在所有实验中,PD-L1特异性mAb(84G09)和LAG-3特异性mAb(25F7)用作对照。还使用了用作阴性对照或用于产生CDC背景活性的IgG同种型对照(4420)。相应抗体和mAb²(排除25F7)的LALA版本也在CDC和ADCC分析中与IgG1野生型版本进行比较,以确定这一突变对这些效应物功能的影响。

[0410] 6.2材料和方法

[0411] 6.2.1 CDC试验

[0412] 包括利妥昔单抗的所有抗体/mAb²在10个点中1到2倍连续稀释。还制备了在含有最高浓度使用的IgG(4420 LALA)的对照孔。分别重组表达LAG-3或PD-L1的Raji细胞的细胞悬浮液在用于LDH释放试验的无血清培养基中制备,并添加到等体积的制备的抗体/mAb²中。

[0413] 对于基于流式细胞术的CDC试验,制备 5×10^7 个细胞的细胞悬浮液,并在无血清培养基中的0.5 μ M CellTracker深红(CellTracker™ Deep Red,Thermo Fisher,#C34565)或5 μ M CellTracker绿(CellTracker™ Green CM FDA(5-氯甲基荧光素二乙酸酯,Thermo Fisher,#C7025)中重悬浮。在37℃下孵育30分钟后,细胞在无血清培养基中洗涤,并直接添加到含有制备的抗体/mAb²的孔中,或其他差异染色的细胞系等体积组合然后如上所述添加到含有抗体/mAb²的孔中。对于两种试验,在细胞培养条件下孵育30分钟之后,用等体积的无血清培养基中10%的幼兔补体(Baby Rabbit Complement,TEBU-bio,#CL3441)补充

孔。在细胞培养条件下孵育平板4小时。对于LDH释放CDC试验,通过将Triton X 100添加至4420 LALA处理的一半的孔中来产生100%裂解对照,并且根据厂家的说明(CytotoxOne.Promega,G7891)进行Cytotox试验。获得读数后,将来自100%裂解对照的信号设定为100%,并将来自样品孔的信号计算为该水平的百分比。

[0414] 对于基于流式细胞术的CDC试验,在孵育期结束时,将死细胞染料(SYTOX® Blue Dead Cell Stain,Thermo Fisher,#S34857)在PBS中1到500倍稀释,并以等体积补充孔。流式细胞术在基于FSC和SSC的完整细胞群上的Cytoflex流式细胞仪上进行,并检测CellTracker™ Deep Red阳性且CellTracker™ Green CM FDA阳性细胞群的Sytox阳性细胞(通道PB450)的百分比。

[0415] 6.3.2 ADCC试验

[0416] 如先前所描述的测量ADCC(Broussas,Matthieu;Broyer,Lucile;and Goetsch,Liliane.(2013)Evaluation of Antibody-Dependent Cell Cytotoxicity Using Lactate Dehydrogenase (LDH) Measurement in Glycosylation Engineering of Biopharmaceuticals:Methods and Protocols,Methods in Molecular Biology.New York:Springer Science+Business Media.Volume 988,pp 305-317)。简短地,以20比1的比例添加来自人PBMC的原代NK细胞(NK细胞分离试剂盒,Miltenyi Biotec,130-092-657)保持4小时之前,靶细胞与抗体预孵育。根据厂家的说明进行细胞毒性试验(CytoTox 96 Non-Radioactive Cytotoxicity Assay,Promega,G1780)。考虑效应物和靶细胞的自发的裂解,裂解百分比基于100%靶细胞裂解来计算。

[0417] 6.3结果和结论

[0418] 6.3.1 CDC试验

[0419] 通过抗CD20抗体利妥昔单抗靶向PD-L1表达Raji细胞被,当通过通用LDH释放测量CDC时,其导致<60%的最大裂解。抗PD-L1抗体84G09(所述抗PD-L1抗体84G09包含mAb² FS18-7-9/84G09的F(ab)₂部分)和IgG1形式中的FS18-7-9/84G09显示了更高的最大裂解以及更高的裂解效能,估计的半最大剂量约为IgG1形式中的利妥昔单抗所需剂量的一半。这显示了将LAG-3结合位点引入84G09抗体并未改变其关于效能或最大反应的PD-L1靶向活性,因为当比较84G09和FS18-7-9/84G09时两者非常相似。LALA突变的引入导致利妥昔单抗、84G09和FS18-7-9/84G09的最大反应的降低,然而,仅84G09和FS18-7-9/84G09的效能降低。如所预期的,抗LAG-3抗体25F7对表达PD-L1的Raji细胞的细胞活力没有影响,因为这些细胞不表达LAG-3。这些结果在图14A中示出。

[0420] 表达LAG-3的Raji细胞通过抗CD20抗体利妥昔单抗靶向CDC,然而,LAG-3抗体25F7显示甚至更好的效能,估计的半最大剂量约为利妥昔单抗所需剂量的一半。没有其他抗体显示出针对表达LAG-3的Raji细胞的任何CDC活性,包括FS18-7-9/84G09。LALA突变的引入对利妥昔单抗的CDC活性的影响非常有限(图14B)。

[0421] 6.3.2差异CDC试验

[0422] 本发明人研制了采用流式细胞术的差异CDC试验,以区分当用FS18-7-9/84G09或对照抗体处理时哪种靶向表达细胞被裂解。该试验用于确认来自上述基础LDH释放CDC试验的结果。与对活细胞百分比没有影响的IgG同种型对照抗体(4420)相比,利妥昔单抗介导PD-L1和LAG-3表达细胞的活细胞减少和死细胞增加。然而,FS18-7-9/84G09对表达LAG-3的

细胞没有影响,但是非常有效地裂解了表达PD-L1的细胞。类似地,LAG-3特异性抗体25F7和PD-L1抗体84G09的混合物也显示活细胞中的剂量依赖性降低和死细胞的相反的增加,然而,表达LAG-3的细胞的最大裂解仅是超过50%的细胞,但已经达到约1nM的浓度,这是所有测试抗体实现最大裂解的最低剂量。这确认了先前FS18-7-9/84G09的CH3结构域中的LAG-3结合位点不诱导CDC介导的LAG-3表达靶细胞的裂解的发现。此外,这个实验显示LAG-3表达细胞的存在对FS18-7-9/84G09对PD-L1表达细胞的CDC活性没有影响。结果在图15中示出。

[0423] 6.3.3 ADCC试验

[0424] 表达PD-L1的Raji细胞通过抗CD20抗体利妥昔单抗、FS18-7-9/84G09和84G09靶向ADCC,具有非常相似的效力和效能,导致约40%细胞的最大裂解。含有LALA突变的利妥昔单抗和84G09未显示ADCC介导的裂解,且含有LALA突变的FS18-7-9/84G09显示没有或非常低的ADCC介导的PD-L1表达靶细胞的裂解。有和没有LALA突变的LAG-3特异性抗体25F7和同种型对照4420在这项试验中显示没有活性。

[0425] 这些结果显示,将所述LAG-3结合位点引入抗体84G09不改变效能或最大反应中它的PD-L1靶向的ADCC活性,因为二者都与PD-L1特异性抗体84G09非常相似。LALA突变的引入导致ADCC活性的取消(图16A)。

[0426] LAG-3表达Raji细胞通过利妥昔单抗和25F7靶向ADCC介导的裂解,导致约40%的最大裂解。FS18-7-9/84G09还通过ADCC介导LAG-3表达细胞的裂解,具有低得多的效能和效力,仅在2.5nM浓度下达到20%之下的裂解。LALA突变的引入取消了利妥昔单抗和FS18-7-9/84G09的所有ADCC活性。如所预期的,具有和不具有LALA突变的84G09和同种型对照4420在该试验中显示没有ADCC活性,因为这些抗体不结合LAG-3(图16B)。

[0427] 序列表

[0428] Fcab FS18-7-9环区的氨基酸序列

[0429] FS18-7-9 AB环-WDEPWGED (SEQ ID NO:1)

[0430] FS18-7-9 CD环-SNGQPENNY (SEQ ID NO:2)

[0431] FS18-7-9 EF环-PYDRVWPDE (SEQ ID NO:3)

[0432] Fcab FS18-7-9 CH3结构域的核苷酸序列 (SEQ ID NO:4)

GGCCAGCCTCGAGAACCACAGGTGTACACCCTGCCCCATCCTGGGATGAGCCGTGGGGTGAA
GACGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAGCGACATCGCCGTGGAGTGGGAG

[0433] AGCAATGGGCAGCCGGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCC
TTCTTCCTCTACAGCAAGCTCACCGTGCCGTATGATAGGTGGGTTTGCCGGATGAGTTCTCATG
CTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCCGGGT

[0434] Fcab FS18-7-9 CH3结构域的CHO密码子优化的核苷酸序列 (SEQ ID NO:142)

GGCCAGCCCCGGGAACCCCAGGTGTACAACTGCCTCCATCCTGGGATGAGCCCTGGGGCGA
GGATGTGTCTCTGACCTGTCTCGTGAAAGGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAG
AGCAACGGCCAGCCCGAGAACAACACTACAAGACCACCCCCCTGTGCTGGACTCCGACGGCTCA
TTCTTCCTGTACAGCAAGCTGACAGTGCCCTACGACAGATGGGTGTGGCCCGACGAGTTCTCCT
GCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCCCTGAGCCCCG
GC

[0436] Fcab FS18-7-9 CH3结构域的氨基酸序列 (SEQ ID NO:5)

GQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFL
YSKLTVPYDRWWPDEFSCSVMEALHNHYTQKSLSLSPG

- [0438] 包含C-末端赖氨酸的Fcab FS18-7-9 CH3结构域的氨基酸序列 (SEQ ID NO:135)
GQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFL
- [0439] YSKLTPYDRWWPDEFSCSV MHEALHNHYTQKSLSLSPG
- [0440] 包括LALA突变(下划线的)Fcab FS18-7-9 CH2和CH3结构域的氨基酸序列 (SEQ ID NO:6)
APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
- [0441] NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGED
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTPYDRWWPDEFSCSV M
HEALHNHYTQKSLSLSPG
- [0442] 没有LALA突变的Fcab FS18-7-9 CH2和CH3结构域的氨基酸序列 (SEQ ID NO:7)
APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
- [0443] STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTPYDRWWPDEFSCSV MHE
ALHNHYTQKSLSLSPG
- [0444] Fcab FS18-7-32环区的氨基酸序列
- [0445] FS18-7-32 AB环-WDEPWGED (SEQ ID NO:1)
- [0446] FS18-7-32 CD环-SNGQPENNY (SEQ ID NO:8)
- [0447] FS18-7-32 EF环-PYDRWWPDE (SEQ ID NO:3)
- [0448] Fcab FS18-7-32 CH3结构域的核苷酸序列 (SEQ ID NO:9)
GGCCAGCCTCGAGAACCACAGGTGTACACCCTGCCCCATCCTGGGATGAGCCGTGGGGTGAA
GACGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAGCGAAATCGCCGTGGAGTGGGAG
- [0449] AGCAATGGGCAGCCGGAGAACAAC TACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCC
TTCTTCCTCTACAGCAAGCTCACCGTGCCGTATGATAGGTGGGTTTGGCCGGATGAGTTCTCATG
CTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCCGGGT
- [0450] Fcab FS18-7-32 CH3结构域的氨基酸序列 (SEQ ID NO:10)
GQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFL
- [0451] YSKLTPYDRWWPDEFSCSV MHEALHNHYTQKSLSLSPG
- [0452] 包括LALA突变的(下划线的)Fcab FS18-7-32 CH2和CH3结构域的氨基酸序列 (SEQ ID NO:11)
APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
- [0453] NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGED
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTPYDRWWPDEFSCSV M
HEALHNHYTQKSLSLSPG
- [0454] 没有LALA突变的Fcab FS18-7-32 CH2和CH3结构域的氨基酸序列 (SEQ ID NO:12)
APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
- [0455] STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTPYDRWWPDEFSCSV MHE
ALHNHYTQKSLSLSPG
- [0456] Fcab FS18-7-33环区的氨基酸序列
- [0457] FS18-7-33 AB环WDEPWGED (SEQ ID NO:1)
- [0458] FS18-7-33 CD环-SNGQPEDNY (SEQ ID NO:13)
- [0459] FS18-7-33 EF环-PYDRWWPDE (SEQ ID NO:3)

- [0460] Fcab FS18-7-33 CH3结构域的核苷酸序列 (SEQ ID NO:14)
GGCCAGCCTCGAGAACCACAGGTGTACACCCTGCCCCATCCTGGGATGAGCCGTGGGGTGAA
GACGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAGCGACATCGCCGTGGAGTGGGAG
- [0461] AGCAATGGGCAGCCGGAGGACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCC
TTCTTCCTCTACAGCAAGCTCACCGTGCCGTATGATAGGTGGGTTTGGCCGGATGAGTTCTCATG
CTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCCGGGT
- [0462] Fcab FS18-7-33 CH3结构域的氨基酸序列 (SEQ ID NO:15)
GQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESNGQPEDNYKTTPVLDSGDSFFL
- [0463] YSKLTPYDRWWPDEFSCSV MHEALHNHYTQKSLSLSPG
- [0464] 包括LALA突变的 (下划线的) Fcab FS18-7-33 CH2和CH3结构域的氨基酸序列 (SEQ ID NO:16)
APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGED
- [0465] VSLTCLVKGFYPSDIAVEWESNGQPEDNYKTTPVLDSGDSFFLYSKLTPYDRWWPDEFSCSV M
HEALHNHYTQKSLSLSPG
- [0466] 没有LALA突变的 Fcab FS18-7-33 CH2和CH3结构域的氨基酸序列 (SEQ ID NO:17)
APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
- [0467] STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVS
LTCLVKGFYPSDIAVEWESNGQPEDNYKTTPVLDSGDSFFLYSKLTPYDRWWPDEFSCSV MHE
ALHNHYTQKSLSLSPG
- [0468] Fcab FS18-7-36环区的氨基酸序列
- [0469] FS18-7-36 AB环WDEPWGED (SEQ ID NO:1)
- [0470] FS18-7-36 CD环-SNGQPENNY (SEQ ID NO:18)
- [0471] FS18-7-36 EF环-PYDRWWPDE (SEQ ID NO:3)
- [0472] Fcab FS18-7-36 CH3结构域的核苷酸序列 (SEQ ID NO:19)
GGCCAGCCTCGAGAACCACAGGTGTACACCCTGCCCCATCCTGGGATGAGCCGTGGGGTGAA
GACGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAGCGACATCGCCGTGGAGTGGGAG
AGCAATGGGCAGCCGGAGGACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCC
- [0473] TACTTCCTCTACAGCAAGCTCACCGTGCCGTATGATAGGTGGGTTTGGCCGGATGAGTTCTCAT
GCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCCGGG
T
- [0474] Fcab FS18-7-36CH3结构域的氨基酸序列 (SEQ ID NO:20)
GQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSYFL
- [0475] YSKLTPYDRWWPDEFSCSV MHEALHNHYTQKSLSLSPG
- [0476] 包括LALA突变的 (下划线的) Fcab FS18-7-36 CH2和CH3结构域的CH2+CH3的氨基
酸序列 (SEQ ID NO:21)
APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGED
- [0477] VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSYFLYSKLTPYDRWWPDEFSCSV M
HEALHNHYTQKSLSLSPG
- [0478] 没有LALA突变的 Fcab FS18-7-36 CH2和CH3结构域的氨基酸序列 (SEQ ID NO:22)

- [0479] APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGYSFLYSKLTVPYDRWWPDEFSCSVMHE
ALHNHYTQKSLSLSPG
- [0480] Fcab FS18-7-58环区的氨基酸序列
- [0481] FS18-7-58 AB环-WDEPWGED (SEQ ID NO:1)
- [0482] FS18-7-58 CD环-SNGYPEIEF (SEQ ID NO:23)
- [0483] FS18-7-58 EF环-PYDRWWPDE (SEQ ID NO:3)
- [0484] FS18-7-58CH3结构域的核苷酸序列 (SEQ ID NO:24)
GGCCAGCCTCGAGAACCACAGGTGTACACCCTGCCCCATCCTGGGATGAGCCGTGGGGTGAA
GACGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAGCGACATCGCCGTGGAGTGGGAG
- [0485] AGCAATGGGTATCCAGAAATCGAATTCAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT
TCTTCCTCTACAGCAAGCTCACCGTGCCTTATGATAGGTGGGTTTGGCCGGATGAGTTCTCATGC
TCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCCGGGT
- [0486] FS18-7-58 CH3结构域的氨基酸序列 (SEQ ID NO:25)
GQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESNGYPEIEFKTTTPVLDSGSFFLY
- [0487] SKLTVPYDRWWPDEFSCSVMHEALHNHYTQKSLSLSPG
- [0488] 包括LALA突变(下划线的) Fcab FS18-7-58 CH2和CH3结构域的氨基酸序列 (SEQ ID NO:26)
APEAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGED
VSLTCLVKGFYPSDIAVEWESNGYPEIEFKTTTPVLDSGSFFLYSKLTVPYDRWWPDEFSCSVMH
EALHNHYTQKSLSLSPG
- [0490] 没有LALA突变的Fcab FS18-7-58 CH2和CH3结构域的氨基酸序列 (SEQ ID NO:27)
APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVVS
- [0491] LTCLVKGFYPSDIAVEWESNGYPEIEFKTTTPVLDSGSFFLYSKLTVPYDRWWPDEFSCSVMHEA
LHNHYTQKSLSLSPG
- [0492] Fcab FS18-7-62环区的氨基酸序列
- [0493] FS18-7-62 AB环-WDEPWGED (SEQ ID NO:1)
- [0494] FS18-7-62 CD环-SNGIPEWNY (SEQ ID NO:28)
- [0495] FS18-7-62 EF环-PYDRWWPDE (SEQ ID NO:3)
- [0496] FS18-7-62 CH3结构域的核苷酸序列 (SEQ ID NO:29)
GGCCAGCCTCGAGAACCACAGGTGTACACCCTGCCCCATCCTGGGATGAGCCGTGGGGTGAA
GACGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAGCGACATCGCCGTGGAGTGGGAG
- [0497] AGCAATGGGATCCCAGAAATGGAATAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT
TCTTCCTCTACAGCAAGCTCACCGTGCCGTATGATAGGTGGGTTTGGCCGGATGAGTTCTCATG
CTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCCGGGT
- [0498] FS18-7-62 CH3结构域的氨基酸序列 (SEQ ID NO:30)
GQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESNGIPEWNYKTTTPVLDSGSFFL
- [0499] YSKLTVPYDRWWPDEFSCSVMHEALHNHYTQKSLSLSPG
- [0500] 包括LALA突变的(下划线的) Fcab FS18-7-62 CH2和CH3结构域的氨基酸序列 (SEQ

ID NO:31)

[0501] APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGED
VSLTCLVKGFYPSDIAVEWESNGIPEWNYKTTTPVLDSGDSFFLYSKLTPYDRWWPDEFSCSVMH
EALHNHYTQKSLSLSPG

[0502] 没有LALA突变的Fcab FS18-7-62 CH2和CH3结构域的氨基酸序列 (SEQ ID NO:32)

[0503] APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVS
LTCLVKGFYPSDIAVEWESNGIPEWNYKTTTPVLDSGDSFFLYSKLTPYDRWWPDEFSCSVMHEA
LHNHYTQKSLSLSPG

[0504] Fcab FS18-7-65环区的氨基酸序列

[0505] FS18-7-65 AB环-WDEPWGED (SEQ ID NO:1)

[0506] FS18-7-65 CD环-SNGYAEYNY (SEQ ID NO:33)

[0507] FS18-7-65 EF环-PYDRWWPDE (SEQ ID NO:3)

[0508] FS18-7-65 CH3结构域的核苷酸序列 (SEQ ID NO:34)

GGCCAGCCTCGAGAACCACAGGTGTACACCCTGCCCCATCCTGGGATGAGCCGTGGGGTGAA
GACGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAG
[0509] AGCAATGGGTATGCAGAATATAACTATAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT
TCTTCCTCTACAGCAAGCTCACCGTGCCGTATGATAGGTGGGTTTGGCCGGATGAGTTCTCATG
CTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCCGGGT

[0510] FS18-7-65 CH3结构域的氨基酸序列 (SEQ ID NO:35)

[0511] GQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESNGYAEYNYKTTTPVLDSGDSFFL
YSKLTVPYDRWWPDEFSCSVMHEALHNHYTQKSLSLSPG

[0512] 包括LALA突变的(下划线的)Fcab FS18-7-65 CH2和CH3结构域的氨基酸序列 (SEQ

ID NO:36)

[0513] APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGED
VSLTCLVKGFYPSDIAVEWESNGYAEYNYKTTTPVLDSGDSFFLYSKLTPYDRWWPDEFSCSVM
HEALHNHYTQKSLSLSPG

[0514] 没有LALA突变的Fcab FS18-7-65 CH2和CH3结构域的氨基酸序列 (SEQ ID NO:37)

[0515] APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVS
LTCLVKGFYPSDIAVEWESNGYAEYNYKTTTPVLDSGDSFFLYSKLTPYDRWWPDEFSCSVMHE
ALHNHYTQKSLSLSPG

[0516] Fcab FS18-7-78环区的氨基酸序列

[0517] FS18-7-78 AB环-WDEPWGED (SEQ ID NO:1)

[0518] FS18-7-78 CD环-SNGYKEENY (SEQ ID NO:38)

[0519] FS18-7-78 EF环-PYDRWWPDE (SEQ ID NO:3)

[0520] FS18-7-78 CH3结构域的核苷酸序列 (SEQ ID NO:39)

- GGCCAGCCTCGAGAACCACAGGTGTACACCCTGCCCCATCCTGGGATGAGCCGTGGGGTGAA
GACGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAG
- [0521] AGCAATGGGTATAAAGAAGAAAACCTATAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT
TCTTCCTCTACAGCAAGCTCACCGTGCCGTATGATAGGTGGGTTTGGCCGGATGAGTTCTCATG
CTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCCGGGT
- [0522] FS18-7-78 CH3结构域的氨基酸序列 (SEQ ID NO:40)
GQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESNGYKEENYKTPPVLDSDGSFFL
- [0523] YSKLTPYDRWWPDEFSCSVMHEALHNHYTQKSLSLSPG
- [0524] 包括LALA突变的 (下划线的)Fcab FS18-7-78 CH2和CH3结构域的氨基酸序列 (SEQ ID NO:41)
APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGED
- [0525] VSLTCLVKGFYPSDIAVEWESNGYKEENYKTPPVLDSDGSFFLYSKLTPYDRWWPDEFSCSVM
HEALHNHYTQKSLSLSPG
- [0526] 没有LALA突变的Fcab FS18-7-78 CH2和CH3结构域的氨基酸序列 (SEQ ID NO:42)
APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVS
- [0527] LTCLVKGFYPSDIAVEWESNGYKEENYKTPPVLDSDGSFFLYSKLTPYDRWWPDEFSCSVMHE
ALHNHYTQKSLSLSPG
- [0528] Fcab FS18-7-88环区的氨基酸序列
- [0529] FS18-7-88 AB环-WDEPWGED (SEQ ID NO:1)
- [0530] FS18-7-88 CD环-SNGVPELV (SEQ ID NO:43)
- [0531] FS18-7-88 EF环-PYDRWWPDE (SEQ ID NO:3)
- [0532] FS18-7-88 CH3结构域的核苷酸序列 (SEQ ID NO:44)
APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVS
- [0533] LTCLVKGFYPSDIAVEWESNGYKEENYKTPPVLDSDGSFFLYSKLTPYDRWWPDEFSCSVMHE
ALHNHYTQKSLSLSPG
- [0534] FS18-7-88 CH3结构域的氨基酸序列 (SEQ ID NO:45)
GQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESNGVPELVNKTTPPVLDSDGSFFL
- [0535] YSKLTPYDRWWPDEFSCSVMHEALHNHYTQKSLSLSPG
- [0536] 包括LALA突变的 (下划线的)Fcab FS18-7-88 CH2和CH3结构域的氨基酸序列 (SEQ ID NO:46)
APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGED
- [0537] VSLTCLVKGFYPSDIAVEWESNGVPELVNKTTPPVLDSDGSFFLYSKLTPYDRWWPDEFSCSVMH
EALHNHYTQKSLSLSPG
- [0538] 没有LALA突变的Fcab FS18-7-88 CH2和CH3结构域的氨基酸序列 (SEQ ID NO:47)
APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVS
- [0539] LTCLVKGFYPSDIAVEWESNGVPELVNKTTPPVLDSDGSFFLYSKLTPYDRWWPDEFSCSVMHEA
LHNHYTQKSLSLSPG
- [0540] Fcab FS18-7-95环区的氨基酸序列

- [0541] FS18-7-95 AB环-WDEPWGED (SEQ ID NO:1)
- [0542] FS18-7-95 CD环-SNGYQEDNY (SEQ ID NO:48)
- [0543] FS18-7-95 EF环-PYDRWWPDE (SEQ ID NO:3)
- [0544] FS18-7-95 CH3结构域的核苷酸序列 (SEQ ID NO:49)
GGCCAGCCTCGAGAACCACAGGTGTACACCCTGCCCCATCCTGGGATGAGCCGTGGGGTGAA
GACGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAG
- [0545] AGCAATGGGTATCAGGAAGATAACTATAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCT
TCTTCCTCTACAGCAAGCTCACCGTGCCGTATGATAGGTGGGTTTGGCCGGATGAGTTCTCATG
CTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCCGGGT
- [0546] FS18-7-95 CH3结构域的氨基酸序列 (SEQ ID NO:50)
GQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESNGYQEDNYKTPPVLDSDGSFFL
- [0547] YSKLTPYDRWWPDEFSCSVMHEALHNHYTQKSLSLSPG
- [0548] 包括LALA突变的 (下划线的) Fcab FS18-7-95 CH2和CH3结构域的氨基酸序列 (SEQ ID NO:51)
APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGED
- [0549] VSLTCLVKGFYPSDIAVEWESNGYQEDNYKTPPVLDSDGSFFLYSKLTPYDRWWPDEFSCSVM
HEALHNHYTQKSLSLSPG
- [0550] 没有LALA突变的Fcab FS18-7-95 CH2和CH3结构域的氨基酸序列 (SEQ ID NO:52)
APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
- [0551] STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVS
LTCLVKGFYPSDIAVEWESNGYQEDNYKTPPVLDSDGSFFLYSKLTPYDRWWPDEFSCSVMHE
ALHNHYTQKSLSLSPG
- [0552] 野生型人类IgG1 CH2结构域的氨基酸序列 (SEQ ID NO:53)
APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
- [0553] STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
- [0554] 包含“LALA突变”的 (下划线的) 人IgG1CH2结构域的氨基酸序列 (SEQ ID NO:54)
APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
- [0555] NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
- [0556] 没有LALA突变的“野生型”Fcab CH2和CH3结构域的氨基酸序列 (SEQ ID NO:55)
APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
- [0557] STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPG
- [0558] 包括LALA突变的 (下划线的) “野生型”Fcab CH2和CH3结构域的氨基酸序列 (SEQ ID NO:56)
APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY
- [0559] NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH
EALHNHYTQKSLSLSPG
- [0560] 人类IgG1绞链区的氨基酸序列 (SEQ ID NO:57)
- [0561] EPKSCDKTHTCPPCP

- [0562] 人类IgG1截短的绞链区的氨基酸序列(SEQ ID NO:58)
- [0563] TCPPCP
- [0564] 包括LALA突变的(下划线的)抗小鼠LAG-3 Fcab FS18-7-108-29的氨基酸序列(SEQ ID NO:59)
- [0565] CH3结构域以斜体字显示。CH3结构域的AB、CD和EF环以粗体和下划线显示。
TCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP
REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS**WDEP**
[0566] **WGEDVSLTCLVKGFYPSDIVVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVPFERWMWPDEFS**
CSVMHEALHNHYTQKSLSLSPG
- [0567] 没有LAL突变的抗小鼠LAG-3 Fcab FS18-7-108-29的氨基酸序列(SEQ ID NO:60)
- [0568] CH3结构域以斜体字显示。CH3结构域的AB、CD和EF环以粗体和下划线显示。
TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP
REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS**WDEP**
[0569] **WGEDVSLTCLVKGFYPSDIVVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVPFERWMWPDEFS**
CSVMHEALHNHYTQKSLSLSPG
- [0570] 包括LALA突变的(下划线的)抗小鼠LAG-3 Fcab FS18-7-108-35的氨基酸序列(SEQ ID NO:61)
- [0571] CH3结构域以斜体字显示。AB、CD和EF环区以粗体和下划线显示。
TCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP
REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS**WDEP**
[0572] **WGEDVSLTCLVKGFYPSDISVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVPFERWMWPDEFS**
CSVMHEALHNHYTQKSLSLSPG
- [0573] 没有LALA突变的抗小鼠LAG-3 Fcab FS18-7-108-35的氨基酸序列(SEQ ID NO:62)
- [0574] CH3结构域以斜体字显示。AB、CD和EF环区以粗体和下划线显示。
TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP
REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS**WDEP**
[0575] **WGEDVSLTCLVKGFYPSDISVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVPFERWMWPDEFS**
CSVMHEALHNHYTQKSLSLSPG
- [0576] 包括LALA突变的抗人LAG-3/FITC mAb² FS18-7-9/4420的重链的氨基酸序列(SEQ ID NO:63)
- [0577] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是粗体的。
EVKLDDETGGGLVQPGRPMKLSCVASGFTFSDYWMNWRQSPEKGLEWVAQIRNKPYNYETYYSDS
VKGRFTISRDDSKSSVYLQMNNLRVEDMGIYYCTGSYYGMDYWGQGTSTVSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTWSNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT
[0578] YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
APIEKTISKAKGQPREPQVYTLPPS**WDEPWGEDVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP**
VLDSDGSFFLYSKLTVPYDRWVWPDEFSCSMHEALHNHYTQKSLSLSPG
- [0579] 没有LALA突变的抗人LAG-3/FITC mAb² FS18-7-9/4420的重链的氨基酸序列(SEQ

ID NO:64)

[0580] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。

EVKLDETGGGLVQPGRPMKLSCVASGFTFSDYWMNWRQSPEKGLEWVAQIRNKPYNYETYYSDS
VKGRFTISRDDSKSSVYLQMNLRVEDMGIYYCTGSYYGMDYWGQGTSTVTSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT
[0581] YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVD
VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPS**WDEPWGED**VSLTCLVKGFYPSDIAVEWES**SNQGPNENYK**TTTPVL
DSDGSFFLYSKLTV**PYDRWWWPDEF**SCSVMEALHNHYTQKSLSLSPG

[0582] 包括LALA突变的抗人LAG-3/FITC mAb² FS18-7-32/4420的重链的氨基酸序列
(SEQ ID NO:65)

[0583] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是粗体的。

EVKLDETGGGLVQPGRPMKLSCVASGFTFSDYWMNWRQSPEKGLEWVAQIRNKPYNYETYYSDS
VKGRFTISRDDSKSSVYLQMNLRVEDMGIYYCTGSYYGMDYWGQGTSTVTSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT
[0584] YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**A**AGGPSVFLFPPKPKDTLMISRTPEVTCVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
APIEKTISKAKGQPREPQVYTLPPS**WDEPWGED**VSLTCLVKGFYPS**E**IAVEWES**SNQGPNENYK**TTTPV
VLDSGSFFLYSKLTV**PYDRWWWPDEF**SCSVMEALHNHYTQKSLSLSPG

[0585] 没有LALA突变的抗人LAG-3/FITC mAb² FS18-7-32/4420的重链的氨基酸序列
(SEQ ID NO:66)

[0586] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。

EVKLDETGGGLVQPGRPMKLSCVASGFTFSDYWMNWRQSPEKGLEWVAQIRNKPYNYETYYSDS
VKGRFTISRDDSKSSVYLQMNLRVEDMGIYYCTGSYYGMDYWGQGTSTVTSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT
[0587] YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVD
VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPS**WDEPWGED**VSLTCLVKGFYPS**E**IAVEWES**SNQGPNENYK**TTTPVL
DSDGSFFLYSKLTV**PYDRWWWPDEF**SCSVMEALHNHYTQKSLSLSPG

[0588] 包括LALA突变的抗人LAG-3/FITC mAb² FS18-7-33/4420的重链的氨基酸序列
(SEQ ID NO:67)

[0589] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是粗体的。

EVKLDETGGGLVQPGRPMKLSCVASGFTFSDYWMNWRQSPEKGLEWVAQIRNKPYNYETYYSDS
VKGRFTISRDDSKSSVYLQMNLRVEDMGIYYCTGSYYGMDYWGQGTSTVTSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT
[0590] YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**A**AGGPSVFLFPPKPKDTLMISRTPEVTCVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
APIEKTISKAKGQPREPQVYTLPPS**WDEPWGED**VSLTCLVKGFYPSDIAVEWES**SNQGPEDNYK**TTTPV
VLDSGSFFLYSKLTV**PYDRWWWPDEF**SCSVMEALHNHYTQKSLSLSPG

[0591] 没有LALA突变的抗人LAG-3/FITC mAb² FS18-7-33/4420的重链的氨基酸序列 (SEQ ID NO:68)

[0592] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。

EVKLD~~ETGGGLVQPGRPMKLSCVAS~~GFTFSDYWMNWRQS~~PEKGLEW~~WAQIRNKPYNYETYSDS
VKGRFTISRDDSKSSVYLQMNNLRVEDMGIYYCTGSYYGMDYWGQGTSVTVSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT
[0593] YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVD
VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESSNQGPEDNYKTTTPVL
DSDGSFFLYSKLTVPYDRWWPDEFSCSVMEALHNHYTQKSLSLSPG

[0594] 包括LALA突变的抗人LAG-3/FITC mAb² FS18-7-36/4420的重链的氨基酸序列 (SEQ ID NO:69)

[0595] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是粗体的。

EVKLD~~ETGGGLVQPGRPMKLSCVAS~~GFTFSDYWMNWRQS~~PEKGLEW~~WAQIRNKPYNYETYSDS
VKGRFTISRDDSKSSVYLQMNNLRVEDMGIYYCTGSYYGMDYWGQGTSVTVSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT

[0596] YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAEAGGPSVFLFPPKPKDTLMISRTPEVTCVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
APIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESSNQGPENNYKTTTP
VLDSGDSYFLYSKLTVPYDRWWPDEFSCSVMEALHNHYTQKSLSLSPG

[0597] 没有LALA突变的抗人LAG-3/FITC mAb² FS18-7-36/4420的重链的氨基酸序列 (SEQ ID NO:70)

[0598] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。

EVKLD~~ETGGGLVQPGRPMKLSCVAS~~GFTFSDYWMNWRQS~~PEKGLEW~~WAQIRNKPYNYETYSDS
VKGRFTISRDDSKSSVYLQMNNLRVEDMGIYYCTGSYYGMDYWGQGTSVTVSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT

[0599] YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVD
VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESSNQGPENNYKTTTPVL
DSDGSYFLYSKLTVPYDRWWPDEFSCSVMEALHNHYTQKSLSLSPG

[0600] 包括LALA突变的抗人LAG-3/FITC mAb² FS18-7-58/4420的重链的氨基酸序列 (SEQ ID NO:71)

[0601] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是粗体的。

EVKLD~~ETGGGLVQPGRPMKLSCVAS~~GFTFSDYWMNWRQS~~PEKGLEW~~WAQIRNKPYNYETYSDS
VKGRFTISRDDSKSSVYLQMNNLRVEDMGIYYCTGSYYGMDYWGQGTSVTVSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT

[0602] YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAEAGGPSVFLFPPKPKDTLMISRTPEVTCVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
APIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESSNGYPEIEFKTTTPV
LDSDGSFFLYSKLTVPYDRWWPDEFSCSVMEALHNHYTQKSLSLSPG

[0603] 没有LALA突变的抗人LAG-3/FITC mAb² FS18-7-58/4420的重链的氨基酸序列 (SEQ ID NO:72)

[0604] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。

EVKLD~~ETGGGLVQPGRPMKLSCVAS~~GFTFSDYWMNWRQSPEKGLEW~~WAQIRNKPYNYET~~YYSDS
VKGRFTISR~~DDSKSSVYLQMN~~NLRVEDMGIYYCTGSYYGMDYWGQTSVTSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVT~~SVWNSGALTSGVHTFPAVLQSSGLYSLSSV~~TVPS~~SSLGTQT~~
YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVD
VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESSNGYPEIEFKTTTPVLD
SDGSFFLYSKLTVPYDRWWPDEFSCSVMEALHNHYTQKSLSLSPG

[0606] 包括LALA突变的抗人LAG-3/FITC mAb² FS18-7-62/4420的重链的氨基酸序列 (SEQ ID NO:73)

[0607] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是粗体的。

EVKLD~~ETGGGLVQPGRPMKLSCVAS~~GFTFSDYWMNWRQSPEKGLEW~~WAQIRNKPYNYET~~YYSDS
VKGRFTISR~~DDSKSSVYLQMN~~NLRVEDMGIYYCTGSYYGMDYWGQTSVTSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVT~~SVWNSGALTSGVHTFPAVLQSSGLYSLSSV~~TVPS~~SSLGTQT~~
YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVW
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
APIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESNGIPEWNYKTTPP
VLDSGDGSFFLYSKLTVPYDRWWPDEFSCSVMEALHNHYTQKSLSLSPG

[0609] 没有LALA突变的抗人LAG-3/FITC mAb² FS18-7-62/4420的重链的氨基酸序列 (SEQ ID NO:74)

[0610] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。

EVKLD~~ETGGGLVQPGRPMKLSCVAS~~GFTFSDYWMNWRQSPEKGLEW~~WAQIRNKPYNYET~~YYSDS
VKGRFTISR~~DDSKSSVYLQMN~~NLRVEDMGIYYCTGSYYGMDYWGQTSVTSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVT~~SVWNSGALTSGVHTFPAVLQSSGLYSLSSV~~TVPS~~SSLGTQT~~
YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVD
VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESNGIPEWNYKTTPPVL
DSDGSFFLYSKLTVPYDRWWPDEFSCSVMEALHNHYTQKSLSLSPG

[0612] 包括LALA突变的抗人LAG-3/FITC mAb² FS18-7-65/4420的重链的氨基酸序列 (SEQ ID NO:75)

[0613] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是粗体的。

EVKLD~~ETGGGLVQPGRPMKLSCVAS~~GFTFSDYWMNWRQSPEKGLEW~~WAQIRNKPYNYET~~YYSDS
VKGRFTISR~~DDSKSSVYLQMN~~NLRVEDMGIYYCTGSYYGMDYWGQTSVTSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVT~~SVWNSGALTSGVHTFPAVLQSSGLYSLSSV~~TVPS~~SSLGTQT~~
YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVW
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
APIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESSNGYAEYNYKTTTPP
VLDSGDGSFFLYSKLTVPYDRWWPDEFSCSVMEALHNHYTQKSLSLSPG

[0615] 没有LALA突变的抗人LAG-3/FITC mAb² FS18-7-65/4420的重链的氨基酸序列
(SEQ ID NO:76)

[0616] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。

EVKLD~~ETGGGLVQPGRPMKLSCVAS~~GFTFSDYWMNWRQSPEKGLEWWQIRNKPNYETYYSDS
VKGRFTISRDDSKSSVYLQMNNLRVEDMGIYYCTGSYYGMDYWGQGTSVTVSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT
YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVD
VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESSNGYAEYNYKTPPVL
DSDGSFFLYSKLTVPYDRWWPDEFSCSVMEALHNHYTQKSLSLSPG

[0618] 包括LALA突变的抗人LAG-3/FITC mAb² FS18-7-78/4420的重链的氨基酸序列
(SEQ ID NO:77)

[0619] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是粗体的。

EVKLD~~ETGGGLVQPGRPMKLSCVAS~~GFTFSDYWMNWRQSPEKGLEWWQIRNKPNYETYYSDS
VKGRFTISRDDSKSSVYLQMNNLRVEDMGIYYCTGSYYGMDYWGQGTSVTVSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT
YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
APIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESSNGYKEENYKTPPV
VLDSGDGSFFLYSKLTVPYDRWWPDEFSCSVMEALHNHYTQKSLSLSPG

[0621] 没有LALA突变的抗人LAG-3/FITC mAb² FS18-7-78/4420的重链的氨基酸序列
(SEQ ID NO:78)

[0622] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。

EVKLD~~ETGGGLVQPGRPMKLSCVAS~~GFTFSDYWMNWRQSPEKGLEWWQIRNKPNYETYYSDS
VKGRFTISRDDSKSSVYLQMNNLRVEDMGIYYCTGSYYGMDYWGQGTSVTVSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT
YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVD
VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESSNGYKEENYKTPPVL
DSDGSFFLYSKLTVPYDRWWPDEFSCSVMEALHNHYTQKSLSLSPG

[0624] 包括LALA突变的抗人LAG-3/FITC mAb² FS18-7-88/4420的重链的氨基酸序列
(SEQ ID NO:79)

[0625] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是粗体的。

EVKLD~~ETGGGLVQPGRPMKLSCVAS~~GFTFSDYWMNWRQSPEKGLEWWQIRNKPNYETYYSDS
VKGRFTISRDDSKSSVYLQMNNLRVEDMGIYYCTGSYYGMDYWGQGTSVTVSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT
YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
APIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESSNGVPELNVKTPPV
VLDSGDGSFFLYSKLTVPYDRWWPDEFSCSVMEALHNHYTQKSLSLSPG

[0627] 没有LALA突变的抗人LAG-3/FITC mAb² FS18-7-88/4420的重链的氨基酸序列 (SEQ ID NO:80)

[0628] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。

EVKLD~~ETGGGLVQPGRPMKLSCVAS~~GFTFSDYWMNWRQS~~PEKGLEW~~WAQIRNKPYNYETYSDS
VKGRFTISRDDSKSSVYLQMNNLRVEDMGIYYCTGSYYGMDYWGQTSVTSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT
YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD
VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESSNGVPELNVKTPPVL
DSDGSFFLYSKLTVPYDRWWPDEFSCSVMEALHNHYTQKSLSLSPG

[0630] 包括LALA突变的抗人LAG-3/FITC mAb² FS18-7-95/4420的重链的氨基酸序列 (SEQ ID NO:81)

[0631] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是粗体的。

EVKLD~~ETGGGLVQPGRPMKLSCVAS~~GFTFSDYWMNWRQS~~PEKGLEW~~WAQIRNKPYNYETYSDS
VKGRFTISRDDSKSSVYLQMNNLRVEDMGIYYCTGSYYGMDYWGQTSVTSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT
YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAEAGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
APIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESSNGYQEDNYKTPPV
VLDSGDSFFLYSKLTVPYDRWWPDEFSCSVMEALHNHYTQKSLSLSPG

[0633] 没有LALA突变的抗人LAG-3/FITC mAb² FS18-7-95/4420的重链的氨基酸序列 (SEQ ID NO:82)

[0634] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。

EVKLD~~ETGGGLVQPGRPMKLSCVAS~~GFTFSDYWMNWRQS~~PEKGLEW~~WAQIRNKPYNYETYSDS
VKGRFTISRDDSKSSVYLQMNNLRVEDMGIYYCTGSYYGMDYWGQTSVTSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT
YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD
VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESSNGYQEDNYKTPPVL
DSDGSFFLYSKLTVPYDRWWPDEFSCSVMEALHNHYTQKSLSLSPG

[0636] 包括LALA突变的抗FITC mAb 4420的重链的氨基酸序列 (SEQ ID NO:83)

[0637] CDR的位置是下划线的。LALA突变的位置是粗体的。

EVKLD~~ETGGGLVQPGRPMKLSCVAS~~GFTFSDYWMNWRQS~~PEKGLEW~~WAQIRNKPYNYETYSDS
VKGRFTISRDDSKSSVYLQMNNLRVEDMGIYYCTGSYYGMDYWGQTSVTSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT
YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAEAGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPV
LDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG

[0639] 没有LALA突变的抗FITC mAb 4420的重链的氨基酸序列 (SEQ ID NO:84)

[0640] CDR的位置是下划线的。

- EVKLDETGGGLVQPGRPMKLSCVASGFTFSDYWMNWVRQSPEKGLEWVAQIRNKPYNYETYSDS
VKGRFTISRDDSKSSVYLQMNLRVEDMGIYYCTGSYYGMDYWGQGTSTVTSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT
[0641] YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVD
VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLD
SDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPG
- [0642] 抗FITC mAb 4420轻链的氨基酸序列 (SEQ ID NO:85)
- [0643] CDR的位置是下划线的。
DVVMTQTPLSLPVSLGDQASISCRSSQSLVHSNGNTYLRWYLQKPGQSPKVLIIYKVSNRFSGVPDRF
SGSGSGTDFTLKISRVEAEDLGVYFCSQSTHVPWTFGGGTKEIKRTVAAPSVFIFPPSDEQLKSGTA
[0644] SVVCLLNFPYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV
THQGLSSPVTKSFNRGEC
- [0645] 抗PD-L1抗体84G09的CDR的氨基酸序列 (根据IMGT)
- | | | |
|--------------|----------------|-----------------|
| HCDR1 | GFTFDDYA | (SEQ ID NO: 86) |
| HCDR2 | ISWKSNI | (SEQ ID NO: 87) |
| HCDR3 | ARDITGSGSYGWFD | (SEQ ID NO: 88) |
| [0646] LCDR1 | QSISSY | (SEQ ID NO: 89) |
| LCDR2 | VAS | (SEQ ID NO: 90) |
| LCDR3 | QQSYSNPIT | (SEQ ID NO: 91) |
- [0647] 抗PD-L1抗体84G09的CDR的氨基酸序列 (根据Kabat)
- | | | |
|--------------|-------------------|------------------|
| HCDR1 | DYAMH | (SEQ ID NO: 136) |
| HCDR2 | GISWKSNIIGYADSVKG | (SEQ ID NO: 137) |
| HCDR3 | DITGSGSYGWFD | (SEQ ID NO: 138) |
| [0648] LCDR1 | RASQSISSYLN | (SEQ ID NO: 139) |
| LCDR2 | VASSLQS | (SEQ ID NO: 140) |
| LCDR3 | QQSYSNPIT | (SEQ ID NO: 141) |
- [0649] 抗PD-L1抗体84G09 VH结构域的氨基酸序列 (SEQ ID NO:92)
- [0650] EVQLVESGGGLVQGRSLRLSCAASGFTFDDYAMHWVRQTPGKGLEWWSGISWKSNIIGYADSVKG
RFTISRDNKNSLYLQMNSLRAEDTALYYCARDITGSGSYGWFDWPWGQGLTVTVSS
- [0651] 抗PD-L1抗体84G09 VL结构域的氨基酸序列 (SEQ ID NO:93)
- [0652] DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKPLIYVASSLQSGVPSSFSGSGS
GTDFTLTISLQPEDFATYYCQQSYSNPITFGQGTRLEIK
- [0653] 具有LALA突变重链的抗人LAG-3/PD-L1 mAb² FS18-7-9/84G09的氨基酸序列 (SEQ
ID NO:94)
- [0654] CDR的位置是下划线的, AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是粗体的。

- [0655] EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQTPGKGLEWWSGISWKSNIIGYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTALYYCARDITGSGSYGWFDPWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESSNGQPENNYKTTTPVLDSDGSFFLYSKLTVPYDRWWPDEFSCSVMEALHNHYTQKSLSLSPG
- [0656] 抗人LAG-3/PD-L1 mAb²FS18-7-9/84G09重链的氨基酸序列 (SEQ ID NO:95)
- [0657] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。
EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQTPGKGLEWWSGISWKSNIIGYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTALYYCARDITGSGSYGWFDPWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESSNGQPENNYKTTTPVLDSDGSFFLYSKLTVPYDRWWPDEFSCSVMEALHNHYTQKSLSLSPG
- [0658] 具有LALA突变重链的抗人LAG-3/PD-L1 mAb² FS18-7-32/84G09的氨基酸序列 (SEQ ID NO:96)
- [0660] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是粗体的。
EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQTPGKGLEWWSGISWKSNIIGYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTALYYCARDITGSGSYGWFDPWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESSNGQPENNYKTTTPVLDSDGSFFLYSKLTVPYDRWWPDEFSCSVMEALHNHYTQKSLSLSPG
- [0661] 抗人LAG-3/PD-L1 mAb² FS18-7-32/84G09重链的氨基酸序列 (SEQ ID NO:97)
- [0663] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。
EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQTPGKGLEWWSGISWKSNIIGYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTALYYCARDITGSGSYGWFDPWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESSNGQPENNYKTTTPVLDSDGSFFLYSKLTVPYDRWWPDEFSCSVMEALHNHYTQKSLSLSPG
- [0664] 具有LALA突变重链的抗人LAG-3/PD-L1 mAb² FS18-7-33/84G09的氨基酸序列 (SEQ ID NO:98)
- [0666] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是粗体的。

- EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQTPGKGLEWWSGISWKSNIIGYADSVKG
RFTISRDNKNSLYLQMNSLRAEDTALYYCARDITGSGSYGWFDPPWGQGTTLTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT
[0667] QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
LPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESNGQPEDNYKTT
PPVLDSDGSFFLYSKLTVPYDRWWPDEFSCSVMEALHNHYTQKSLSLSPG
- [0668] 抗人LAG-3/PD-L1 mAb²FS18-7-33/84G09重链的氨基酸序列 (SEQ ID NO:99)
- [0669] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。
EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQTPGKGLEWWSGISWKSNIIGYADSVKG
RFTISRDNKNSLYLQMNSLRAEDTALYYCARDITGSGSYGWFDPPWGQGTTLTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT
[0670] QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL
PAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESNGQPEDNYKTT
PPVLDSDGSFFLYSKLTVPYDRWWPDEFSCSVMEALHNHYTQKSLSLSPG
- [0671] 具有LALA突变重链的抗人LAG-3/PD-L1 mAb² FS18-7-36/84G09的氨基酸序列
(SEQ ID NO:100)
- [0672] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是
粗体的。
EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQTPGKGLEWWSGISWKSNIIGYADSVKG
RFTISRDNKNSLYLQMNSLRAEDTALYYCARDITGSGSYGWFDPPWGQGTTLTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT
[0673] QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV
VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
LPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSYFLYSLKTVPYDRWWPDEFSCSVMEALHNHYTQKSLSLSPG
- [0674] 抗人LAG-3/PD-L1 mAb²FS18-7-36/84G09重链的氨基酸序列 (SEQ ID NO:101)
- [0675] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。
EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQTPGKGLEWWSGISWKSNIIGYADSVKG
RFTISRDNKNSLYLQMNSLRAEDTALYYCARDITGSGSYGWFDPPWGQGTTLTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT
[0676] QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL
PAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSYFLYSLKTVPYDRWWPDEFSCSVMEALHNHYTQKSLSLSPG
- [0677] 具有LALA突变重链的抗人LAG-3/PD-L1 mAb² FS18-7-58/84G09的氨基酸序列
(SEQ ID NO:102)
- [0678] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是
粗体的。

- EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQTPGKGLEWWSGISWKSNIIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCARDITGSGSYGWFDPWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT
- [0679] QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESNGYPEIEFKTTTPVLDSGDSFFLYSKLTVPYDRWWWPDEFSCSVMEALHNHYTQKSLSLSPG
- [0680] 抗人LAG-3/PD-L1 mAb²FS18-7-58/84G09重链的氨基酸序列 (SEQ ID NO:103)
- [0681] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。
- EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQTPGKGLEWWSGISWKSNIIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCARDITGSGSYGWFDPWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT
- [0682] QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESNGYPEIEFKTTTPVLDSGDSFFLYSKLTVPYDRWWWPDEFSCSVMEALHNHYTQKSLSLSPG
- [0683] 具有LALA突变重链的抗人LAG-3/PD-L1 mAb² FS18-7-62/84G09的氨基酸序列 (SEQ ID NO:104)
- [0684] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是粗体的。
- EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQTPGKGLEWWSGISWKSNIIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCARDITGSGSYGWFDPWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT
- [0685] QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESNGIPEWNYKTTTPVLDSGDSFFLYSKLTVPYDRWWWPDEFSCSVMEALHNHYTQKSLSLSPG
- [0686] 抗人LAG-3/PD-L1 mAb²FS18-7-62/84G09重链的氨基酸序列 (SEQ ID NO:105)
- [0687] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。
- EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQTPGKGLEWWSGISWKSNIIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCARDITGSGSYGWFDPWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT
- [0688] QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESNGIPEWNYKTTTPVLDSGDSFFLYSKLTVPYDRWWWPDEFSCSVMEALHNHYTQKSLSLSPG
- [0689] 具有LALA突变重链的抗人LAG-3/PD-L1 mAb² FS18-7-65/84G09的氨基酸序列 (SEQ ID NO:106)
- [0690] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是粗体的。

- EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQTPGKGLEWWSGISWKSNIIGYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTALYYCARDITGSGSYGWFDPWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT
- [0691] QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESSNGYAEYNYKTTPPVLDSDGSFFLYSKLTVPYDRWWWPDEFSCSVMHEALHNHYTQKSLSLSPG
- [0692] 抗人LAG-3/PD-L1 mAb² FS18-7-65/84G09重链的氨基酸序列 (SEQ ID NO:107)
- [0693] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。
EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQTPGKGLEWWSGISWKSNIIGYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTALYYCARDITGSGSYGWFDPWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT
- [0694] QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESSNGYAEYNYKTTPPVLDSDGSFFLYSKLTVPYDRWWWPDEFSCSVMHEALHNHYTQKSLSLSPG
- [0695] 具有LALA突变重链的抗人LAG-3/PD-L1 mAb² FS18-7-78/84G09的氨基酸序列 (SEQ ID NO:108)
- [0696] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是粗体的。
EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQTPGKGLEWWSGISWKSNIIGYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTALYYCARDITGSGSYGWFDPWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT
- [0697] QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESSNGYKEENYKTTPPVLDSDGSFFLYSKLTVPYDRWWWPDEFSCSVMHEALHNHYTQKSLSLSPG
- [0698] 抗人LAG-3/PD-L1 mAb² FS18-7-78/84G09重链的氨基酸序列 (SEQ ID NO:109)
- [0699] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。
EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQTPGKGLEWWSGISWKSNIIGYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTALYYCARDITGSGSYGWFDPWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGT
- [0700] QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESSNGYKEENYKTTPPVLDSDGSFFLYSKLTVPYDRWWWPDEFSCSVMHEALHNHYTQKSLSLSPG
- [0701] 具有LALA突变重链的抗人LAG-3/PD-L1 mAb² FS18-7-88/84G09的氨基酸序列 (SEQ ID NO:110)
- [0702] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是粗体的。

- [0703] EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQTPGKGLEWWSGISWKSNIIGYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTALYYCARDITGSGSYGWFDPWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESSNGVPELNVKTTTPVLDSGDGSFFLYSKLTVPYDRWWVPDEFSFSVMHEALHNHYTQKSLSLSPG
- [0704] 抗人LAG-3/PD-L1 mAb²FS18-7-88/84G09重链的氨基酸序列 (SEQ ID NO:111)
- [0705] CDR的位置是下划线的, AB、CD和EF环序列是粗体和下划线的。
EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQTPGKGLEWWSGISWKSNIIGYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTALYYCARDITGSGSYGWFDPWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESSNGVPELNVKTTTPVLDSGDGSFFLYSKLTVPYDRWWVPDEFSFSVMHEALHNHYTQKSLSLSPG
- [0706] 具有LALA突变重链的抗人LAG-3/PD-L1 mAb² FS18-7-95/84G09的氨基酸序列 (SEQ ID NO:112)
- [0707] CDR的位置是下划线的, AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是粗体的。
EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQTPGKGLEWWSGISWKSNIIGYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTALYYCARDITGSGSYGWFDPWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESSNGYQEDNYKTTTPVLDSGDGSFFLYSKLTVPYDRWWVPDEFSFSVMHEALHNHYTQKSLSLSPG
- [0709] 抗人LAG-3/PD-L1 mAb² FS18-7-95/84G09重链的氨基酸序列 (SEQ ID NO:113)
- [0710] CDR的位置是下划线的, AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是粗体的。
EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQTPGKGLEWWSGISWKSNIIGYADSVKGRFTISRDNANKNSLYLQMNSLRAEDTALYYCARDITGSGSYGWFDPWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIAVEWESSNGYQEDNYKTTTPVLDSGDGSFFLYSKLTVPYDRWWVPDEFSFSVMHEALHNHYTQKSLSLSPG
- [0712] 具有LALA重链的抗人PD-L1 mAb84G09的氨基酸序列 (SEQ ID NO:114)
- [0713] CDR的位置是下划线的。LALA突变的位置是粗体的。

- [0715] EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQTPGKGLEWWSGISWKSNIIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCARDITGSGSYGWFDPWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
- [0716] 抗人PD-L1 mAb84G09重链的氨基酸序列(SEQ ID NO:115)
- [0717] CDR的位置是下划线的。
EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQTPGKGLEWWSGISWKSNIIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCARDITGSGSYGWFDPWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
- [0718] 抗人PD-L1 mAb 84G09轻链的氨基酸序列(SEQ ID NO:116)
- [0719] CDR的位置是下划线的。
DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKPLIYVASSLQSGVPSSFSGSGSGTDFTLTISLQPEDFATYYCQQSYSNPITFGQGRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC
- [0720] 具有LALA突变重链的抗小鼠LAG-3/PD-L1 mAb² FS18-7-108-29/S1的氨基酸序列(SEQ ID NO:117)
- [0721] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是粗体的。
EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWWAWISPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCCARRHWPGGFDYWGQGTTLTVSAASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIVVEWESSNQGQPENNYKTPPVLDSDGSFFLYSKLTVPFERWMWPDEFFCFSVMHEALHNHYTQKSLSLSPG
- [0722] 抗小鼠LAG-3/PD-L1 mAb²FS18-7-108-29/S1重链的氨基酸序列(SEQ ID NO:118)
- [0723] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。
EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWWAWISPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCCARRHWPGGFDYWGQGTTLTVSAASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIVVEWESSNQGQPENNYKTPPVLDSDGSFFLYSKLTVPFERWMWPDEFFCFSVMHEALHNHYTQKSLSLSPG
- [0724] 抗小鼠LAG-3/PD-L1 mAb²FS18-7-108-29/S1轻链的氨基酸序列(SEQ ID NO:119)
- [0725] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。
DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKPLIYVASSLQSGVPSSFSGSGSGTDFTLTISLQPEDFATYYCQQSYSNPITFGQGRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC
- [0726] 具有LALA突变重链的抗小鼠LAG-3/PD-L1 mAb² FS18-7-108-29/S1的氨基酸序列(SEQ ID NO:120)
- [0727] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是粗体的。
EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWVRQAPGKGLEWWAWISPYGGSTYYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCCARRHWPGGFDYWGQGTTLTVSAASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDIVVEWESSNQGQPENNYKTPPVLDSDGSFFLYSKLTVPFERWMWPDEFFCFSVMHEALHNHYTQKSLSLSPG

- [0728] 抗小鼠PD-L1 mAb S1轻链的氨基酸序列 (SEQ ID NO:119)
- [0729] CDR的位置是下划线的。
DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAWYQQKPGKAPKLLIYSASFLYSGVPSRFSGSGS
GTDFTLTISSLQPEDFATYYCQQYLFTPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVCLL
- [0730] NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLS
SPVTKSFNRGEC
- [0731] 具有LALA突变重链的抗小鼠LAG-3/PD-L1 mAb² FS18-7-108-35/S1的氨基酸序列 (SEQ ID NO:120)
- [0732] CDR的位置是下划线的, AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是粗体的。
EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWRQAPGKGLEWWAWISPYGGSTYYADSVK
GRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLLTVSAASTKGPSVFPLAP
- [0733] SSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT
YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVWV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
APIEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDISVEWESNGQPENNYKTTTP
- [0734] VLDSGDSFFLYSKLTVPFERWMWPDEFSCSVMEALHNHYTQKSLSLSPG
- [0735] 抗小鼠LAG-3/PD-L1 mAb²FS18-7-108-35/S1重链的氨基酸序列 (SEQ ID NO:121)
- [0736] CDR的位置是下划线的, AB、CD和EF环序列是粗体和下划线的。
EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWRQAPGKGLEWWAWISPYGGSTYYADSVK
GRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLLTVSAASTKGPSVFPLAP
- [0737] SSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT
YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVD
VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSWDEPWGEDVSLTCLVKGFYPSDISVEWESNGQPENNYKTTTPVL
DSDGDSFFLYSKLTVPFERWMWPDEFSCSVMEALHNHYTQKSLSLSPG
- [0738] 具有LALA突变重链的对照PD-L1 mAb S1的氨基酸序列 (SEQ ID NO:122)
- [0739] CDR的位置是下划线的。LALA突变的位置是粗体的。
EVQLVESGGGLVQPGGSLRLSCAASGFTFSDSWIHWRQAPGKGLEWWAWISPYGGSTYYADSVK
GRFTISADTSKNTAYLQMNSLRAEDTAVYYCARRHWPGGFDYWGQGTLLTVSAASTKGPSVFPLAP
- [0740] SSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQT
YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVWV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPV
LDSDGDSFFLYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQKSLSLSPG
- [0741] 对照PD-L1 mAb S1重链的氨基酸序列 (SEQ ID NO:123)
- [0742] CDR的位置是下划线的。LALA突变的位置是粗体的。

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- [0755] MWEAQFLGLLFLQPLWWAPVKPPQPGAIEISVVWAQEGAPALPCSPITPLQDLSLLRRAGVTWQHQPDSGPPAAAPGHPPVPGHRPAAPYSWGPRPRRYTVLSVGPGLRSGRLPLQPRVQLDERGRQGRDFSLWLRPARRADAGEYRATVHLRDRALSCRLRLRVGQASMTASPPGSLRTSDWILNCSFSRPDRPASVHWFRSRGQGRVPVQGSPPHHLAESFLFLPHVGPMDSGLWGCILTYRDGFNVSIMYNLTVLGL
EPATPLTVYAGAGSRVELPCRLPPAVGTQSFLTAKWAPPGGGPDLLVAGDNGDFTLRLEDVSQAQAGTYICHIRLQGQQLNATVTLAIITVTPKSFGSPGSLGKLLCEVTPASGQEHFVWSPLNTPSQRSFSGPWLEAQEAQLLSQPWQCQLHQGERLLGAAVYFTELSSPGAQRSGRAPGALRAGHLPLFLILGVLFLLLLVTGAFGFHLWRRQWRPRRFSALEQGIHPPQAQSKIEELEQEPELEPELERELGPEPEPGPEPEPEQL
- [0756] 人PD-L1的氨基酸序列 (SEQ ID NO:129)
MRIFAVFIFMTYWHLLNAFTVTVPKDLYVVEYGSNMIECKFPVEKQLDLAALIVYWEMEDKNIIQFVHGEEDLKVQHSSYRQARLLKDQLSLGNAALQITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVDPTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLFNVTSTLRINTTTNEIFYCTFRRLDPEENHTAELVIPELPLAHPNERTHLVILGAILLCLGVALTFIFRLRKGRMMMDVKKCGIQDTNSKKQSDTHLEET
- [0757] 鼠类PD-L1的氨基酸序列 (SEQ ID NO:130)
MRIFAGIIFTACCHLLRAFTITAPKDLYVVEYGSNVTMECRFPVERELDLLALVYWEKEDEQVIQFVAGEEDLKQHSNFRGRASLPKDQLLKGNALQITDVKLQDAGVYCCIIISYGGADYKRITLKVNPYRKINQRISVDPATSEHELICQAEGYPEAEVIWTNSDHQVPVSGKRSVTTSRTEGMLLNVTSSLRVNATANVDFYCTFWRSQPGQNHTAELIPELPAHPNERTHWLLGSILLFLIVVSTVLLFLRKQVRMLDVEKCGVEDTSSKNRNDTQFEET
- [0758] 食蟹猴PD-L1的氨基酸序列 (SEQ ID NO:131)
MRIFAVFIFTIYWHLLNAFTVTVPKDLYVVEYGSNMIECKFPVEKQLDLTSLIVYWEMEDKNIIQFVHGEEDLKVQHSNRYRQAQLLKDQLSLGNAALRITDVKLQDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVDPTSEHELTCQAEGYPKAEVIWTSSDHQVLSGKTTTTNSKREEKLLNVTSTLRINTTANEIFYCFRRLDPEENHTAELVIPELPLALPPNERTHLVILGAIFLLLGVALTFIFYLRKGRMMMDMKCGIRVTNSKKQRDTQLEET
- [0760] 包括LALA突变的抗小鼠LAG-3/FITC mAb² FS18-7-108-29/4420的重链的氨基酸序列 (SEQ ID NO:132)
EVKLDETGGGLVQPGRPMKLSCVASGFTFSDYWMNWRQSPEKGLEWQAQIRNKPYNYETYYSDSVKGRFTISRDDSKSSVYLQMNLRVEDMGIYYCTGSYYGMDYWGQGTSVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS**WDEPWGED**VSLTCLVKGFYPSDIVVEWES**SNQGPENNY**KTTTPPVLDSDGSFFLYSKLTV**PFERWMWPDEF**SCSVMHENHHTYQKSLSLSPG
- [0761] 包括LALA突变的抗小鼠LAG-3/FITC mAb² FS18-7-108-35/4420的重链的氨基酸序列 (SEQ ID NO:133)
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- [0762] CDR的位置是下划线的, AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是粗体的。
- [0763] CDR的位置是下划线的, AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是粗体的。
- [0764] CDR的位置是下划线的, AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是粗体的。
- [0765] CDR的位置是下划线的, AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是粗体的。
- [0766] CDR的位置是下划线的, AB、CD和EF环序列是粗体和下划线的。LALA突变的位置是粗体的。

- EVKLDETGGGLVQGRPMKLSCVASGFTFSDYWMNWWRQSPEKGLEWVAQIRNKPYN~~YETY~~SD
SVKGRFTISRDDSKSSVYLQMN~~NLRVEDMGIYYCTGSYYGMDY~~WGQGTSTVTSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVT~~SVWNSGALTSGVHTFPAVLQSSGLYSLSSV~~TPSSSLG
- [0767] TQTYICNVNHKPSNTKVDKKVEPKSCDKHTCPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVT
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KALPAPIEKTISKAKGQPREPQVYTLPPS**WDEPWGED**VSLTCLVKGFYPSDISEVWE**SNGQPENNY**
YKTPPVLDSDGSFFLYSKLT**V****P**FERWMWP**D**EFSCSVMH~~EALHNHYTQKSLS~~SPG
- [0768] 抗小鼠LAG-3/FITC mAb²FS18-7-108-29/4420的重链的氨基酸序列(SEQ ID NO:
134)
- [0769] CDR的位置是下划线的,AB、CD和EF环序列是粗体和下划线的。
EVKLDETGGGLVQGRPMKLSCVASGFTFSDYWMNWWRQSPEKGLEWVAQIRNKPYN~~YETY~~SD
SVKGRFTISRDDSKSSVYLQMN~~NLRVEDMGIYYCTGSYYGMDY~~WGQGTSTVTSSASTKGPSVFPL
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- [0770] TQTYICNVNHKPSNTKVDKKVEPKSCDKHTCPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC
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KALPAPIEKTISKAKGQPREPQVYTLPPS**WDEPWGED**VSLTCLVKGFYPSD**I**VEWE**SNGQPENNY**
KTPPVLDSDGSFFLYSKLT**V****P**FERWMWP**D**EFSCSVMH~~EALHNHYTQKSLS~~SPG
- [0771] 参考文献
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- [0001] 序列表
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[0271]	ggccagcctc gagaaccaca ggtgtacacc ctgcccccat cctgggatga gccgtggggt	60	
[0272]	gaagacgtca gcctgacctg cctgggtcaaa ggcttctatc ccagcgacat cgccgtggag	120	

[0273] tgggagagca atgggcagcc ggaggacaac tacaagacca cgcctcccgt gctggactcc 180
 [0274] gacggctcct tcttcctcta cagcaagctc accgtgccgt atgatagggtg ggtttgcccg 240
 [0275] gatgagttct catgctccgt gatgcatgag gctctgcaca accactacac acagaagagc 300
 [0276] ctctccctgt ctccgggt 318
 [0277] <210> 15
 [0278] <211> 106
 [0279] <212> PRT
 [0280] <213> 人工序列
 [0281] <220>
 [0282] <223> Fcab FS18-7-33 CH3结构域的氨基酸序列
 [0283] <400> 15
 [0284] Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Trp Asp
 [0285] 1 5 10 15
 [0286] Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys Leu Val Lys Gly Phe
 [0287] 20 25 30
 [0288] Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
 [0289] 35 40 45
 [0290] Asp Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
 [0291] 50 55 60
 [0292] Phe Leu Tyr Ser Lys Leu Thr Val Pro Tyr Asp Arg Trp Val Trp Pro
 [0293] 65 70 75 80
 [0294] Asp Glu Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
 [0295] 85 90 95
 [0296] Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
 [0297] 100 105
 [0298] <210> 16
 [0299] <211> 216
 [0300] <212> PRT
 [0301] <213> 人工序列
 [0302] <220>
 [0303] <223> Fcab FS18-7-33 CH2和CH3结构域的氨基酸序列,包括LALA突变
 [0304] <400> 16
 [0305] Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 [0306] 1 5 10 15
 [0307] Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
 [0308] 20 25 30
 [0309] Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
 [0310] 35 40 45
 [0311] Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu

[0312]	50	55	60
[0313]	Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His		
[0314]	65	70	75
[0315]	Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys		
[0316]	85	90	95
[0317]	Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln		
[0318]	100	105	110
[0319]	Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro		
[0320]	115	120	125
[0321]	Trp Gly Glu Asp Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro		
[0322]	130	135	140
[0323]	Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asp Asn		
[0324]	145	150	155
[0325]	Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu		
[0326]	165	170	175
[0327]	Tyr Ser Lys Leu Thr Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu		
[0328]	180	185	190
[0329]	Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln		
[0330]	195	200	205
[0331]	Lys Ser Leu Ser Leu Ser Pro Gly		
[0332]	210	215	
[0333]	<210> 17		
[0334]	<211> 216		
[0335]	<212> PRT		
[0336]	<213> 人工序列		
[0337]	<220>		
[0338]	<223> Fcab FS18-7-33 CH2和CH3结构域的氨基酸序列,没有LALA突变		
[0339]	<400> 17		
[0340]	Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys		
[0341]	1	5	10
[0342]	Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val		
[0343]	20	25	30
[0344]	Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr		
[0345]	35	40	45
[0346]	Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu		
[0347]	50	55	60
[0348]	Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His		
[0349]	65	70	75
[0350]	Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys		

[0351]	85	90	95
[0352]	Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln		
[0353]	100	105	110
[0354]	Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro		
[0355]	115	120	125
[0356]	Trp Gly Glu Asp Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro		
[0357]	130	135	140
[0358]	Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asp Asn		
[0359]	145	150	155
[0360]	Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu		
[0361]	165	170	175
[0362]	Tyr Ser Lys Leu Thr Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu		
[0363]	180	185	190
[0364]	Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln		
[0365]	195	200	205
[0366]	Lys Ser Leu Ser Leu Ser Pro Gly		
[0367]	210	215	
[0368]	<210> 18		
[0369]	<211> 9		
[0370]	<212> PRT		
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[0372]	<220>		
[0373]	<223> FS18-7-36 CD环		
[0374]	<400> 18		
[0375]	Ser Asn Gly Gln Pro Glu Asn Asn Tyr		
[0376]	1	5	
[0377]	<210> 19		
[0378]	<211> 318		
[0379]	<212> DNA		
[0380]	<213> 人工序列		
[0381]	<220>		
[0382]	<223> Fcab FS18-7-36 CH3结构域的核苷酸序列		
[0383]	<400> 19		
[0384]	ggccagcctc gagaaccaca ggtgtacacc ctgccccat cctgggatga gccgtggggt 60		
[0385]	gaagacgtca gctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag 120		
[0386]	tgggagagca atgggcagcc ggagaacaac tacaagacca cgctcccggt gctggactcc 180		
[0387]	gacggctcct acttctctta cagcaagctc accgtgccgt atgatagggtg ggtttggccg 240		
[0388]	gatgagttct catgctccgt gatgcatgag gctctgcaca accactacac acagaagagc 300		
[0389]	ctctccctgt ctccgggt 318		

[0390]	<210> 20
[0391]	<211> 106
[0392]	<212> PRT
[0393]	<213> 人工序列
[0394]	<220>
[0395]	<223> Fcab FS18-7-36 CH3结构域的氨基酸序列
[0396]	<400> 20
[0397]	Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Trp Asp
[0398]	1 5 10 15
[0399]	Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys Leu Val Lys Gly Phe
[0400]	20 25 30
[0401]	Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
[0402]	35 40 45
[0403]	Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Tyr
[0404]	50 55 60
[0405]	Phe Leu Tyr Ser Lys Leu Thr Val Pro Tyr Asp Arg Trp Val Trp Pro
[0406]	65 70 75 80
[0407]	Asp Glu Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
[0408]	85 90 95
[0409]	Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[0410]	100 105
[0411]	<210> 21
[0412]	<211> 216
[0413]	<212> PRT
[0414]	<213> 人工序列
[0415]	<220>
[0416]	<223> FS18-7-36的CH2和CH3结构域的CH2+CH3氨基酸序列,包括LALA突变
[0417]	<400> 21
[0418]	Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
[0419]	1 5 10 15
[0420]	Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
[0421]	20 25 30
[0422]	Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
[0423]	35 40 45
[0424]	Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
[0425]	50 55 60
[0426]	Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
[0427]	65 70 75 80
[0428]	Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys

[0429]	85																90				95							
[0430]	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln												
[0431]	100																105				110							
[0432]	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Trp	Asp	Glu	Pro												
[0433]	115																120				125							
[0434]	Trp	Gly	Glu	Asp	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro												
[0435]	130																135				140							
[0436]	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn												
[0437]	145																150				155				160			
[0438]	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Tyr	Phe	Leu												
[0439]	165																170				175							
[0440]	Tyr	Ser	Lys	Leu	Thr	Val	Pro	Tyr	Asp	Arg	Trp	Val	Trp	Pro	Asp	Glu												
[0441]	180																185				190							
[0442]	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln												
[0443]	195																200				205							
[0444]	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly																				
[0445]	210																215											
[0446]	<210> 22																											
[0447]	<211> 216																											
[0448]	<212> PRT																											
[0449]	<213> 人工序列																											
[0450]	<220>																											
[0451]	<223> Fcab FS18-7-36 CH2和CH3结构域的氨基酸序列,没有LALA突变																											
[0452]	<400> 22																											
[0453]	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys												
[0454]	1	5														10				15								
[0455]	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val												
[0456]	20																25				30							
[0457]	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr												
[0458]	35																40				45							
[0459]	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu												
[0460]	50																55				60							
[0461]	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His												
[0462]	65																70				75				80			
[0463]	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys												
[0464]	85																90				95							
[0465]	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln												
[0466]	100																105				110							
[0467]	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Trp	Asp	Glu	Pro												

[0468]	115	120	125
[0469]	Trp Gly Glu Asp Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro		
[0470]	130	135	140
[0471]	Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn		
[0472]	145	150	155
[0473]	Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Tyr Phe Leu		
[0474]	165	170	175
[0475]	Tyr Ser Lys Leu Thr Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu		
[0476]	180	185	190
[0477]	Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln		
[0478]	195	200	205
[0479]	Lys Ser Leu Ser Leu Ser Pro Gly		
[0480]	210	215	
[0481]	<210> 23		
[0482]	<211> 9		
[0483]	<212> PRT		
[0484]	<213> 人工序列		
[0485]	<220>		
[0486]	<223> FS18-7-58 CD环		
[0487]	<400> 23		
[0488]	Ser Asn Gly Tyr Pro Glu Ile Glu Phe		
[0489]	1	5	
[0490]	<210> 24		
[0491]	<211> 318		
[0492]	<212> DNA		
[0493]	<213> 人工序列		
[0494]	<220>		
[0495]	<223> Fcab FS18-7-58 CH3结构域的核苷酸序列		
[0496]	<400> 24		
[0497]	ggccagcctc gagaaccaca ggtgtacacc ctgccccat cctgggatga gccgtggggt 60		
[0498]	gaagacgtca gcctgacctg cctgggtcaaa ggcttctatc ccagcgacat cgccgtggag 120		
[0499]	tgggagagca atgggtatcc agaaatcgaa ttcaagacca cgcctcccggt gctggactcc 180		
[0500]	gacggctcct tcttctctcta cagcaagctc accgtgcctt atgatagggtg ggtttggccg 240		
[0501]	gatgagttct catgtctcgt gatgcatgag gctctgcaca accactacac acagaagagc 300		
[0502]	ctctccctgt ctccgggt 318		
[0503]	<210> 25		
[0504]	<211> 106		
[0505]	<212> PRT		
[0506]	<213> 人工序列		

[0507]	<220>
[0508]	<223> Fcab FS18-7-58 CH3结构域的氨基酸序列
[0509]	<400> 25
[0510]	Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Trp Asp
[0511]	1 5 10 15
[0512]	Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys Leu Val Lys Gly Phe
[0513]	20 25 30
[0514]	Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Tyr Pro Glu
[0515]	35 40 45
[0516]	Ile Glu Phe Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
[0517]	50 55 60
[0518]	Phe Leu Tyr Ser Lys Leu Thr Val Pro Tyr Asp Arg Trp Val Trp Pro
[0519]	65 70 75 80
[0520]	Asp Glu Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
[0521]	85 90 95
[0522]	Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[0523]	100 105
[0524]	<210> 26
[0525]	<211> 216
[0526]	<212> PRT
[0527]	<213> 人工序列
[0528]	<220>
[0529]	<223> Fcab FS18-7-58 CH2和CH3结构域的氨基酸序列,包括LALA突变
[0530]	<400> 26
[0531]	Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
[0532]	1 5 10 15
[0533]	Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
[0534]	20 25 30
[0535]	Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
[0536]	35 40 45
[0537]	Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
[0538]	50 55 60
[0539]	Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
[0540]	65 70 75 80
[0541]	Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
[0542]	85 90 95
[0543]	Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
[0544]	100 105 110
[0545]	Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro

[0546]	115	120	125
[0547]	Trp Gly Glu Asp Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro		
[0548]	130	135	140
[0549]	Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Tyr Pro Glu Ile Glu		
[0550]	145	150	155
[0551]	Phe Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu		
[0552]	165	170	175
[0553]	Tyr Ser Lys Leu Thr Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu		
[0554]	180	185	190
[0555]	Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln		
[0556]	195	200	205
[0557]	Lys Ser Leu Ser Leu Ser Pro Gly		
[0558]	210	215	
[0559]	<210> 27		
[0560]	<211> 216		
[0561]	<212> PRT		
[0562]	<213> 人工序列		
[0563]	<220>		
[0564]	<223> Fcab FS18-7-58 CH2和CH3结构域的氨基酸序列,没有LALA突变		
[0565]	<400> 27		
[0566]	Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys		
[0567]	1	5	10
[0568]	Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val		
[0569]	20	25	30
[0570]	Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr		
[0571]	35	40	45
[0572]	Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu		
[0573]	50	55	60
[0574]	Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His		
[0575]	65	70	75
[0576]	Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys		
[0577]	85	90	95
[0578]	Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln		
[0579]	100	105	110
[0580]	Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro		
[0581]	115	120	125
[0582]	Trp Gly Glu Asp Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro		
[0583]	130	135	140
[0584]	Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Tyr Pro Glu Ile Glu		

[0585]	145	150	155	160
[0586]	Phe Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu			
[0587]		165	170	175
[0588]	Tyr Ser Lys Leu Thr Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu			
[0589]		180	185	190
[0590]	Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln			
[0591]		195	200	205
[0592]	Lys Ser Leu Ser Leu Ser Pro Gly			
[0593]		210	215	
[0594]	<210> 28			
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[0596]	<212> PRT			
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[0598]	<220>			
[0599]	<223> FS18-7-62 CD环			
[0600]	<400> 28			
[0601]	Ser Asn Gly Ile Pro Glu Trp Asn Tyr			
[0602]	1	5		
[0603]	<210> 29			
[0604]	<211> 318			
[0605]	<212> DNA			
[0606]	<213> 人工序列			
[0607]	<220>			
[0608]	<223> Fcab FS18-7-62 CH3结构域的核苷酸序列			
[0609]	<400> 29			
[0610]	ggccagcctc gagaaccaca ggtgtacacc ctgcccccat cctgggatga gccgtggggt 60			
[0611]	gaagacgtca gcctgacctg cctgggtcaaa ggcttctatc ccagcgacat cgccgtggag 120			
[0612]	tgggagagca atgggatccc agaatggaac tataagacca cgcctcccgt gctggactcc 180			
[0613]	gacggctcct tcttcctcta cagcaagctc accgtgccgt atgataggtg ggtttgccg 240			
[0614]	gatgagttct catgctccgt gatgcatgag gctctgcaca accactacac acagaagagc 300			
[0615]	ctctccctgt ctccgggt 318			
[0616]	<210> 30			
[0617]	<211> 106			
[0618]	<212> PRT			
[0619]	<213> 人工序列			
[0620]	<220>			
[0621]	<223> Fcab FS18-7-62 CH3结构域的氨基酸序列			
[0622]	<400> 30			
[0623]	Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Trp Asp			

[0624]	1	5	10	15
[0625]	Glu Pro Trp Gly	Glu Asp Val Ser Leu Thr Cys Leu Val Lys Gly Phe		
[0626]	20	25	30	
[0627]	Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Ile Pro Glu			
[0628]	35	40	45	
[0629]	Trp Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe			
[0630]	50	55	60	
[0631]	Phe Leu Tyr Ser Lys Leu Thr Val Pro Tyr Asp Arg Trp Val Trp Pro			
[0632]	65	70	75	80
[0633]	Asp Glu Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr			
[0634]	85	90	95	
[0635]	Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly			
[0636]	100	105		
[0637]	<210> 31			
[0638]	<211> 216			
[0639]	<212> PRT			
[0640]	<213> 人工序列			
[0641]	<220>			
[0642]	<223> Fcab FS18-7-62 CH2和CH3结构域的氨基酸序列,包括LALA突变			
[0643]	<400> 31			
[0644]	Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys			
[0645]	1	5	10	15
[0646]	Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val			
[0647]	20	25	30	
[0648]	Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr			
[0649]	35	40	45	
[0650]	Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu			
[0651]	50	55	60	
[0652]	Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His			
[0653]	65	70	75	80
[0654]	Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys			
[0655]	85	90	95	
[0656]	Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln			
[0657]	100	105	110	
[0658]	Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro			
[0659]	115	120	125	
[0660]	Trp Gly Glu Asp Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro			
[0661]	130	135	140	
[0662]	Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Ile Pro Glu Trp Asn			

[0663]	145	150	155	160
[0664]	Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu			
[0665]		165	170	175
[0666]	Tyr Ser Lys Leu Thr Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu			
[0667]		180	185	190
[0668]	Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln			
[0669]		195	200	205
[0670]	Lys Ser Leu Ser Leu Ser Pro Gly			
[0671]		210	215	
[0672]	<210> 32			
[0673]	<211> 216			
[0674]	<212> PRT			
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[0676]	<220>			
[0677]	<223> Fcab FS18-7-62 CH2和CH3结构域的氨基酸序列,没有LALA突变			
[0678]	<400> 32			
[0679]	Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys			
[0680]	1	5	10	15
[0681]	Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val			
[0682]		20	25	30
[0683]	Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr			
[0684]		35	40	45
[0685]	Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu			
[0686]		50	55	60
[0687]	Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His			
[0688]	65	70	75	80
[0689]	Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys			
[0690]		85	90	95
[0691]	Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln			
[0692]		100	105	110
[0693]	Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro			
[0694]		115	120	125
[0695]	Trp Gly Glu Asp Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro			
[0696]		130	135	140
[0697]	Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Ile Pro Glu Trp Asn			
[0698]	145	150	155	160
[0699]	Tyr Lys Thr Thr Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu			
[0700]		165	170	175
[0701]	Tyr Ser Lys Leu Thr Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu			

[0702]	180	185	190
[0703]	Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln		
[0704]	195	200	205
[0705]	Lys Ser Leu Ser Leu Ser Pro Gly		
[0706]	210	215	
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[0711]	<220>		
[0712]	<223> FS18-7-65 CD环		
[0713]	<400> 33		
[0714]	Ser Asn Gly Tyr Ala Glu Tyr Asn Tyr		
[0715]	1	5	
[0716]	<210> 34		
[0717]	<211> 318		
[0718]	<212> DNA		
[0719]	<213> 人工序列		
[0720]	<220>		
[0721]	<223> Fcab FS18-7-65 CH3结构域的核苷酸序列		
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[0723]	ggccagcctc gagaaccaca ggtgtacacc ctgcccccat cctgggatga gccgtggggt 60		
[0724]	gaagacgtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag 120		
[0725]	tgggagagca atgggtatgc agaataaac tataagacca cgcctcccgt gctggactcc 180		
[0726]	gacggctcct tcttcctcta cagcaagctc accgtgccgt atgatagggtg ggtttggccg 240		
[0727]	gatgagttct catgctccgt gatgcatgag gctctgcaca accactacac acagaagagc 300		
[0728]	ctctccctgt ctccgggt 318		
[0729]	<210> 35		
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[0732]	<213> 人工序列		
[0733]	<220>		
[0734]	<223> Fcab FS18-7-65 CH3结构域的氨基酸序列		
[0735]	<400> 35		
[0736]	Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Trp Asp		
[0737]	1	5	10 15
[0738]	Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys Leu Val Lys Gly Phe		
[0739]	20	25	30
[0740]	Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Tyr Ala Glu		

[0741]	35	40	45
[0742]	Tyr Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe		
[0743]	50	55	60
[0744]	Phe Leu Tyr Ser Lys Leu Thr Val Pro Tyr Asp Arg Trp Val Trp Pro		
[0745]	65	70	75
[0746]	Asp Glu Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr		
[0747]	85	90	95
[0748]	Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
[0749]	100	105	
[0750]	<210> 36		
[0751]	<211> 216		
[0752]	<212> PRT		
[0753]	<213> 人工序列		
[0754]	<220>		
[0755]	<223> Fcab FS18-7-65 CH2和CH3结构域的氨基酸序列,包括LALA突变		
[0756]	<400> 36		
[0757]	Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys		
[0758]	1	5	10
[0759]	Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val		
[0760]	20	25	30
[0761]	Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr		
[0762]	35	40	45
[0763]	Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu		
[0764]	50	55	60
[0765]	Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His		
[0766]	65	70	75
[0767]	Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys		
[0768]	85	90	95
[0769]	Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln		
[0770]	100	105	110
[0771]	Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro		
[0772]	115	120	125
[0773]	Trp Gly Glu Asp Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro		
[0774]	130	135	140
[0775]	Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Tyr Ala Glu Tyr Asn		
[0776]	145	150	155
[0777]	Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu		
[0778]	165	170	175
[0779]	Tyr Ser Lys Leu Thr Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu		

[0780]	180	185	190
[0781]	Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln		
[0782]	195	200	205
[0783]	Lys Ser Leu Ser Leu Ser Pro Gly		
[0784]	210	215	
[0785]	<210> 37		
[0786]	<211> 216		
[0787]	<212> PRT		
[0788]	<213> 人工序列		
[0789]	<220>		
[0790]	<223> Fcab FS18-7-65 CH2和CH3结构域的氨基酸序列,没有LALA突变		
[0791]	<400> 37		
[0792]	Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys		
[0793]	1 5 10 15		
[0794]	Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val		
[0795]	20 25 30		
[0796]	Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr		
[0797]	35 40 45		
[0798]	Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu		
[0799]	50 55 60		
[0800]	Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His		
[0801]	65 70 75 80		
[0802]	Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys		
[0803]	85 90 95		
[0804]	Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln		
[0805]	100 105 110		
[0806]	Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro		
[0807]	115 120 125		
[0808]	Trp Gly Glu Asp Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro		
[0809]	130 135 140		
[0810]	Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Tyr Ala Glu Tyr Asn		
[0811]	145 150 155 160		
[0812]	Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu		
[0813]	165 170 175		
[0814]	Tyr Ser Lys Leu Thr Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu		
[0815]	180 185 190		
[0816]	Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln		
[0817]	195 200 205		
[0818]	Lys Ser Leu Ser Leu Ser Pro Gly		

[0819]	210	215
[0820]	<210> 38	
[0821]	<211> 9	
[0822]	<212> PRT	
[0823]	<213> 人工序列	
[0824]	<220>	
[0825]	<223> FS18-7-78 CD环	
[0826]	<400> 38	
[0827]	Ser Asn Gly Tyr Lys Glu Glu Asn Tyr	
[0828]	1	5
[0829]	<210> 39	
[0830]	<211> 318	
[0831]	<212> DNA	
[0832]	<213> 人工序列	
[0833]	<220>	
[0834]	<223> Fcab FS18-7-78 CH3结构域的核苷酸序列	
[0835]	<400> 39	
[0836]	ggccagcctc gagaaccaca ggtgtacacc ctgcccccat cctgggatga gccgtggggt	60
[0837]	gaagacgtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag	120
[0838]	tgggagagca atgggtataa agaagaaaac tataagacca cgcctcccgt gctggactcc	180
[0839]	gacggctcct tcttctctta cagcaagctc accgtgccgt atgatagggtg ggtttggccg	240
[0840]	gatgagttct catgctccgt gatgcatgag gctctgcaca accactacac acagaagagc	300
[0841]	ctctccctgt ctccgggt	318
[0842]	<210> 40	
[0843]	<211> 106	
[0844]	<212> PRT	
[0845]	<213> 人工序列	
[0846]	<220>	
[0847]	<223> Fcab FS18-7-78 CH3结构域的氨基酸序列	
[0848]	<400> 40	
[0849]	Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Trp Asp	
[0850]	1	5 10 15
[0851]	Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys Leu Val Lys Gly Phe	
[0852]	20	25 30
[0853]	Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Tyr Lys Glu	
[0854]	35	40 45
[0855]	Glu Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe	
[0856]	50	55 60
[0857]	Phe Leu Tyr Ser Lys Leu Thr Val Pro Tyr Asp Arg Trp Val Trp Pro	

[0858]	65	70	75	80
[0859]	Asp Glu Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr			
[0860]		85	90	95
[0861]	Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly			
[0862]		100	105	
[0863]	<210> 41			
[0864]	<211> 216			
[0865]	<212> PRT			
[0866]	<213> 人工序列			
[0867]	<220>			
[0868]	<223> Fcab FS18-7-78 CH2和CH3结构域的氨基酸序列,包括LALA突变			
[0869]	<400> 41			
[0870]	Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys			
[0871]	1	5	10	15
[0872]	Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val			
[0873]		20	25	30
[0874]	Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr			
[0875]		35	40	45
[0876]	Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu			
[0877]	50	55	60	
[0878]	Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His			
[0879]	65	70	75	80
[0880]	Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys			
[0881]		85	90	95
[0882]	Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln			
[0883]		100	105	110
[0884]	Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro			
[0885]		115	120	125
[0886]	Trp Gly Glu Asp Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro			
[0887]	130	135	140	
[0888]	Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Tyr Lys Glu Glu Asn			
[0889]	145	150	155	160
[0890]	Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu			
[0891]		165	170	175
[0892]	Tyr Ser Lys Leu Thr Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu			
[0893]		180	185	190
[0894]	Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln			
[0895]		195	200	205
[0896]	Lys Ser Leu Ser Leu Ser Pro Gly			

[0897]	210	215
[0898]	<210> 42	
[0899]	<211> 216	
[0900]	<212> PRT	
[0901]	<213> 人工序列	
[0902]	<220>	
[0903]	<223> Fcab FS18-7-78 CH2和CH3结构域的氨基酸序列,没有LALA突变	
[0904]	<400> 42	
[0905]	Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys	
[0906]	1 5 10 15	
[0907]	Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val	
[0908]	20 25 30	
[0909]	Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr	
[0910]	35 40 45	
[0911]	Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu	
[0912]	50 55 60	
[0913]	Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His	
[0914]	65 70 75 80	
[0915]	Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys	
[0916]	85 90 95	
[0917]	Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln	
[0918]	100 105 110	
[0919]	Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro	
[0920]	115 120 125	
[0921]	Trp Gly Glu Asp Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro	
[0922]	130 135 140	
[0923]	Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Tyr Lys Glu Glu Asn	
[0924]	145 150 155 160	
[0925]	Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu	
[0926]	165 170 175	
[0927]	Tyr Ser Lys Leu Thr Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu	
[0928]	180 185 190	
[0929]	Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln	
[0930]	195 200 205	
[0931]	Lys Ser Leu Ser Leu Ser Pro Gly	
[0932]	210 215	
[0933]	<210> 43	
[0934]	<211> 9	
[0935]	<212> PRT	

[0936]	<213>	人工序列
[0937]	<220>	
[0938]	<223>	FS18-7-88 CD环
[0939]	<400>	43
[0940]		Ser Asn Gly Val Pro Glu Leu Asn Val
[0941]	1	5
[0942]	<210>	44
[0943]	<211>	318
[0944]	<212>	DNA
[0945]	<213>	人工序列
[0946]	<220>	
[0947]	<223>	Fcab FS18-7-88 CH3结构域的核苷酸序列
[0948]	<400>	44
[0949]		ggccagcctc gagaaccaca ggtgtacacc ctgcccccat cctgggatga gccgtggggt 60
[0950]		gaagacgtca gctgacctg cctgggtcaaa ggcttctatc ccagcgacat cgccgtggag 120
[0951]		tgggagagca atggggttcc agaactgaac gttaagacca cgcctcccgt gctggactcc 180
[0952]		gacggctcct tcttctctta cagcaagctc accgtgccgt atgatagggtg ggtttggccg 240
[0953]		gatgagttct catgctccgt gatgcatgag gctctgcaca accactacac acagaagagc 300
[0954]		ctctccctgt ctccgggt 318
[0955]	<210>	45
[0956]	<211>	106
[0957]	<212>	PRT
[0958]	<213>	人工序列
[0959]	<220>	
[0960]	<223>	Fcab FS18-7-88 CH3结构域的氨基酸序列
[0961]	<400>	45
[0962]		Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Trp Asp
[0963]	1	5 10 15
[0964]		Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys Leu Val Lys Gly Phe
[0965]		20 25 30
[0966]		Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Val Pro Glu
[0967]		35 40 45
[0968]		Leu Asn Val Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
[0969]		50 55 60
[0970]		Phe Leu Tyr Ser Lys Leu Thr Val Pro Tyr Asp Arg Trp Val Trp Pro
[0971]		65 70 75 80
[0972]		Asp Glu Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
[0973]		85 90 95
[0974]		Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly

[0975]	100	105
[0976]	<210> 46	
[0977]	<211> 216	
[0978]	<212> PRT	
[0979]	<213> 人工序列	
[0980]	<220>	
[0981]	<223> Fcab FS18-7-88 CH2和CH3结构域的氨基酸序列,包括LALA突变	
[0982]	<400> 46	
[0983]	Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys	
[0984]	1 5 10 15	
[0985]	Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val	
[0986]	20 25 30	
[0987]	Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr	
[0988]	35 40 45	
[0989]	Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu	
[0990]	50 55 60	
[0991]	Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His	
[0992]	65 70 75 80	
[0993]	Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys	
[0994]	85 90 95	
[0995]	Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln	
[0996]	100 105 110	
[0997]	Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro	
[0998]	115 120 125	
[0999]	Trp Gly Glu Asp Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro	
[1000]	130 135 140	
[1001]	Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Val Pro Glu Leu Asn	
[1002]	145 150 155 160	
[1003]	Val Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu	
[1004]	165 170 175	
[1005]	Tyr Ser Lys Leu Thr Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu	
[1006]	180 185 190	
[1007]	Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln	
[1008]	195 200 205	
[1009]	Lys Ser Leu Ser Leu Ser Pro Gly	
[1010]	210 215	
[1011]	<210> 47	
[1012]	<211> 216	
[1013]	<212> PRT	

[1014]	<213>	人工序列
[1015]	<220>	
[1016]	<223>	Fcab FS18-7-88 CH2和CH3结构域的氨基酸序列,没有LALA突变
[1017]	<400>	47
[1018]	Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys	
[1019]	1 5 10 15	
[1020]	Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val	
[1021]	20 25 30	
[1022]	Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr	
[1023]	35 40 45	
[1024]	Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu	
[1025]	50 55 60	
[1026]	Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His	
[1027]	65 70 75 80	
[1028]	Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys	
[1029]	85 90 95	
[1030]	Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln	
[1031]	100 105 110	
[1032]	Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro	
[1033]	115 120 125	
[1034]	Trp Gly Glu Asp Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro	
[1035]	130 135 140	
[1036]	Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Val Pro Glu Leu Asn	
[1037]	145 150 155 160	
[1038]	Val Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu	
[1039]	165 170 175	
[1040]	Tyr Ser Lys Leu Thr Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu	
[1041]	180 185 190	
[1042]	Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln	
[1043]	195 200 205	
[1044]	Lys Ser Leu Ser Leu Ser Pro Gly	
[1045]	210 215	
[1046]	<210>	48
[1047]	<211>	9
[1048]	<212>	PRT
[1049]	<213>	人工序列
[1050]	<220>	
[1051]	<223>	FS18-7-95 CD环
[1052]	<400>	48

[1053]	Ser Asn Gly Tyr Gln Glu Asp Asn Tyr
[1054]	1 5
[1055]	<210> 49
[1056]	<211> 318
[1057]	<212> DNA
[1058]	<213> 人工序列
[1059]	<220>
[1060]	<223> Fcab FS18-7-95 CH3结构域的核苷酸序列
[1061]	<400> 49
[1062]	ggccagcctc gagaaccaca ggtgtacacc ctgcccccat cctgggatga gccgtggggt 60
[1063]	gaagacgtca gctgacctg cctgggtcaaa ggcttctatc ccagcgacat cgccgtggag 120
[1064]	tgggagagca atgggtatca ggaagataac tataagacca cgcctcccggt gctggactcc 180
[1065]	gacggctcct tcttctcteta cagcaagctc accgtgccgt atgatagggtg ggtttggccg 240
[1066]	gatgagttct catgctccgt gatgcatgag gctctgcaca accactacac acagaagagc 300
[1067]	ctctccctgt ctccgggt 318
[1068]	<210> 50
[1069]	<211> 106
[1070]	<212> PRT
[1071]	<213> 人工序列
[1072]	<220>
[1073]	<223> Fcab FS18-7-95 CH3结构域的氨基酸序列
[1074]	<400> 50
[1075]	Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Trp Asp
[1076]	1 5 10 15
[1077]	Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys Leu Val Lys Gly Phe
[1078]	20 25 30
[1079]	Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Tyr Gln Glu
[1080]	35 40 45
[1081]	Asp Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
[1082]	50 55 60
[1083]	Phe Leu Tyr Ser Lys Leu Thr Val Pro Tyr Asp Arg Trp Val Trp Pro
[1084]	65 70 75 80
[1085]	Asp Glu Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
[1086]	85 90 95
[1087]	Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[1088]	100 105
[1089]	<210> 51
[1090]	<211> 216
[1091]	<212> PRT

[1092]	<213>	人工序列
[1093]	<220>	
[1094]	<223>	Fcab FS18-7-95 CH2和CH3结构域的氨基酸序列,包括LALA突变
[1095]	<400>	51
[1096]	Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys	
[1097]	1 5 10 15	
[1098]	Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val	
[1099]	20 25 30	
[1100]	Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr	
[1101]	35 40 45	
[1102]	Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu	
[1103]	50 55 60	
[1104]	Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His	
[1105]	65 70 75 80	
[1106]	Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys	
[1107]	85 90 95	
[1108]	Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln	
[1109]	100 105 110	
[1110]	Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro	
[1111]	115 120 125	
[1112]	Trp Gly Glu Asp Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro	
[1113]	130 135 140	
[1114]	Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Tyr Gln Glu Asp Asn	
[1115]	145 150 155 160	
[1116]	Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu	
[1117]	165 170 175	
[1118]	Tyr Ser Lys Leu Thr Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu	
[1119]	180 185 190	
[1120]	Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln	
[1121]	195 200 205	
[1122]	Lys Ser Leu Ser Leu Ser Pro Gly	
[1123]	210 215	
[1124]	<210>	52
[1125]	<211>	216
[1126]	<212>	PRT
[1127]	<213>	人工序列
[1128]	<220>	
[1129]	<223>	Fcab FS18-7-95 CH2和CH3结构域的氨基酸序列,没有LALA突变
[1130]	<400>	52

[1131]	Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
[1132]	1 5 10 15
[1133]	Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
[1134]	20 25 30
[1135]	Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
[1136]	35 40 45
[1137]	Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
[1138]	50 55 60
[1139]	Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
[1140]	65 70 75 80
[1141]	Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
[1142]	85 90 95
[1143]	Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
[1144]	100 105 110
[1145]	Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro
[1146]	115 120 125
[1147]	Trp Gly Glu Asp Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
[1148]	130 135 140
[1149]	Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Tyr Gln Glu Asp Asn
[1150]	145 150 155 160
[1151]	Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
[1152]	165 170 175
[1153]	Tyr Ser Lys Leu Thr Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu
[1154]	180 185 190
[1155]	Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
[1156]	195 200 205
[1157]	Lys Ser Leu Ser Leu Ser Pro Gly
[1158]	210 215
[1159]	<210> 53
[1160]	<211> 110
[1161]	<212> PRT
[1162]	<213> 人工序列
[1163]	<220>
[1164]	<223> 野生型人IgG1 CH2结构域的氨基酸序列
[1165]	<400> 53
[1166]	Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
[1167]	1 5 10 15
[1168]	Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
[1169]	20 25 30

[1170]	Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
[1171]	35 40 45
[1172]	Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
[1173]	50 55 60
[1174]	Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
[1175]	65 70 75 80
[1176]	Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
[1177]	85 90 95
[1178]	Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
[1179]	100 105 110
[1180]	<210> 54
[1181]	<211> 110
[1182]	<212> PRT
[1183]	<213> 人工序列
[1184]	<220>
[1185]	<223> 人IgG1 CH2结构域的氨基酸序列,包括“LALA突变”
[1186]	<400> 54
[1187]	Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
[1188]	1 5 10 15
[1189]	Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
[1190]	20 25 30
[1191]	Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
[1192]	35 40 45
[1193]	Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
[1194]	50 55 60
[1195]	Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
[1196]	65 70 75 80
[1197]	Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
[1198]	85 90 95
[1199]	Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
[1200]	100 105 110
[1201]	<210> 55
[1202]	<211> 216
[1203]	<212> PRT
[1204]	<213> 人工序列
[1205]	<220>
[1206]	<223> “野生型”Fcab CH2和CH3结构域的氨基酸序列,没有LALA突变
[1207]	<400> 55
[1208]	Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys

[1209]	1	5	10	15
[1210]	Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val			
[1211]	20	25	30	
[1212]	Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr			
[1213]	35	40	45	
[1214]	Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu			
[1215]	50	55	60	
[1216]	Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His			
[1217]	65	70	75	80
[1218]	Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys			
[1219]	85	90	95	
[1220]	Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln			
[1221]	100	105	110	
[1222]	Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu			
[1223]	115	120	125	
[1224]	Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro			
[1225]	130	135	140	
[1226]	Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn			
[1227]	145	150	155	160
[1228]	Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu			
[1229]	165	170	175	
[1230]	Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val			
[1231]	180	185	190	
[1232]	Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln			
[1233]	195	200	205	
[1234]	Lys Ser Leu Ser Leu Ser Pro Gly			
[1235]	210	215		
[1236]	<210> 56			
[1237]	<211> 216			
[1238]	<212> PRT			
[1239]	<213> 人工序列			
[1240]	<220>			
[1241]	<223> “野生型”Fcab CH2和CH3结构域的氨基酸序列,包括LALA突变			
[1242]	<400> 56			
[1243]	Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys			
[1244]	1	5	10	15
[1245]	Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val			
[1246]	20	25	30	
[1247]	Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr			

[1248]	35	40	45
[1249]	Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu		
[1250]	50	55	60
[1251]	Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His		
[1252]	65	70	75
[1253]	Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys		
[1254]	85	90	95
[1255]	Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln		
[1256]	100	105	110
[1257]	Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu		
[1258]	115	120	125
[1259]	Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro		
[1260]	130	135	140
[1261]	Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn		
[1262]	145	150	155
[1263]	Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu		
[1264]	165	170	175
[1265]	Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val		
[1266]	180	185	190
[1267]	Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln		
[1268]	195	200	205
[1269]	Lys Ser Leu Ser Leu Ser Pro Gly		
[1270]	210	215	
[1271]	<210> 57		
[1272]	<211> 15		
[1273]	<212> PRT		
[1274]	<213> 人工序列		
[1275]	<220>		
[1276]	<223> 人IgG1铰链区的氨基酸序列		
[1277]	<400> 57		
[1278]	Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro		
[1279]	1	5	10
[1280]	<210> 58		
[1281]	<211> 6		
[1282]	<212> PRT		
[1283]	<213> 人工序列		
[1284]	<220>		
[1285]	<223> 人IgG1截短的铰链区的氨基酸序列		
[1286]	<400> 58		

[1287]	Thr Cys Pro Pro Cys Pro
[1288]	1 5
[1289]	<210> 59
[1290]	<211> 222
[1291]	<212> PRT
[1292]	<213> 人工序列
[1293]	<220>
[1294]	<223> 抗小鼠LAG-3 Fcab FS18-7-108-29的氨基酸序列,包括LALA突变
[1295]	<400> 59
[1296]	Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
[1297]	1 5 10 15
[1298]	Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
[1299]	20 25 30
[1300]	Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
[1301]	35 40 45
[1302]	Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
[1303]	50 55 60
[1304]	Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
[1305]	65 70 75 80
[1306]	Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
[1307]	85 90 95
[1308]	Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
[1309]	100 105 110
[1310]	Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
[1311]	115 120 125
[1312]	Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys Leu
[1313]	130 135 140
[1314]	Val Lys Gly Phe Tyr Pro Ser Asp Ile Val Val Glu Trp Glu Ser Asn
[1315]	145 150 155 160
[1316]	Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
[1317]	165 170 175
[1318]	Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Phe Glu Arg
[1319]	180 185 190
[1320]	Trp Met Trp Pro Asp Glu Phe Ser Cys Ser Val Met His Glu Ala Leu
[1321]	195 200 205
[1322]	His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[1323]	210 215 220
[1324]	<210> 60
[1325]	<211> 222

[1326]	<212>	PRT
[1327]	<213>	人工序列
[1328]	<220>	
[1329]	<223>	抗小鼠LAG-3 Fcab FS18-7-108-29的氨基酸序列,没有LALA突变
[1330]	<400>	60
[1331]	Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val	
[1332]	1	5 10 15
[1333]	Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr	
[1334]	20 25 30	
[1335]	Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu	
[1336]	35 40 45	
[1337]	Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys	
[1338]	50 55 60	
[1339]	Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser	
[1340]	65 70 75 80	
[1341]	Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys	
[1342]	85 90 95	
[1343]	Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile	
[1344]	100 105 110	
[1345]	Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro	
[1346]	115 120 125	
[1347]	Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys Leu	
[1348]	130 135 140	
[1349]	Val Lys Gly Phe Tyr Pro Ser Asp Ile Val Val Glu Trp Glu Ser Asn	
[1350]	145 150 155 160	
[1351]	Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser	
[1352]	165 170 175	
[1353]	Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Phe Glu Arg	
[1354]	180 185 190	
[1355]	Trp Met Trp Pro Asp Glu Phe Ser Cys Ser Val Met His Glu Ala Leu	
[1356]	195 200 205	
[1357]	His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly	
[1358]	210 215 220	
[1359]	<210>	61
[1360]	<211>	222
[1361]	<212>	PRT
[1362]	<213>	人工序列
[1363]	<220>	
[1364]	<223>	抗小鼠LAG-3 Fcab FS18-7-108-35的氨基酸序列,包括LALA突变

[1365]	<400> 61
[1366]	Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
[1367]	1 5 10 15
[1368]	Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
[1369]	20 25 30
[1370]	Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
[1371]	35 40 45
[1372]	Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
[1373]	50 55 60
[1374]	Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
[1375]	65 70 75 80
[1376]	Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
[1377]	85 90 95
[1378]	Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
[1379]	100 105 110
[1380]	Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
[1381]	115 120 125
[1382]	Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys Leu
[1383]	130 135 140
[1384]	Val Lys Gly Phe Tyr Pro Ser Asp Ile Ser Val Glu Trp Glu Ser Asn
[1385]	145 150 155 160
[1386]	Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
[1387]	165 170 175
[1388]	Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Phe Glu Arg
[1389]	180 185 190
[1390]	Trp Met Trp Pro Asp Glu Phe Ser Cys Ser Val Met His Glu Ala Leu
[1391]	195 200 205
[1392]	His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[1393]	210 215 220
[1394]	<210> 62
[1395]	<211> 222
[1396]	<212> PRT
[1397]	<213> 人工序列
[1398]	<220>
[1399]	<223> 抗小鼠LAG-3 Fcab FS18-7-108-35的氨基酸序列,没有LALA突变
[1400]	<400> 62
[1401]	Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
[1402]	1 5 10 15
[1403]	Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr

[1404]	20	25	30
[1405]	Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu		
[1406]	35	40	45
[1407]	Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys		
[1408]	50	55	60
[1409]	Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser		
[1410]	65	70	75
[1411]	Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys		
[1412]	85	90	95
[1413]	Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile		
[1414]	100	105	110
[1415]	Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro		
[1416]	115	120	125
[1417]	Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys Leu		
[1418]	130	135	140
[1419]	Val Lys Gly Phe Tyr Pro Ser Asp Ile Ser Val Glu Trp Glu Ser Asn		
[1420]	145	150	155
[1421]	Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser		
[1422]	165	170	175
[1423]	Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Phe Glu Arg		
[1424]	180	185	190
[1425]	Trp Met Trp Pro Asp Glu Phe Ser Cys Ser Val Met His Glu Ala Leu		
[1426]	195	200	205
[1427]	His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
[1428]	210	215	220
[1429]	<210> 63		
[1430]	<211> 447		
[1431]	<212> PRT		
[1432]	<213> 人工序列		
[1433]	<220>		
[1434]	<223> 抗人LAG-3/FITC mAb2 FS18-7-9/4420的重链的氨基酸序列,包括LALA突		
	变		
[1435]	<400> 63		
[1436]	Glu Val Lys Leu Asp Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Arg		
[1437]	1	5	10
[1438]	Pro Met Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Tyr		
[1439]	20	25	30
[1440]	Trp Met Asn Trp Val Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val		
[1441]	35	40	45

[1442]	Ala	Gln	Ile	Arg	Asn	Lys	Pro	Tyr	Asn	Tyr	Glu	Thr	Tyr	Tyr	Ser	Asp
[1443]	50						55					60				
[1444]	Ser	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Ser	Ser
[1445]	65					70					75					80
[1446]	Val	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Arg	Val	Glu	Asp	Met	Gly	Ile	Tyr
[1447]					85					90					95	
[1448]	Tyr	Cys	Thr	Gly	Ser	Tyr	Tyr	Gly	Met	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
[1449]				100					105					110		
[1450]	Ser	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro
[1451]				115					120					125		
[1452]	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly
[1453]		130					135					140				
[1454]	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn
[1455]	145					150					155					160
[1456]	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln
[1457]					165					170					175	
[1458]	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser
[1459]				180					185					190		
[1460]	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser
[1461]			195					200					205			
[1462]	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr
[1463]		210					215					220				
[1464]	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser
[1465]	225					230					235					240
[1466]	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
[1467]				245						250					255	
[1468]	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro
[1469]				260					265					270		
[1470]	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
[1471]			275					280					285			
[1472]	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val
[1473]		290					295					300				
[1474]	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr
[1475]	305					310					315					320
[1476]	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr
[1477]					325					330				335		
[1478]	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu
[1479]				340					345					350		
[1480]	Pro	Pro	Ser	Trp	Asp	Glu	Pro	Trp	Gly	Glu	Asp	Val	Ser	Leu	Thr	Cys

[1481]	355	360	365
[1482]	Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser		
[1483]	370	375	380
[1484]	Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp		
[1485]	385	390	395
[1486]	Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Tyr Asp		
[1487]	405	410	415
[1488]	Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val Met His Glu Ala		
[1489]	420	425	430
[1490]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
[1491]	435	440	445
[1492]	<210> 64		
[1493]	<211> 447		
[1494]	<212> PRT		
[1495]	<213> 人工序列		
[1496]	<220>		
[1497]	<223> 抗人LAG-3/FITC mAb2 FS18-7-9/4420的重链的氨基酸序列,没有LALA突变		
[1498]	<400> 64		
[1499]	Glu Val Lys Leu Asp Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Arg		
[1500]	1	5	10
[1501]	Pro Met Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Tyr		
[1502]	20	25	30
[1503]	Trp Met Asn Trp Val Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val		
[1504]	35	40	45
[1505]	Ala Gln Ile Arg Asn Lys Pro Tyr Asn Tyr Glu Thr Tyr Tyr Ser Asp		
[1506]	50	55	60
[1507]	Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser		
[1508]	65	70	75
[1509]	Val Tyr Leu Gln Met Asn Asn Leu Arg Val Glu Asp Met Gly Ile Tyr		
[1510]	85	90	95
[1511]	Tyr Cys Thr Gly Ser Tyr Tyr Gly Met Asp Tyr Trp Gly Gln Gly Thr		
[1512]	100	105	110
[1513]	Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro		
[1514]	115	120	125
[1515]	Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly		
[1516]	130	135	140
[1517]	Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn		
[1518]	145	150	155
			160

[1519]	Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln		
[1520]		165	170
[1521]	Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser		175
[1522]		180	185
[1523]	Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser		190
[1524]		195	200
[1525]	Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr		205
[1526]		210	215
[1527]	His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser		220
[1528]		225	230
[1529]	Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg		235
[1530]		245	250
[1531]	Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro		255
[1532]		260	265
[1533]	Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala		270
[1534]		275	280
[1535]	Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val		285
[1536]		290	295
[1537]	Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr		300
[1538]		305	310
[1539]	Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr		315
[1540]		325	330
[1541]	Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu		335
[1542]		340	345
[1543]	Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys		350
[1544]		355	360
[1545]	Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser		365
[1546]		370	375
[1547]	Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp		380
[1548]		385	390
[1549]	Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Tyr Asp		395
[1550]		405	410
[1551]	Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val Met His Glu Ala		415
[1552]		420	425
[1553]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		430
[1554]		435	440
[1555]	<210> 65		445
[1556]	<211> 447		
[1557]	<212> PRT		

[1558]	<213> 人工序列															
[1559]	<220>															
[1560]	<223> 抗人LAG-3/FITC mAb2 FS18-7-32/4420的重链的氨基酸序列,包括LALA突变															
[1561]	<400> 65															
[1562]	Glu	Val	Lys	Leu	Asp	Glu	Thr	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Arg
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[1564]	Pro	Met	Lys	Leu	Ser	Cys	Val	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Asp	Tyr
[1565]				20					25					30		
[1566]	Trp	Met	Asn	Trp	Val	Arg	Gln	Ser	Pro	Glu	Lys	Gly	Leu	Glu	Trp	Val
[1567]				35					40					45		
[1568]	Ala	Gln	Ile	Arg	Asn	Lys	Pro	Tyr	Asn	Tyr	Glu	Thr	Tyr	Tyr	Ser	Asp
[1569]		50					55						60			
[1570]	Ser	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Ser	Ser
[1571]	65					70					75				80	
[1572]	Val	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Arg	Val	Glu	Asp	Met	Gly	Ile	Tyr
[1573]					85					90					95	
[1574]	Tyr	Cys	Thr	Gly	Ser	Tyr	Tyr	Gly	Met	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
[1575]				100					105					110		
[1576]	Ser	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro
[1577]				115					120					125		
[1578]	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly
[1579]		130						135					140			
[1580]	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn
[1581]	145					150					155				160	
[1582]	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln
[1583]					165					170					175	
[1584]	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser
[1585]				180						185					190	
[1586]	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser
[1587]				195						200				205		
[1588]	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr
[1589]		210						215					220			
[1590]	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser
[1591]	225					230					235				240	
[1592]	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
[1593]					245					250					255	
[1594]	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro
[1595]				260						265					270	

[1596]	Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
[1597]	275 280 285
[1598]	Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
[1599]	290 295 300
[1600]	Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
[1601]	305 310 315 320
[1602]	Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
[1603]	325 330 335
[1604]	Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
[1605]	340 345 350
[1606]	Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys
[1607]	355 360 365
[1608]	Leu Val Lys Gly Phe Tyr Pro Ser Glu Ile Ala Val Glu Trp Glu Ser
[1609]	370 375 380
[1610]	Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
[1611]	385 390 395 400
[1612]	Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Tyr Asp
[1613]	405 410 415
[1614]	Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val Met His Glu Ala
[1615]	420 425 430
[1616]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[1617]	435 440 445
[1618]	<210> 66
[1619]	<211> 447
[1620]	<212> PRT
[1621]	<213> 人工序列
[1622]	<220>
[1623]	<223> 抗人LAG-3/FITC mAb2 FS18-7-32的重链的氨基酸序列,没有LALA突变
[1624]	<400> 66
[1625]	Glu Val Lys Leu Asp Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Arg
[1626]	1 5 10 15
[1627]	Pro Met Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[1628]	20 25 30
[1629]	Trp Met Asn Trp Val Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val
[1630]	35 40 45
[1631]	Ala Gln Ile Arg Asn Lys Pro Tyr Asn Tyr Glu Thr Tyr Tyr Ser Asp
[1632]	50 55 60
[1633]	Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser
[1634]	65 70 75 80

[1635]	Val	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Arg	Val	Glu	Asp	Met	Gly	Ile	Tyr
[1636]					85				90						95	
[1637]	Tyr	Cys	Thr	Gly	Ser	Tyr	Tyr	Gly	Met	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
[1638]				100				105						110		
[1639]	Ser	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro
[1640]			115					120					125			
[1641]	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly
[1642]		130						135				140				
[1643]	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn
[1644]	145					150					155				160	
[1645]	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln
[1646]				165						170					175	
[1647]	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser
[1648]				180						185				190		
[1649]	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser
[1650]			195					200					205			
[1651]	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr
[1652]		210					215					220				
[1653]	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser
[1654]	225					230					235				240	
[1655]	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
[1656]				245						250					255	
[1657]	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro
[1658]			260							265				270		
[1659]	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
[1660]		275						280					285			
[1661]	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val
[1662]		290						295				300				
[1663]	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr
[1664]	305					310					315				320	
[1665]	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr
[1666]				325						330				335		
[1667]	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu
[1668]			340							345				350		
[1669]	Pro	Pro	Ser	Trp	Asp	Glu	Pro	Trp	Gly	Glu	Asp	Val	Ser	Leu	Thr	Cys
[1670]			355						360				365			
[1671]	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Glu	Ile	Ala	Val	Glu	Trp	Glu	Ser
[1672]		370						375				380				
[1673]	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp

[1674]	385	390	395	400
[1675]	Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Tyr Asp			
[1676]	405	410	415	
[1677]	Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val Met His Glu Ala			
[1678]	420	425	430	
[1679]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly			
[1680]	435	440	445	
[1681]	<210> 67			
[1682]	<211> 447			
[1683]	<212> PRT			
[1684]	<213> 人工序列			
[1685]	<220>			
[1686]	<223> 抗人LAG-3/FITC mAb2 FS18-7-33/4420的重链的氨基酸序列,包括LALA突变			
[1687]	<400> 67			
[1688]	Glu Val Lys Leu Asp Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Arg			
[1689]	1	5	10	15
[1690]	Pro Met Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Tyr			
[1691]	20	25	30	
[1692]	Trp Met Asn Trp Val Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val			
[1693]	35	40	45	
[1694]	Ala Gln Ile Arg Asn Lys Pro Tyr Asn Tyr Glu Thr Tyr Tyr Ser Asp			
[1695]	50	55	60	
[1696]	Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser			
[1697]	65	70	75	80
[1698]	Val Tyr Leu Gln Met Asn Asn Leu Arg Val Glu Asp Met Gly Ile Tyr			
[1699]	85	90	95	
[1700]	Tyr Cys Thr Gly Ser Tyr Tyr Gly Met Asp Tyr Trp Gly Gln Gly Thr			
[1701]	100	105	110	
[1702]	Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro			
[1703]	115	120	125	
[1704]	Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly			
[1705]	130	135	140	
[1706]	Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn			
[1707]	145	150	155	160
[1708]	Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln			
[1709]	165	170	175	
[1710]	Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser			
[1711]	180	185	190	

[1712]	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser
[1713]		195						200						205		
[1714]	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr
[1715]		210						215						220		
[1716]	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser
[1717]	225						230					235				240
[1718]	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
[1719]					245					250						255
[1720]	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro
[1721]				260						265					270	
[1722]	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
[1723]			275							280					285	
[1724]	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val
[1725]		290						295					300			
[1726]	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr
[1727]	305						310					315				320
[1728]	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr
[1729]					325						330					335
[1730]	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu
[1731]				340						345					350	
[1732]	Pro	Pro	Ser	Trp	Asp	Glu	Pro	Trp	Gly	Glu	Asp	Val	Ser	Leu	Thr	Cys
[1733]			355						360					365		
[1734]	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser
[1735]		370							375					380		
[1736]	Asn	Gly	Gln	Pro	Glu	Asp	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp
[1737]	385					390						395				400
[1738]	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Pro	Tyr	Asp
[1739]					405					410					415	
[1740]	Arg	Trp	Val	Trp	Pro	Asp	Glu	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala
[1741]				420						425					430	
[1742]	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	
[1743]			435						440						445	
[1744]	<210> 68															
[1745]	<211> 447															
[1746]	<212> PRT															
[1747]	<213> 人工序列															
[1748]	<220>															
[1749]	<223> 抗人LAG-3/FITC mAb2 FS18-7-33/4420的重链的氨基酸序列,没有LALA突变															

[1750]	<400> 68
[1751]	Glu Val Lys Leu Asp Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Arg
[1752]	1 5 10 15
[1753]	Pro Met Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[1754]	20 25 30
[1755]	Trp Met Asn Trp Val Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val
[1756]	35 40 45
[1757]	Ala Gln Ile Arg Asn Lys Pro Tyr Asn Tyr Glu Thr Tyr Tyr Ser Asp
[1758]	50 55 60
[1759]	Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser
[1760]	65 70 75 80
[1761]	Val Tyr Leu Gln Met Asn Asn Leu Arg Val Glu Asp Met Gly Ile Tyr
[1762]	85 90 95
[1763]	Tyr Cys Thr Gly Ser Tyr Tyr Gly Met Asp Tyr Trp Gly Gln Gly Thr
[1764]	100 105 110
[1765]	Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
[1766]	115 120 125
[1767]	Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
[1768]	130 135 140
[1769]	Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
[1770]	145 150 155 160
[1771]	Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
[1772]	165 170 175
[1773]	Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
[1774]	180 185 190
[1775]	Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
[1776]	195 200 205
[1777]	Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
[1778]	210 215 220
[1779]	His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
[1780]	225 230 235 240
[1781]	Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
[1782]	245 250 255
[1783]	Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
[1784]	260 265 270
[1785]	Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
[1786]	275 280 285
[1787]	Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
[1788]	290 295 300

[1789]	Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
[1790]	305 310 315 320
[1791]	Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
[1792]	325 330 335
[1793]	Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
[1794]	340 345 350
[1795]	Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys
[1796]	355 360 365
[1797]	Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
[1798]	370 375 380
[1799]	Asn Gly Gln Pro Glu Asp Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
[1800]	385 390 395 400
[1801]	Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Tyr Asp
[1802]	405 410 415
[1803]	Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val Met His Glu Ala
[1804]	420 425 430
[1805]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[1806]	435 440 445
[1807]	<210> 69
[1808]	<211> 447
[1809]	<212> PRT
[1810]	<213> 人工序列
[1811]	<220>
[1812]	<223> 抗人LAG-3/FITC mAb2 FS18-7-36/4420的重链的氨基酸序列,包括LALA突变
[1813]	<400> 69
[1814]	Glu Val Lys Leu Asp Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Arg
[1815]	1 5 10 15
[1816]	Pro Met Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[1817]	20 25 30
[1818]	Trp Met Asn Trp Val Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val
[1819]	35 40 45
[1820]	Ala Gln Ile Arg Asn Lys Pro Tyr Asn Tyr Glu Thr Tyr Tyr Ser Asp
[1821]	50 55 60
[1822]	Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser
[1823]	65 70 75 80
[1824]	Val Tyr Leu Gln Met Asn Asn Leu Arg Val Glu Asp Met Gly Ile Tyr
[1825]	85 90 95
[1826]	Tyr Cys Thr Gly Ser Tyr Tyr Gly Met Asp Tyr Trp Gly Gln Gly Thr

[1827]		100		105		110											
[1828]	Ser	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	
[1829]		115															
[1830]	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	
[1831]		130															
[1832]	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	
[1833]		145															
[1834]	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	
[1835]																	
[1836]	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	
[1837]																	
[1838]	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	
[1839]																	
[1840]	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	
[1841]																	
[1842]	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser	
[1843]																	
[1844]	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	
[1845]																	
[1846]	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	
[1847]																	
[1848]	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	
[1849]																	
[1850]	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	
[1851]																	
[1852]	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	
[1853]																	
[1854]	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	
[1855]																	
[1856]	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	
[1857]																	
[1858]	Pro	Pro	Ser	Trp	Asp	Glu	Pro	Trp	Gly	Glu	Asp	Val	Ser	Leu	Thr	Cys	
[1859]																	
[1860]	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	
[1861]																	
[1862]	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	
[1863]																	
[1864]	Ser	Asp	Gly	Ser	Tyr	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Pro	Tyr	Asp	
[1865]																	

[1866]	Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val Met His Glu Ala
[1867]	420 425 430
[1868]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[1869]	435 440 445
[1870]	<210> 70
[1871]	<211> 447
[1872]	<212> PRT
[1873]	<213> 人工序列
[1874]	<220>
[1875]	<223> 抗人LAG-3/FITC mAb2 FS18-7-36/4420的重链的氨基酸序列,没有LALA突变
[1876]	<400> 70
[1877]	Glu Val Lys Leu Asp Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Arg
[1878]	1 5 10 15
[1879]	Pro Met Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[1880]	20 25 30
[1881]	Trp Met Asn Trp Val Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val
[1882]	35 40 45
[1883]	Ala Gln Ile Arg Asn Lys Pro Tyr Asn Tyr Glu Thr Tyr Tyr Ser Asp
[1884]	50 55 60
[1885]	Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser
[1886]	65 70 75 80
[1887]	Val Tyr Leu Gln Met Asn Asn Leu Arg Val Glu Asp Met Gly Ile Tyr
[1888]	85 90 95
[1889]	Tyr Cys Thr Gly Ser Tyr Tyr Gly Met Asp Tyr Trp Gly Gln Gly Thr
[1890]	100 105 110
[1891]	Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
[1892]	115 120 125
[1893]	Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
[1894]	130 135 140
[1895]	Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
[1896]	145 150 155 160
[1897]	Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
[1898]	165 170 175
[1899]	Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
[1900]	180 185 190
[1901]	Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
[1902]	195 200 205
[1903]	Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr

[1904]	210	215	220
[1905]	His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser		
[1906]	225	230	235 240
[1907]	Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg		
[1908]	245	250	255
[1909]	Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro		
[1910]	260	265	270
[1911]	Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala		
[1912]	275	280	285
[1913]	Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val		
[1914]	290	295	300
[1915]	Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr		
[1916]	305	310	315 320
[1917]	Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr		
[1918]	325	330	335
[1919]	Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu		
[1920]	340	345	350
[1921]	Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys		
[1922]	355	360	365
[1923]	Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser		
[1924]	370	375	380
[1925]	Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp		
[1926]	385	390	395 400
[1927]	Ser Asp Gly Ser Tyr Phe Leu Tyr Ser Lys Leu Thr Val Pro Tyr Asp		
[1928]	405	410	415
[1929]	Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val Met His Glu Ala		
[1930]	420	425	430
[1931]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
[1932]	435	440	445
[1933]	<210> 71		
[1934]	<211> 447		
[1935]	<212> PRT		
[1936]	<213> 人工序列		
[1937]	<220>		
[1938]	<223> 抗人LAG-3/FITC mAb2 FS18-7-58/4420的重链的氨基酸序列,包括LALA突		
	变		
[1939]	<400> 71		
[1940]	Glu Val Lys Leu Asp Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Arg		
[1941]	1	5	10 15

[1942]	Pro	Met	Lys	Leu	Ser	Cys	Val	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Asp	Tyr
[1943]				20					25					30		
[1944]	Trp	Met	Asn	Trp	Val	Arg	Gln	Ser	Pro	Glu	Lys	Gly	Leu	Glu	Trp	Val
[1945]			35					40					45			
[1946]	Ala	Gln	Ile	Arg	Asn	Lys	Pro	Tyr	Asn	Tyr	Glu	Thr	Tyr	Tyr	Ser	Asp
[1947]		50					55					60				
[1948]	Ser	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Ser	Ser
[1949]	65					70				75					80	
[1950]	Val	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Arg	Val	Glu	Asp	Met	Gly	Ile	Tyr
[1951]					85					90				95		
[1952]	Tyr	Cys	Thr	Gly	Ser	Tyr	Tyr	Gly	Met	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
[1953]				100					105					110		
[1954]	Ser	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro
[1955]			115					120					125			
[1956]	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly
[1957]		130						135				140				
[1958]	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn
[1959]	145					150				155					160	
[1960]	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln
[1961]					165					170					175	
[1962]	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser
[1963]				180					185					190		
[1964]	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser
[1965]			195					200					205			
[1966]	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr
[1967]		210					215					220				
[1968]	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser
[1969]	225					230				235					240	
[1970]	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
[1971]					245					250					255	
[1972]	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro
[1973]				260					265					270		
[1974]	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
[1975]			275					280					285			
[1976]	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val
[1977]		290						295					300			
[1978]	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr
[1979]	305					310				315					320	
[1980]	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr

[1981]		325		330		335
[1982]	Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu					
[1983]		340		345		350
[1984]	Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys					
[1985]		355		360		365
[1986]	Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser					
[1987]		370		375		380
[1988]	Asn Gly Tyr Pro Glu Ile Glu Phe Lys Thr Thr Pro Pro Val Leu Asp					
[1989]		385		390		395
[1990]	Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Tyr Asp					
[1991]		405		410		415
[1992]	Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val Met His Glu Ala					
[1993]		420		425		430
[1994]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly					
[1995]		435		440		445
[1996]	<210> 72					
[1997]	<211> 447					
[1998]	<212> PRT					
[1999]	<213> 人工序列					
[2000]	<220>					
[2001]	<223> 抗人LAG-3/FITC mAb2 FS18-7-58/4420的重链的氨基酸序列,没有LALA突变					
[2002]	<400> 72					
[2003]	Glu Val Lys Leu Asp Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Arg					
[2004]	1	5		10		15
[2005]	Pro Met Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Tyr					
[2006]		20		25		30
[2007]	Trp Met Asn Trp Val Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val					
[2008]		35		40		45
[2009]	Ala Gln Ile Arg Asn Lys Pro Tyr Asn Tyr Glu Thr Tyr Tyr Ser Asp					
[2010]		50		55		60
[2011]	Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser					
[2012]	65		70		75	80
[2013]	Val Tyr Leu Gln Met Asn Asn Leu Arg Val Glu Asp Met Gly Ile Tyr					
[2014]		85		90		95
[2015]	Tyr Cys Thr Gly Ser Tyr Tyr Gly Met Asp Tyr Trp Gly Gln Gly Thr					
[2016]		100		105		110
[2017]	Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro					
[2018]		115		120		125

[2019]	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly
[2020]	130						135					140				
[2021]	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn
[2022]	145					150					155					160
[2023]	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln
[2024]					165					170					175	
[2025]	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser
[2026]				180					185					190		
[2027]	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser
[2028]		195						200					205			
[2029]	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr
[2030]	210						215					220				
[2031]	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser
[2032]	225					230					235					240
[2033]	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
[2034]					245					250					255	
[2035]	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro
[2036]				260						265				270		
[2037]	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
[2038]			275						280					285		
[2039]	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val
[2040]	290						295					300				
[2041]	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr
[2042]	305					310					315					320
[2043]	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr
[2044]				325						330				335		
[2045]	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu
[2046]				340					345					350		
[2047]	Pro	Pro	Ser	Trp	Asp	Glu	Pro	Trp	Gly	Glu	Asp	Val	Ser	Leu	Thr	Cys
[2048]			355						360				365			
[2049]	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser
[2050]	370						375					380				
[2051]	Asn	Gly	Tyr	Pro	Glu	Ile	Glu	Phe	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp
[2052]	385					390					395					400
[2053]	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Pro	Tyr	Asp
[2054]				405						410				415		
[2055]	Arg	Trp	Val	Trp	Pro	Asp	Glu	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala
[2056]				420					425				430			
[2057]	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	

[2058]	435	440	445
[2059]	<210> 73		
[2060]	<211> 447		
[2061]	<212> PRT		
[2062]	<213> 人工序列		
[2063]	<220>		
[2064]	<223> 抗人LAG-3/FITC mAb2 FS18-7-62/4420的重链的氨基酸序列,包括LALA突变		
[2065]	<400> 73		
[2066]	Glu Val Lys Leu Asp Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Arg		
[2067]	1 5 10 15		
[2068]	Pro Met Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Tyr		
[2069]	20 25 30		
[2070]	Trp Met Asn Trp Val Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val		
[2071]	35 40 45		
[2072]	Ala Gln Ile Arg Asn Lys Pro Tyr Asn Tyr Glu Thr Tyr Tyr Ser Asp		
[2073]	50 55 60		
[2074]	Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser		
[2075]	65 70 75 80		
[2076]	Val Tyr Leu Gln Met Asn Asn Leu Arg Val Glu Asp Met Gly Ile Tyr		
[2077]	85 90 95		
[2078]	Tyr Cys Thr Gly Ser Tyr Tyr Gly Met Asp Tyr Trp Gly Gln Gly Thr		
[2079]	100 105 110		
[2080]	Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro		
[2081]	115 120 125		
[2082]	Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly		
[2083]	130 135 140		
[2084]	Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn		
[2085]	145 150 155 160		
[2086]	Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln		
[2087]	165 170 175		
[2088]	Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser		
[2089]	180 185 190		
[2090]	Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser		
[2091]	195 200 205		
[2092]	Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr		
[2093]	210 215 220		
[2094]	His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser		
[2095]	225 230 235 240		

[2096]	Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
[2097]	245 250 255
[2098]	Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
[2099]	260 265 270
[2100]	Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
[2101]	275 280 285
[2102]	Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
[2103]	290 295 300
[2104]	Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
[2105]	305 310 315 320
[2106]	Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
[2107]	325 330 335
[2108]	Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
[2109]	340 345 350
[2110]	Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys
[2111]	355 360 365
[2112]	Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
[2113]	370 375 380
[2114]	Asn Gly Ile Pro Glu Trp Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
[2115]	385 390 395 400
[2116]	Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Tyr Asp
[2117]	405 410 415
[2118]	Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val Met His Glu Ala
[2119]	420 425 430
[2120]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[2121]	435 440 445
[2122]	<210> 74
[2123]	<211> 447
[2124]	<212> PRT
[2125]	<213> 人工序列
[2126]	<220>
[2127]	<223> 抗人LAG-3/FITC mAb2 FS18-7-62/4420的重链的氨基酸序列,没有LALA突变
[2128]	<400> 74
[2129]	Glu Val Lys Leu Asp Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Arg
[2130]	1 5 10 15
[2131]	Pro Met Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[2132]	20 25 30
[2133]	Trp Met Asn Trp Val Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val

[2134]	35	40	45
[2135]	Ala Gln Ile Arg Asn Lys Pro Tyr Asn Tyr Glu Thr Tyr Tyr Ser Asp		
[2136]	50	55	60
[2137]	Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser		
[2138]	65	70	75
[2139]	Val Tyr Leu Gln Met Asn Asn Leu Arg Val Glu Asp Met Gly Ile Tyr		
[2140]	85	90	95
[2141]	Tyr Cys Thr Gly Ser Tyr Tyr Gly Met Asp Tyr Trp Gly Gln Gly Thr		
[2142]	100	105	110
[2143]	Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro		
[2144]	115	120	125
[2145]	Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly		
[2146]	130	135	140
[2147]	Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn		
[2148]	145	150	155
[2149]	Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln		
[2150]	165	170	175
[2151]	Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser		
[2152]	180	185	190
[2153]	Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser		
[2154]	195	200	205
[2155]	Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr		
[2156]	210	215	220
[2157]	His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser		
[2158]	225	230	235
[2159]	Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg		
[2160]	245	250	255
[2161]	Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro		
[2162]	260	265	270
[2163]	Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala		
[2164]	275	280	285
[2165]	Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val		
[2166]	290	295	300
[2167]	Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr		
[2168]	305	310	315
[2169]	Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr		
[2170]	325	330	335
[2171]	Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu		
[2172]	340	345	350

[2173]	Pro	Pro	Ser	Trp	Asp	Glu	Pro	Trp	Gly	Glu	Asp	Val	Ser	Leu	Thr	Cys
[2174]			355					360					365			
[2175]	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser
[2176]			370					375					380			
[2177]	Asn	Gly	Ile	Pro	Glu	Trp	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp
[2178]	385						390					395				400
[2179]	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Pro	Tyr	Asp
[2180]					405					410					415	
[2181]	Arg	Trp	Val	Trp	Pro	Asp	Glu	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala
[2182]					420					425					430	
[2183]	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	
[2184]			435					440							445	
[2185]	<210> 75															
[2186]	<211> 447															
[2187]	<212> PRT															
[2188]	<213> 人工序列															
[2189]	<220>															
[2190]	<223> 抗人LAG-3/FITC mAb2 FS18-7-65/4420的重链的氨基酸序列,包括LALA突变															
[2191]	<400> 75															
[2192]	Glu	Val	Lys	Leu	Asp	Glu	Thr	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Arg
[2193]	1				5					10					15	
[2194]	Pro	Met	Lys	Leu	Ser	Cys	Val	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Asp	Tyr
[2195]					20					25					30	
[2196]	Trp	Met	Asn	Trp	Val	Arg	Gln	Ser	Pro	Glu	Lys	Gly	Leu	Glu	Trp	Val
[2197]					35					40					45	
[2198]	Ala	Gln	Ile	Arg	Asn	Lys	Pro	Tyr	Asn	Tyr	Glu	Thr	Tyr	Tyr	Ser	Asp
[2199]					50					55					60	
[2200]	Ser	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Ser	Ser
[2201]	65					70					75					80
[2202]	Val	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Arg	Val	Glu	Asp	Met	Gly	Ile	Tyr
[2203]						85					90					95
[2204]	Tyr	Cys	Thr	Gly	Ser	Tyr	Tyr	Gly	Met	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
[2205]						100					105				110	
[2206]	Ser	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro
[2207]						115					120				125	
[2208]	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly
[2209]						130					135				140	
[2210]	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn

[2211]	145	150	155	160
[2212]	Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln			
[2213]		165	170	175
[2214]	Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser			
[2215]		180	185	190
[2216]	Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser			
[2217]		195	200	205
[2218]	Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr			
[2219]		210	215	220
[2220]	His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser			
[2221]	225	230	235	240
[2222]	Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg			
[2223]		245	250	255
[2224]	Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro			
[2225]		260	265	270
[2226]	Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala			
[2227]		275	280	285
[2228]	Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val			
[2229]		290	295	300
[2230]	Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr			
[2231]	305	310	315	320
[2232]	Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr			
[2233]		325	330	335
[2234]	Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu			
[2235]		340	345	350
[2236]	Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys			
[2237]		355	360	365
[2238]	Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser			
[2239]		370	375	380
[2240]	Asn Gly Tyr Ala Glu Tyr Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp			
[2241]	385	390	395	400
[2242]	Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Tyr Asp			
[2243]		405	410	415
[2244]	Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val Met His Glu Ala			
[2245]		420	425	430
[2246]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly			
[2247]		435	440	445
[2248]	<210> 76			
[2249]	<211> 447			

[2250]	<212>	PRT
[2251]	<213>	人工序列
[2252]	<220>	
[2253]	<223>	抗人LAG-3/FITC mAb2 FS18-7-65/4420的重链的氨基酸序列,没有LALA突变
[2254]	<400>	76
[2255]	Glu Val Lys Leu Asp Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Arg	
[2256]	1	5 10 15
[2257]	Pro Met Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Tyr	
[2258]	20	25 30
[2259]	Trp Met Asn Trp Val Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val	
[2260]	35	40 45
[2261]	Ala Gln Ile Arg Asn Lys Pro Tyr Asn Tyr Glu Thr Tyr Tyr Ser Asp	
[2262]	50	55 60
[2263]	Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser	
[2264]	65	70 75 80
[2265]	Val Tyr Leu Gln Met Asn Asn Leu Arg Val Glu Asp Met Gly Ile Tyr	
[2266]	85	90 95
[2267]	Tyr Cys Thr Gly Ser Tyr Tyr Gly Met Asp Tyr Trp Gly Gln Gly Thr	
[2268]	100	105 110
[2269]	Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro	
[2270]	115	120 125
[2271]	Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly	
[2272]	130	135 140
[2273]	Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn	
[2274]	145	150 155 160
[2275]	Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln	
[2276]	165	170 175
[2277]	Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser	
[2278]	180	185 190
[2279]	Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser	
[2280]	195	200 205
[2281]	Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr	
[2282]	210	215 220
[2283]	His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser	
[2284]	225	230 235 240
[2285]	Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg	
[2286]	245	250 255
[2287]	Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro	

[2288]	260	265	270
[2289]	Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala		
[2290]	275	280	285
[2291]	Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val		
[2292]	290	295	300
[2293]	Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr		
[2294]	305	310	315
[2295]	Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr		
[2296]	325	330	335
[2297]	Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu		
[2298]	340	345	350
[2299]	Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys		
[2300]	355	360	365
[2301]	Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser		
[2302]	370	375	380
[2303]	Asn Gly Tyr Ala Glu Tyr Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp		
[2304]	385	390	395
[2305]	Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Tyr Asp		
[2306]	405	410	415
[2307]	Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val Met His Glu Ala		
[2308]	420	425	430
[2309]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
[2310]	435	440	445
[2311]	<210> 77		
[2312]	<211> 447		
[2313]	<212> PRT		
[2314]	<213> 人工序列		
[2315]	<220>		
[2316]	<223> 的重链的氨基酸序列抗人LAG-3/FITC mAb2 FS18-7-78/4420,包括LALA突变		
[2317]	<400> 77		
[2318]	Glu Val Lys Leu Asp Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Arg		
[2319]	1	5	10
[2320]	Pro Met Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Tyr		
[2321]	20	25	30
[2322]	Trp Met Asn Trp Val Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val		
[2323]	35	40	45
[2324]	Ala Gln Ile Arg Asn Lys Pro Tyr Asn Tyr Glu Thr Tyr Tyr Ser Asp		
[2325]	50	55	60

[2326]	Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser
[2327]	65 70 75 80
[2328]	Val Tyr Leu Gln Met Asn Asn Leu Arg Val Glu Asp Met Gly Ile Tyr
[2329]	85 90 95
[2330]	Tyr Cys Thr Gly Ser Tyr Tyr Gly Met Asp Tyr Trp Gly Gln Gly Thr
[2331]	100 105 110
[2332]	Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
[2333]	115 120 125
[2334]	Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
[2335]	130 135 140
[2336]	Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
[2337]	145 150 155 160
[2338]	Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
[2339]	165 170 175
[2340]	Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
[2341]	180 185 190
[2342]	Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
[2343]	195 200 205
[2344]	Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
[2345]	210 215 220
[2346]	His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
[2347]	225 230 235 240
[2348]	Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
[2349]	245 250 255
[2350]	Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
[2351]	260 265 270
[2352]	Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
[2353]	275 280 285
[2354]	Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
[2355]	290 295 300
[2356]	Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
[2357]	305 310 315 320
[2358]	Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
[2359]	325 330 335
[2360]	Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
[2361]	340 345 350
[2362]	Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys
[2363]	355 360 365
[2364]	Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser

[2365]	370	375	380
[2366]	Asn Gly Tyr Lys Glu Glu Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp		
[2367]	385	390	395 400
[2368]	Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Tyr Asp		
[2369]	405	410	415
[2370]	Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val Met His Glu Ala		
[2371]	420	425	430
[2372]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
[2373]	435	440	445
[2374]	<210> 78		
[2375]	<211> 447		
[2376]	<212> PRT		
[2377]	<213> 人工序列		
[2378]	<220>		
[2379]	<223> 抗人LAG-3/FITC mAb2 FS18-7-78/4420的重链的氨基酸序列,没有LALA突变		
[2380]	<400> 78		
[2381]	Glu Val Lys Leu Asp Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Arg		
[2382]	1 5 10 15		
[2383]	Pro Met Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Tyr		
[2384]	20 25 30		
[2385]	Trp Met Asn Trp Val Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val		
[2386]	35 40 45		
[2387]	Ala Gln Ile Arg Asn Lys Pro Tyr Asn Tyr Glu Thr Tyr Tyr Ser Asp		
[2388]	50 55 60		
[2389]	Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser		
[2390]	65 70 75 80		
[2391]	Val Tyr Leu Gln Met Asn Asn Leu Arg Val Glu Asp Met Gly Ile Tyr		
[2392]	85 90 95		
[2393]	Tyr Cys Thr Gly Ser Tyr Tyr Gly Met Asp Tyr Trp Gly Gln Gly Thr		
[2394]	100 105 110		
[2395]	Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro		
[2396]	115 120 125		
[2397]	Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly		
[2398]	130 135 140		
[2399]	Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn		
[2400]	145 150 155 160		
[2401]	Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln		
[2402]	165 170 175		

[2403]	Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
[2404]	180 185 190
[2405]	Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
[2406]	195 200 205
[2407]	Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
[2408]	210 215 220
[2409]	His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
[2410]	225 230 235 240
[2411]	Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
[2412]	245 250 255
[2413]	Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
[2414]	260 265 270
[2415]	Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
[2416]	275 280 285
[2417]	Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
[2418]	290 295 300
[2419]	Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
[2420]	305 310 315 320
[2421]	Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
[2422]	325 330 335
[2423]	Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
[2424]	340 345 350
[2425]	Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys
[2426]	355 360 365
[2427]	Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
[2428]	370 375 380
[2429]	Asn Gly Tyr Lys Glu Glu Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
[2430]	385 390 395 400
[2431]	Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Tyr Asp
[2432]	405 410 415
[2433]	Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val Met His Glu Ala
[2434]	420 425 430
[2435]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[2436]	435 440 445
[2437]	<210> 79
[2438]	<211> 447
[2439]	<212> PRT
[2440]	<213> 人工序列
[2441]	<220>

[2442]	<223> 抗人LAG-3/FITC mAb2 FS18-7-88/4420的重链的氨基酸序列,包括LALA突变															
[2443]	<400> 79															
[2444]	Glu	Val	Lys	Leu	Asp	Glu	Thr	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Arg
[2445]	1			5					10					15		
[2446]	Pro	Met	Lys	Leu	Ser	Cys	Val	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Asp	Tyr
[2447]				20					25					30		
[2448]	Trp	Met	Asn	Trp	Val	Arg	Gln	Ser	Pro	Glu	Lys	Gly	Leu	Glu	Trp	Val
[2449]				35					40					45		
[2450]	Ala	Gln	Ile	Arg	Asn	Lys	Pro	Tyr	Asn	Tyr	Glu	Thr	Tyr	Tyr	Ser	Asp
[2451]		50						55					60			
[2452]	Ser	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Ser	Ser
[2453]	65					70				75				80		
[2454]	Val	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Arg	Val	Glu	Asp	Met	Gly	Ile	Tyr
[2455]					85					90				95		
[2456]	Tyr	Cys	Thr	Gly	Ser	Tyr	Tyr	Gly	Met	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
[2457]				100					105					110		
[2458]	Ser	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro
[2459]				115					120					125		
[2460]	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly
[2461]		130						135					140			
[2462]	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn
[2463]	145					150					155			160		
[2464]	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln
[2465]					165					170				175		
[2466]	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser
[2467]				180						185				190		
[2468]	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser
[2469]			195					200					205			
[2470]	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr
[2471]		210						215					220			
[2472]	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser
[2473]	225					230					235				240	
[2474]	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
[2475]					245					250					255	
[2476]	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro
[2477]				260						265				270		
[2478]	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
[2479]			275						280					285		

[2480]	Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
[2481]	290 295 300
[2482]	Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
[2483]	305 310 315 320
[2484]	Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
[2485]	325 330 335
[2486]	Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
[2487]	340 345 350
[2488]	Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys
[2489]	355 360 365
[2490]	Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
[2491]	370 375 380
[2492]	Asn Gly Val Pro Glu Leu Asn Val Lys Thr Thr Pro Pro Val Leu Asp
[2493]	385 390 395 400
[2494]	Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Tyr Asp
[2495]	405 410 415
[2496]	Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val Met His Glu Ala
[2497]	420 425 430
[2498]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[2499]	435 440 445
[2500]	<210> 80
[2501]	<211> 447
[2502]	<212> PRT
[2503]	<213> 人工序列
[2504]	<220>
[2505]	<223> 抗人LAG-3/FITC mAb2 FS18-7-88/4420的重链的氨基酸序列,没有LALA突变
[2506]	<400> 80
[2507]	Glu Val Lys Leu Asp Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Arg
[2508]	1 5 10 15
[2509]	Pro Met Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[2510]	20 25 30
[2511]	Trp Met Asn Trp Val Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val
[2512]	35 40 45
[2513]	Ala Gln Ile Arg Asn Lys Pro Tyr Asn Tyr Glu Thr Tyr Tyr Ser Asp
[2514]	50 55 60
[2515]	Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser
[2516]	65 70 75 80
[2517]	Val Tyr Leu Gln Met Asn Asn Leu Arg Val Glu Asp Met Gly Ile Tyr

[2518]					85					90						95
[2519]	Tyr	Cys	Thr	Gly	Ser	Tyr	Tyr	Gly	Met	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
[2520]					100					105						110
[2521]	Ser	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro
[2522]					115					120						125
[2523]	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly
[2524]					130					135						140
[2525]	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn
[2526]					145					150						160
[2527]	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln
[2528]					165					170						175
[2529]	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser
[2530]					180					185						190
[2531]	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser
[2532]					195					200						205
[2533]	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr
[2534]					210					215						220
[2535]	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser
[2536]					225					230						240
[2537]	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
[2538]					245					250						255
[2539]	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro
[2540]					260					265						270
[2541]	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
[2542]					275					280						285
[2543]	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val
[2544]					290					295						300
[2545]	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr
[2546]					305					310						320
[2547]	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr
[2548]					325					330						335
[2549]	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu
[2550]					340					345						350
[2551]	Pro	Pro	Ser	Trp	Asp	Glu	Pro	Trp	Gly	Glu	Asp	Val	Ser	Leu	Thr	Cys
[2552]					355					360						365
[2553]	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser
[2554]					370					375						380
[2555]	Asn	Gly	Val	Pro	Glu	Leu	Asn	Val	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp
[2556]					385					390						400

[2557]	Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Tyr Asp
[2558]	405 410 415
[2559]	Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val Met His Glu Ala
[2560]	420 425 430
[2561]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[2562]	435 440 445
[2563]	<210> 81
[2564]	<211> 447
[2565]	<212> PRT
[2566]	<213> 人工序列
[2567]	<220>
[2568]	<223> 抗人LAG-3/FITC mAb2 FS18-7-95/4420的重链的氨基酸序列,包括LALA突变
[2569]	<400> 81
[2570]	Glu Val Lys Leu Asp Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Arg
[2571]	1 5 10 15
[2572]	Pro Met Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[2573]	20 25 30
[2574]	Trp Met Asn Trp Val Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val
[2575]	35 40 45
[2576]	Ala Gln Ile Arg Asn Lys Pro Tyr Asn Tyr Glu Thr Tyr Tyr Ser Asp
[2577]	50 55 60
[2578]	Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser
[2579]	65 70 75 80
[2580]	Val Tyr Leu Gln Met Asn Asn Leu Arg Val Glu Asp Met Gly Ile Tyr
[2581]	85 90 95
[2582]	Tyr Cys Thr Gly Ser Tyr Tyr Gly Met Asp Tyr Trp Gly Gln Gly Thr
[2583]	100 105 110
[2584]	Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
[2585]	115 120 125
[2586]	Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
[2587]	130 135 140
[2588]	Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
[2589]	145 150 155 160
[2590]	Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
[2591]	165 170 175
[2592]	Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
[2593]	180 185 190
[2594]	Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser

[2595]	195	200	205
[2596]	Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr		
[2597]	210	215	220
[2598]	His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser		
[2599]	225	230	235
[2600]	Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg		
[2601]	245	250	255
[2602]	Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro		
[2603]	260	265	270
[2604]	Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala		
[2605]	275	280	285
[2606]	Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val		
[2607]	290	295	300
[2608]	Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr		
[2609]	305	310	315
[2610]	Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr		
[2611]	325	330	335
[2612]	Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu		
[2613]	340	345	350
[2614]	Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys		
[2615]	355	360	365
[2616]	Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser		
[2617]	370	375	380
[2618]	Asn Gly Tyr Gln Glu Asp Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp		
[2619]	385	390	395
[2620]	Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Tyr Asp		
[2621]	405	410	415
[2622]	Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val Met His Glu Ala		
[2623]	420	425	430
[2624]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
[2625]	435	440	445
[2626]	<210> 82		
[2627]	<211> 447		
[2628]	<212> PRT		
[2629]	<213> 人工序列		
[2630]	<220>		
[2631]	<223> 抗人LAG-3/FITC mAb2 FS18-7-95/4420的重链的氨基酸序列,没有LALA突 变		
[2632]	<400> 82		

[2633]	Glu	Val	Lys	Leu	Asp	Glu	Thr	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Arg
[2634]	1			5					10					15		
[2635]	Pro	Met	Lys	Leu	Ser	Cys	Val	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Asp	Tyr
[2636]				20					25					30		
[2637]	Trp	Met	Asn	Trp	Val	Arg	Gln	Ser	Pro	Glu	Lys	Gly	Leu	Glu	Trp	Val
[2638]				35					40					45		
[2639]	Ala	Gln	Ile	Arg	Asn	Lys	Pro	Tyr	Asn	Tyr	Glu	Thr	Tyr	Tyr	Ser	Asp
[2640]		50						55					60			
[2641]	Ser	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asp	Ser	Lys	Ser	Ser
[2642]	65					70					75					80
[2643]	Val	Tyr	Leu	Gln	Met	Asn	Asn	Leu	Arg	Val	Glu	Asp	Met	Gly	Ile	Tyr
[2644]					85					90					95	
[2645]	Tyr	Cys	Thr	Gly	Ser	Tyr	Tyr	Gly	Met	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
[2646]				100					105					110		
[2647]	Ser	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro
[2648]				115					120					125		
[2649]	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly
[2650]		130						135					140			
[2651]	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn
[2652]	145					150					155					160
[2653]	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln
[2654]					165					170					175	
[2655]	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser
[2656]				180					185					190		
[2657]	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser
[2658]				195					200					205		
[2659]	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr
[2660]		210						215					220			
[2661]	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser
[2662]	225					230					235					240
[2663]	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
[2664]					245					250					255	
[2665]	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro
[2666]				260					265					270		
[2667]	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
[2668]				275					280					285		
[2669]	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val
[2670]		290						295					300			
[2671]	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr

[2672]	305	310	315	320
[2673]	Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr			
[2674]		325	330	335
[2675]	Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu			
[2676]		340	345	350
[2677]	Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys			
[2678]		355	360	365
[2679]	Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser			
[2680]		370	375	380
[2681]	Asn Gly Tyr Gln Glu Asp Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp			
[2682]	385	390	395	400
[2683]	Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Tyr Asp			
[2684]		405	410	415
[2685]	Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val Met His Glu Ala			
[2686]		420	425	430
[2687]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly			
[2688]		435	440	445
[2689]	<210> 83			
[2690]	<211> 447			
[2691]	<212> PRT			
[2692]	<213> 人工序列			
[2693]	<220>			
[2694]	<223> 抗FITC mAb 4420 的重链的氨基酸序列,包括LALA突变			
[2695]	<400> 83			
[2696]	Glu Val Lys Leu Asp Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Arg			
[2697]	1	5	10	15
[2698]	Pro Met Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Tyr			
[2699]		20	25	30
[2700]	Trp Met Asn Trp Val Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val			
[2701]		35	40	45
[2702]	Ala Gln Ile Arg Asn Lys Pro Tyr Asn Tyr Glu Thr Tyr Tyr Ser Asp			
[2703]		50	55	60
[2704]	Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser			
[2705]	65	70	75	80
[2706]	Val Tyr Leu Gln Met Asn Asn Leu Arg Val Glu Asp Met Gly Ile Tyr			
[2707]		85	90	95
[2708]	Tyr Cys Thr Gly Ser Tyr Tyr Gly Met Asp Tyr Trp Gly Gln Gly Thr			
[2709]		100	105	110
[2710]	Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro			

[2711]	115	120	125
[2712]	Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly		
[2713]	130	135	140
[2714]	Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn		
[2715]	145	150	155
[2716]	Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln		
[2717]	165	170	175
[2718]	Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser		
[2719]	180	185	190
[2720]	Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser		
[2721]	195	200	205
[2722]	Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr		
[2723]	210	215	220
[2724]	His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser		
[2725]	225	230	235
[2726]	Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg		
[2727]	245	250	255
[2728]	Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro		
[2729]	260	265	270
[2730]	Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala		
[2731]	275	280	285
[2732]	Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val		
[2733]	290	295	300
[2734]	Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr		
[2735]	305	310	315
[2736]	Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr		
[2737]	325	330	335
[2738]	Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu		
[2739]	340	345	350
[2740]	Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys		
[2741]	355	360	365
[2742]	Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser		
[2743]	370	375	380
[2744]	Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp		
[2745]	385	390	395
[2746]	Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser		
[2747]	405	410	415
[2748]	Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala		
[2749]	420	425	430

[2750]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[2751]	435 440 445
[2752]	<210> 84
[2753]	<211> 447
[2754]	<212> PRT
[2755]	<213> 人工序列
[2756]	<220>
[2757]	<223> 抗FITC mAb 4420 的重链的氨基酸序列,没有LALA突变
[2758]	<400> 84
[2759]	Glu Val Lys Leu Asp Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Arg
[2760]	1 5 10 15
[2761]	Pro Met Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[2762]	20 25 30
[2763]	Trp Met Asn Trp Val Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val
[2764]	35 40 45
[2765]	Ala Gln Ile Arg Asn Lys Pro Tyr Asn Tyr Glu Thr Tyr Tyr Ser Asp
[2766]	50 55 60
[2767]	Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser
[2768]	65 70 75 80
[2769]	Val Tyr Leu Gln Met Asn Asn Leu Arg Val Glu Asp Met Gly Ile Tyr
[2770]	85 90 95
[2771]	Tyr Cys Thr Gly Ser Tyr Tyr Gly Met Asp Tyr Trp Gly Gln Gly Thr
[2772]	100 105 110
[2773]	Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
[2774]	115 120 125
[2775]	Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
[2776]	130 135 140
[2777]	Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
[2778]	145 150 155 160
[2779]	Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
[2780]	165 170 175
[2781]	Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
[2782]	180 185 190
[2783]	Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
[2784]	195 200 205
[2785]	Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
[2786]	210 215 220
[2787]	His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
[2788]	225 230 235 240

[2789]	Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
[2790]	245 250 255
[2791]	Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
[2792]	260 265 270
[2793]	Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
[2794]	275 280 285
[2795]	Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
[2796]	290 295 300
[2797]	Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
[2798]	305 310 315 320
[2799]	Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
[2800]	325 330 335
[2801]	Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
[2802]	340 345 350
[2803]	Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
[2804]	355 360 365
[2805]	Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
[2806]	370 375 380
[2807]	Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
[2808]	385 390 395 400
[2809]	Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
[2810]	405 410 415
[2811]	Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
[2812]	420 425 430
[2813]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[2814]	435 440 445
[2815]	<210> 85
[2816]	<211> 219
[2817]	<212> PRT
[2818]	<213> 人工序列
[2819]	<220>
[2820]	<223> 抗FITC mAb 4420轻链的氨基酸序列
[2821]	<400> 85
[2822]	Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
[2823]	1 5 10 15
[2824]	Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
[2825]	20 25 30
[2826]	Asn Gly Asn Thr Tyr Leu Arg Trp Tyr Leu Gln Lys Pro Gly Gln Ser
[2827]	35 40 45

[2828]	Pro Lys Val Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
[2829]	50 55 60
[2830]	Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
[2831]	65 70 75 80
[2832]	Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Ser
[2833]	85 90 95
[2834]	Thr His Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
[2835]	100 105 110
[2836]	Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
[2837]	115 120 125
[2838]	Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
[2839]	130 135 140
[2840]	Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
[2841]	145 150 155 160
[2842]	Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
[2843]	165 170 175
[2844]	Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
[2845]	180 185 190
[2846]	Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
[2847]	195 200 205
[2848]	Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
[2849]	210 215
[2850]	<210> 86
[2851]	<211> 8
[2852]	<212> PRT
[2853]	<213> 人工序列
[2854]	<220>
[2855]	<223> 抗PD-L1抗体84G09的CDR的氨基酸序列(根据IMGT) HCDR1
[2856]	<400> 86
[2857]	Gly Phe Thr Phe Asp Asp Tyr Ala
[2858]	1 5
[2859]	<210> 87
[2860]	<211> 8
[2861]	<212> PRT
[2862]	<213> 人工序列
[2863]	<220>
[2864]	<223> 抗PD-L1抗体84G09的CDR的氨基酸序列(根据IMGT) HCDR2
[2865]	<400> 87
[2866]	Ile Ser Trp Lys Ser Asn Ile Ile

[2867]	1	5	
[2868]	<210>	88	
[2869]	<211>	15	
[2870]	<212>	PRT	
[2871]	<213>	人工序列	
[2872]	<220>		
[2873]	<223>	抗PD-L1抗体84G09的CDR的氨基酸序列(根据IMGT)	HCDR3
[2874]	<400>	88	
[2875]	Ala Arg Asp Ile Thr Gly Ser Gly Ser Tyr Gly Trp Phe Asp Pro		
[2876]	1	5	10 15
[2877]	<210>	89	
[2878]	<211>	6	
[2879]	<212>	PRT	
[2880]	<213>	人工序列	
[2881]	<220>		
[2882]	<223>	抗PD-L1抗体84G09的CDR的氨基酸序列(根据IMGT)	LCDR1
[2883]	<400>	89	
[2884]	Gln Ser Ile Ser Ser Tyr		
[2885]	1	5	
[2886]	<210>	90	
[2887]	<211>	3	
[2888]	<212>	PRT	
[2889]	<213>	人工序列	
[2890]	<220>		
[2891]	<223>	抗PD-L1抗体84G09的CDR的氨基酸序列(根据IMGT)	LCDR2
[2892]	<400>	90	
[2893]	Val Ala Ser		
[2894]	1		
[2895]	<210>	91	
[2896]	<211>	9	
[2897]	<212>	PRT	
[2898]	<213>	人工序列	
[2899]	<220>		
[2900]	<223>	抗PD-L1抗体84G09的CDR的氨基酸序列(根据IMGT)	LCDR3
[2901]	<400>	91	
[2902]	Gln Gln Ser Tyr Ser Asn Pro Ile Thr		
[2903]	1	5	
[2904]	<210>	92	
[2905]	<211>	122	

[2906]	<212>	PRT															
[2907]	<213>	人工序列															
[2908]	<220>																
[2909]	<223>	抗PD-L1抗体84G09 VH结构域的氨基酸序列															
[2910]	<400>	92															
[2911]	Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg																
[2912]	1	5				10				15							
[2913]	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asp	Asp	Tyr	
[2914]	20				25				30								
[2915]	Ala	Met	His	Trp	Val	Arg	Gln	Thr	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
[2916]	35				40				45								
[2917]	Ser	Gly	Ile	Ser	Trp	Lys	Ser	Asn	Ile	Ile	Gly	Tyr	Ala	Asp	Ser	Val	
[2918]	50				55				60								
[2919]	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Ser	Leu	Tyr	
[2920]	65	70				75				80							
[2921]	Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Leu	Tyr	Tyr	Cys	
[2922]	85				90				95								
[2923]	Ala	Arg	Asp	Ile	Thr	Gly	Ser	Gly	Ser	Tyr	Gly	Trp	Phe	Asp	Pro	Trp	
[2924]	100				105				110								
[2925]	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser							
[2926]	115				120												
[2927]	<210>	93															
[2928]	<211>	107															
[2929]	<212>	PRT															
[2930]	<213>	人工序列															
[2931]	<220>																
[2932]	<223>	抗PD-L1抗体84G09 VL结构域的氨基酸序列															
[2933]	<400>	93															
[2934]	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly	
[2935]	1	5				10				15							
[2936]	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Ser	Ser	Tyr	
[2937]	20				25				30								
[2938]	Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Pro	Leu	Ile	
[2939]	35				40				45								
[2940]	Tyr	Val	Ala	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Ser	Phe	Ser	Gly	
[2941]	50				55				60								
[2942]	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro	
[2943]	65	70				75				80							
[2944]	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Tyr	Ser	Asn	Pro	Ile	

[2945]		85		90		95
[2946]	Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys					
[2947]		100		105		
[2948]	<210> 94					
[2949]	<211> 451					
[2950]	<212> PRT					
[2951]	<213> 人工序列					
[2952]	<220>					
[2953]	<223> 抗人LAG-3/PD-L1 mAb2 FS18-7-9/84G09的氨基酸序列,带有LALA突变重链					
[2954]	<400> 94					
[2955]	Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg					
[2956]	1	5		10		15
[2957]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr					
[2958]		20		25		30
[2959]	Ala Met His Trp Val Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val					
[2960]		35		40		45
[2961]	Ser Gly Ile Ser Trp Lys Ser Asn Ile Ile Gly Tyr Ala Asp Ser Val					
[2962]		50		55		60
[2963]	Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr					
[2964]		65		70		75
[2965]	Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys					
[2966]		85		90		95
[2967]	Ala Arg Asp Ile Thr Gly Ser Gly Ser Tyr Gly Trp Phe Asp Pro Trp					
[2968]		100		105		110
[2969]	Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro					
[2970]		115		120		125
[2971]	Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr					
[2972]		130		135		140
[2973]	Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr					
[2974]		145		150		155
[2975]	Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro					
[2976]		165		170		175
[2977]	Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr					
[2978]		180		185		190
[2979]	Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn					
[2980]		195		200		205
[2981]	His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser					
[2982]		210		215		220

[2983]	Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala		
[2984]	225	230	235 240
[2985]	Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu		
[2986]		245	250 255
[2987]	Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser		
[2988]		260	265 270
[2989]	His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu		
[2990]		275	280 285
[2991]	Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr		
[2992]		290	295 300
[2993]	Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn		
[2994]	305	310	315 320
[2995]	Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro		
[2996]		325	330 335
[2997]	Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln		
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[2999]	Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val		
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[3001]	Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val		
[3002]		370	375 380
[3003]	Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro		
[3004]	385	390	395 400
[3005]	Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr		
[3006]		405	410 415
[3007]	Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val		
[3008]		420	425 430
[3009]	Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu		
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[3011]	Ser Pro Gly		
[3012]	450		
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[3025]			35					40					45			
[3026]	Ser	Gly	Ile	Ser	Trp	Lys	Ser	Asn	Ile	Ile	Gly	Tyr	Ala	Asp	Ser	Val
[3027]		50					55					60				
[3028]	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Ser	Leu	Tyr
[3029]	65					70					75					80
[3030]	Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Leu	Tyr	Tyr	Cys
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[3032]	Ala	Arg	Asp	Ile	Thr	Gly	Ser	Gly	Ser	Tyr	Gly	Trp	Phe	Asp	Pro	Trp
[3033]				100					105					110		
[3034]	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro
[3035]			115					120					125			
[3036]	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr
[3037]		130						135					140			
[3038]	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr
[3039]	145					150					155					160
[3040]	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro
[3041]				165						170					175	
[3042]	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr
[3043]			180						185					190		
[3044]	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn
[3045]			195						200					205		
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[3048]	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu
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[3050]	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu
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[3052]	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser
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[3054]	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu
[3055]			275						280					285		
[3056]	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr
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[3058]	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn
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[3060]	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro

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[3062]	Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln					
[3063]		340		345		350
[3064]	Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val					
[3065]		355		360		365
[3066]	Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val					
[3067]		370		375		380
[3068]	Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro					
[3069]	385		390		395	400
[3070]	Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr					
[3071]		405		410		415
[3072]	Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val					
[3073]		420		425		430
[3074]	Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu					
[3075]		435		440		445
[3076]	Ser Pro Gly					
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[3087]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr					
[3088]		20		25		30
[3089]	Ala Met His Trp Val Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val					
[3090]		35		40		45
[3091]	Ser Gly Ile Ser Trp Lys Ser Asn Ile Ile Gly Tyr Ala Asp Ser Val					
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[3093]	Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr					
[3094]	65		70		75	80
[3095]	Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys					
[3096]		85		90		95
[3097]	Ala Arg Asp Ile Thr Gly Ser Gly Ser Tyr Gly Trp Phe Asp Pro Trp					
[3098]		100		105		110

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[3103]	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr
[3104]	145					150					155					160
[3105]	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro
[3106]					165					170					175	
[3107]	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr
[3108]				180					185					190		
[3109]	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn
[3110]			195					200					205			
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[3113]	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala
[3114]	225					230					235					240
[3115]	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu
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[3118]				260					265					270		
[3119]	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu
[3120]			275					280					285			
[3121]	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr
[3122]		290						295				300				
[3123]	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn
[3124]	305					310					315					320
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[3129]	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Trp	Asp	Glu	Pro	Trp	Gly	Glu	Asp	Val
[3130]			355					360					365			
[3131]	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Glu	Ile	Ala	Val
[3132]		370						375				380				
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[3134]	385					390					395					400
[3135]	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr
[3136]					405					410				415		
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[3152]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr		
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[3154]	Ala Met His Trp Val Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val		
[3155]	35 40 45		
[3156]	Ser Gly Ile Ser Trp Lys Ser Asn Ile Ile Gly Tyr Ala Asp Ser Val		
[3157]	50 55 60		
[3158]	Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr		
[3159]	65 70 75 80		
[3160]	Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys		
[3161]	85 90 95		
[3162]	Ala Arg Asp Ile Thr Gly Ser Gly Ser Tyr Gly Trp Phe Asp Pro Trp		
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[3164]	Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro		
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[3166]	Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr		
[3167]	130 135 140		
[3168]	Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr		
[3169]	145 150 155 160		
[3170]	Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro		
[3171]	165 170 175		
[3172]	Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr		
[3173]	180 185 190		
[3174]	Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn		
[3175]	195 200 205		
[3176]	His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser		

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[3178]	Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu		
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[3180]	Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu		
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[3182]	Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser		
[3183]	260	265	270
[3184]	His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu		
[3185]	275	280	285
[3186]	Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr		
[3187]	290	295	300
[3188]	Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn		
[3189]	305	310	315 320
[3190]	Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro		
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[3192]	Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln		
[3193]	340	345	350
[3194]	Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val		
[3195]	355	360	365
[3196]	Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Glu Ile Ala Val		
[3197]	370	375	380
[3198]	Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro		
[3199]	385	390	395 400
[3200]	Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr		
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[3202]	Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val		
[3203]	420	425	430
[3204]	Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu		
[3205]	435	440	445
[3206]	Ser Pro Gly		
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[3217]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
[3218]	20 25 30
[3219]	Ala Met His Trp Val Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
[3220]	35 40 45
[3221]	Ser Gly Ile Ser Trp Lys Ser Asn Ile Ile Gly Tyr Ala Asp Ser Val
[3222]	50 55 60
[3223]	Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[3224]	65 70 75 80
[3225]	Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
[3226]	85 90 95
[3227]	Ala Arg Asp Ile Thr Gly Ser Gly Ser Tyr Gly Trp Phe Asp Pro Trp
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[3229]	Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
[3230]	115 120 125
[3231]	Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
[3232]	130 135 140
[3233]	Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
[3234]	145 150 155 160
[3235]	Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
[3236]	165 170 175
[3237]	Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
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[3239]	Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
[3240]	195 200 205
[3241]	His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
[3242]	210 215 220
[3243]	Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
[3244]	225 230 235 240
[3245]	Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
[3246]	245 250 255
[3247]	Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
[3248]	260 265 270
[3249]	His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
[3250]	275 280 285
[3251]	Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
[3252]	290 295 300
[3253]	Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn

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[3255]	Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro			
[3256]		325	330	335
[3257]	Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln			
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[3259]	Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val			
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[3261]	Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val			
[3262]		370	375	380
[3263]	Glu Trp Glu Ser Asn Gly Gln Pro Glu Asp Asn Tyr Lys Thr Thr Pro			
[3264]	385	390	395	400
[3265]	Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr			
[3266]		405	410	415
[3267]	Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val			
[3268]		420	425	430
[3269]	Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu			
[3270]		435	440	445
[3271]	Ser Pro Gly			
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[3282]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr			
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[3284]	Ala Met His Trp Val Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val			
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[3286]	Ser Gly Ile Ser Trp Lys Ser Asn Ile Ile Gly Tyr Ala Asp Ser Val			
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[3288]	Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr			
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[3299]	145					150					155					160	
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[3302]	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	
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[3304]	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	
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[3306]	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	
[3307]			210						215					220			
[3308]	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	
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[3315]			275							280						285	
[3316]	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	
[3317]			290							295						300	
[3318]	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	
[3319]	305					310					315					320	
[3320]	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	
[3321]					325						330					335	
[3322]	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	
[3323]				340						345						350	
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[3326]	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	
[3327]			370							375						380	
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[3331]					405						410					415	

[3332]	Val	Pro	Tyr	Asp	Arg	Trp	Val	Trp	Pro	Asp	Glu	Phe	Ser	Cys	Ser	Val
[3333]				420					425					430		
[3334]	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu
[3335]				435				440						445		
[3336]	Ser	Pro	Gly													
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[3341]	<213>	人工序列														
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[3343]	<223>	抗人LAG-3/PD-L1 mAb2 FS18-7-36/84G09的氨基酸序列,带有LALA突变重链														
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[3379]	His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu		
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[3381]	Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr		
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[3383]	Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn		
[3384]	305	310	315 320
[3385]	Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro		
[3386]	325	330	335
[3387]	Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln		
[3388]	340	345	350
[3389]	Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val		
[3390]	355	360	365
[3391]	Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val		
[3392]	370	375	380
[3393]	Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro		
[3394]	385	390	395 400
[3395]	Pro Val Leu Asp Ser Asp Gly Ser Tyr Phe Leu Tyr Ser Lys Leu Thr		
[3396]	405	410	415
[3397]	Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val		
[3398]	420	425	430
[3399]	Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu		
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[3414]	Ala	Met	His	Trp	Val	Arg	Gln	Thr	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
[3415]	35				40				45								
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[3417]	50			55			60										
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[3429]	145			150			155			160							
[3430]	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	
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[3434]	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	
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[3444]	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	
[3445]	275				280				285								
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[3447]	290			295			300										

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[3449]	305 310 315 320
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[3451]	325 330 335
[3452]	Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
[3453]	340 345 350
[3454]	Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val
[3455]	355 360 365
[3456]	Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[3457]	370 375 380
[3458]	Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
[3459]	385 390 395 400
[3460]	Pro Val Leu Asp Ser Asp Gly Ser Tyr Phe Leu Tyr Ser Lys Leu Thr
[3461]	405 410 415
[3462]	Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val
[3463]	420 425 430
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[3479]	Ala Met His Trp Val Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
[3480]	35 40 45
[3481]	Ser Gly Ile Ser Trp Lys Ser Asn Ile Ile Gly Tyr Ala Asp Ser Val
[3482]	50 55 60
[3483]	Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[3484]	65 70 75 80
[3485]	Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys

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[3492]					130				135				140					
[3493]	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr		
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[3497]	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr		
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[3499]	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn		
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[3507]	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser		
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[3511]	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr		
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[3542]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
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[3544]	Ala Met His Trp Val Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
[3545]	35 40 45
[3546]	Ser Gly Ile Ser Trp Lys Ser Asn Ile Ile Gly Tyr Ala Asp Ser Val
[3547]	50 55 60
[3548]	Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[3549]	65 70 75 80
[3550]	Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
[3551]	85 90 95
[3552]	Ala Arg Asp Ile Thr Gly Ser Gly Ser Tyr Gly Trp Phe Asp Pro Trp
[3553]	100 105 110
[3554]	Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
[3555]	115 120 125
[3556]	Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
[3557]	130 135 140
[3558]	Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
[3559]	145 150 155 160
[3560]	Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
[3561]	165 170 175
[3562]	Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
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[3567]			210					215					220			
[3568]	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu
[3569]	225						230				235					240
[3570]	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu
[3571]						245					250					255
[3572]	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser
[3573]						260					265				270	
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[3575]						275								280		285
[3576]	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr
[3577]						290								295		300
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[3591]						405						410				415
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[3594]	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu
[3595]						435								440		445
[3596]	Ser	Pro	Gly													
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[3611]	Ser	Gly	Ile	Ser	Trp	Lys	Ser	Asn	Ile	Ile	Gly	Tyr	Ala	Asp	Ser	Val			
[3612]					50					55					60				
[3613]	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Ser	Leu	Tyr			
[3614]	65							70					75			80			
[3615]	Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Leu	Tyr	Tyr	Cys			
[3616]						85					90					95			
[3617]	Ala	Arg	Asp	Ile	Thr	Gly	Ser	Gly	Ser	Tyr	Gly	Trp	Phe	Asp	Pro	Trp			
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[3626]								165					170			175			
[3627]	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr			
[3628]						180					185					190			
[3629]	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn			
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[3651]	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val
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[3661]	Ser	Pro	Gly													
[3662]	450															
[3663]	<210>	105														
[3664]	<211>	451														
[3665]	<212>	PRT														
[3666]	<213>	人工序列														
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[3672]	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asp	Asp	Tyr
[3673]				20						25					30	
[3674]	Ala	Met	His	Trp	Val	Arg	Gln	Thr	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
[3675]			35					40					45			
[3676]	Ser	Gly	Ile	Ser	Trp	Lys	Ser	Asn	Ile	Ile	Gly	Tyr	Ala	Asp	Ser	Val
[3677]		50						55				60				
[3678]	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Ser	Leu	Tyr
[3679]	65					70					75					80

[3680]	Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Leu	Tyr	Tyr	Cys
[3681]					85					90					95	
[3682]	Ala	Arg	Asp	Ile	Thr	Gly	Ser	Gly	Ser	Tyr	Gly	Trp	Phe	Asp	Pro	Trp
[3683]					100					105					110	
[3684]	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro
[3685]					115					120					125	
[3686]	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr
[3687]					130					135					140	
[3688]	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr
[3689]	145									150				155		160
[3690]	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro
[3691]					165					170						175
[3692]	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr
[3693]					180					185					190	
[3694]	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn
[3695]					195					200					205	
[3696]	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser
[3697]					210					215					220	
[3698]	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu
[3699]	225									230				235		240
[3700]	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu
[3701]					245					250					255	
[3702]	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser
[3703]					260					265					270	
[3704]	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu
[3705]					275					280					285	
[3706]	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr
[3707]					290					295					300	
[3708]	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn
[3709]	305									310				315		320
[3710]	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro
[3711]					325					330					335	
[3712]	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln
[3713]					340					345					350	
[3714]	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Trp	Asp	Glu	Pro	Trp	Gly	Glu	Asp	Val
[3715]					355					360					365	
[3716]	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val
[3717]					370					375					380	
[3718]	Glu	Trp	Glu	Ser	Asn	Gly	Ile	Pro	Glu	Trp	Asn	Tyr	Lys	Thr	Thr	Pro

[3719]	385	390	395	400
[3720]	Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr			
[3721]	405	410	415	
[3722]	Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val			
[3723]	420	425	430	
[3724]	Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu			
[3725]	435	440	445	
[3726]	Ser Pro Gly			
[3727]	450			
[3728]	<210> 106			
[3729]	<211> 451			
[3730]	<212> PRT			
[3731]	<213> 人工序列			
[3732]	<220>			
[3733]	<223> 抗人LAG-3/PD-L1 mAb2 FS18-7-65/84G09的氨基酸序列,带有LALA突变重链			
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[3735]	Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg			
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[3737]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr			
[3738]	20	25	30	
[3739]	Ala Met His Trp Val Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val			
[3740]	35	40	45	
[3741]	Ser Gly Ile Ser Trp Lys Ser Asn Ile Ile Gly Tyr Ala Asp Ser Val			
[3742]	50	55	60	
[3743]	Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr			
[3744]	65	70	75	80
[3745]	Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys			
[3746]	85	90	95	
[3747]	Ala Arg Asp Ile Thr Gly Ser Gly Ser Tyr Gly Trp Phe Asp Pro Trp			
[3748]	100	105	110	
[3749]	Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro			
[3750]	115	120	125	
[3751]	Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr			
[3752]	130	135	140	
[3753]	Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr			
[3754]	145	150	155	160
[3755]	Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro			
[3756]	165	170	175	

[3757]	Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr		
[3758]		180	185
[3759]	Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn		190
[3760]		195	200
[3761]	His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser		205
[3762]		210	215
[3763]	Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala		220
[3764]		225	230
[3765]	Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu		235
[3766]		245	250
[3767]	Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser		240
[3768]		260	265
[3769]	His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu		255
[3770]		275	280
[3771]	Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr		285
[3772]		290	295
[3773]	Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn		300
[3774]		305	310
[3775]	Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro		315
[3776]		325	330
[3777]	Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln		335
[3778]		340	345
[3779]	Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val		350
[3780]		355	360
[3781]	Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val		365
[3782]		370	375
[3783]	Glu Trp Glu Ser Asn Gly Tyr Ala Glu Tyr Asn Tyr Lys Thr Thr Pro		380
[3784]		385	390
[3785]	Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr		395
[3786]		405	410
[3787]	Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val		415
[3788]		420	425
[3789]	Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu		430
[3790]		435	440
[3791]	Ser Pro Gly		445
[3792]		450	
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[3799]	<400> 107															
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[3802]	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asp	Asp	Tyr
[3803]				20						25					30	
[3804]	Ala	Met	His	Trp	Val	Arg	Gln	Thr	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
[3805]			35					40					45			
[3806]	Ser	Gly	Ile	Ser	Trp	Lys	Ser	Asn	Ile	Ile	Gly	Tyr	Ala	Asp	Ser	Val
[3807]		50					55					60				
[3808]	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Ser	Leu	Tyr
[3809]	65					70					75					80
[3810]	Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Leu	Tyr	Tyr	Cys
[3811]				85						90					95	
[3812]	Ala	Arg	Asp	Ile	Thr	Gly	Ser	Gly	Ser	Tyr	Gly	Trp	Phe	Asp	Pro	Trp
[3813]				100						105					110	
[3814]	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro
[3815]			115							120					125	
[3816]	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr
[3817]		130						135						140		
[3818]	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr
[3819]	145					150					155					160
[3820]	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro
[3821]				165						170					175	
[3822]	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr
[3823]				180						185					190	
[3824]	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn
[3825]			195						200					205		
[3826]	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser
[3827]		210						215					220			
[3828]	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu
[3829]	225						230					235				240
[3830]	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu
[3831]					245						250				255	
[3832]	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser
[3833]				260						265					270	
[3834]	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu

[3835]	275	280	285
[3836]	Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr		
[3837]	290	295	300
[3838]	Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn		
[3839]	305	310	315
[3840]	Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro		
[3841]	325	330	335
[3842]	Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln		
[3843]	340	345	350
[3844]	Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val		
[3845]	355	360	365
[3846]	Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val		
[3847]	370	375	380
[3848]	Glu Trp Glu Ser Asn Gly Tyr Ala Glu Tyr Asn Tyr Lys Thr Thr Pro		
[3849]	385	390	395
[3850]	Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr		
[3851]	405	410	415
[3852]	Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val		
[3853]	420	425	430
[3854]	Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu		
[3855]	435	440	445
[3856]	Ser Pro Gly		
[3857]	450		
[3858]	<210> 108		
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[3863]	<223> 抗人LAG-3/PD-L1 mAb2 FS18-7-78/84G09的氨基酸序列,带有LALA突变重链		
[3864]	<400> 108		
[3865]	Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg		
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[3867]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr		15
[3868]	20	25	30
[3869]	Ala Met His Trp Val Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val		
[3870]	35	40	45
[3871]	Ser Gly Ile Ser Trp Lys Ser Asn Ile Ile Gly Tyr Ala Asp Ser Val		
[3872]	50	55	60

[3873]	Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[3874]	65 70 75 80
[3875]	Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
[3876]	85 90 95
[3877]	Ala Arg Asp Ile Thr Gly Ser Gly Ser Tyr Gly Trp Phe Asp Pro Trp
[3878]	100 105 110
[3879]	Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
[3880]	115 120 125
[3881]	Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
[3882]	130 135 140
[3883]	Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
[3884]	145 150 155 160
[3885]	Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
[3886]	165 170 175
[3887]	Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
[3888]	180 185 190
[3889]	Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
[3890]	195 200 205
[3891]	His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
[3892]	210 215 220
[3893]	Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
[3894]	225 230 235 240
[3895]	Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
[3896]	245 250 255
[3897]	Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
[3898]	260 265 270
[3899]	His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
[3900]	275 280 285
[3901]	Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
[3902]	290 295 300
[3903]	Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
[3904]	305 310 315 320
[3905]	Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
[3906]	325 330 335
[3907]	Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
[3908]	340 345 350
[3909]	Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val
[3910]	355 360 365
[3911]	Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val

[3912]	370	375	380
[3913]	Glu Trp Glu Ser Asn Gly Tyr Lys Glu Glu Asn Tyr Lys Thr Thr Pro		
[3914]	385	390	395 400
[3915]	Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr		
[3916]	405	410	415
[3917]	Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val		
[3918]	420	425	430
[3919]	Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu		
[3920]	435	440	445
[3921]	Ser Pro Gly		
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[3928]	<223> 抗人LAG-3/PD-L1 mAb2 FS18-7-78/84G09重链的氨基酸序列		
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[3930]	Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg		
[3931]	1 5 10 15		
[3932]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr		
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[3934]	Ala Met His Trp Val Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val		
[3935]	35 40 45		
[3936]	Ser Gly Ile Ser Trp Lys Ser Asn Ile Ile Gly Tyr Ala Asp Ser Val		
[3937]	50 55 60		
[3938]	Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr		
[3939]	65 70 75 80		
[3940]	Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys		
[3941]	85 90 95		
[3942]	Ala Arg Asp Ile Thr Gly Ser Gly Ser Tyr Gly Trp Phe Asp Pro Trp		
[3943]	100 105 110		
[3944]	Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro		
[3945]	115 120 125		
[3946]	Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr		
[3947]	130 135 140		
[3948]	Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr		
[3949]	145 150 155 160		
[3950]	Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro		

[3951]		165		170		175
[3952]	Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr					
[3953]		180		185		190
[3954]	Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn					
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[3956]	His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser					
[3957]		210		215		220
[3958]	Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu					
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[3960]	Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu					
[3961]		245		250		255
[3962]	Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser					
[3963]		260		265		270
[3964]	His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu					
[3965]		275		280		285
[3966]	Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr					
[3967]		290		295		300
[3968]	Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn					
[3969]	305		310		315	320
[3970]	Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro					
[3971]		325		330		335
[3972]	Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln					
[3973]		340		345		350
[3974]	Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val					
[3975]		355		360		365
[3976]	Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val					
[3977]		370		375		380
[3978]	Glu Trp Glu Ser Asn Gly Tyr Lys Glu Glu Asn Tyr Lys Thr Thr Pro					
[3979]	385		390		395	400
[3980]	Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr					
[3981]		405		410		415
[3982]	Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val					
[3983]		420		425		430
[3984]	Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu					
[3985]		435		440		445
[3986]	Ser Pro Gly					
[3987]		450				
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[3990]	<212>	PRT
[3991]	<213>	人工序列
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[3993]	<223>	抗人LAG-3/PD-L1 mAb2 FS18-7-88/84G09的氨基酸序列,带有LALA突变重链
[3994]	<400>	110
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[3997]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr	
[3998]	20	25 30
[3999]	Ala Met His Trp Val Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val	
[4000]	35	40 45
[4001]	Ser Gly Ile Ser Trp Lys Ser Asn Ile Ile Gly Tyr Ala Asp Ser Val	
[4002]	50	55 60
[4003]	Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr	
[4004]	65	70 75 80
[4005]	Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys	
[4006]	85	90 95
[4007]	Ala Arg Asp Ile Thr Gly Ser Gly Ser Tyr Gly Trp Phe Asp Pro Trp	
[4008]	100	105 110
[4009]	Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro	
[4010]	115	120 125
[4011]	Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr	
[4012]	130	135 140
[4013]	Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr	
[4014]	145	150 155 160
[4015]	Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro	
[4016]	165	170 175
[4017]	Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr	
[4018]	180	185 190
[4019]	Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn	
[4020]	195	200 205
[4021]	His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser	
[4022]	210	215 220
[4023]	Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala	
[4024]	225	230 235 240
[4025]	Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu	
[4026]	245	250 255
[4027]	Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser	

[4028]	260	265	270
[4029]	His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu		
[4030]	275	280	285
[4031]	Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr		
[4032]	290	295	300
[4033]	Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn		
[4034]	305	310	315
[4035]	Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro		
[4036]	325	330	335
[4037]	Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln		
[4038]	340	345	350
[4039]	Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val		
[4040]	355	360	365
[4041]	Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val		
[4042]	370	375	380
[4043]	Glu Trp Glu Ser Asn Gly Val Pro Glu Leu Asn Val Lys Thr Thr Pro		
[4044]	385	390	395
[4045]	Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr		
[4046]	405	410	415
[4047]	Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val		
[4048]	420	425	430
[4049]	Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu		
[4050]	435	440	445
[4051]	Ser Pro Gly		
[4052]	450		
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[4061]	1	5	10
[4062]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr		
[4063]	20	25	30
[4064]	Ala Met His Trp Val Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val		
[4065]	35	40	45
[4066]	Ser Gly Ile Ser Trp Lys Ser Asn Ile Ile Gly Tyr Ala Asp Ser Val		

[4067]	50	55	60
[4068]	Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr		
[4069]	65	70	75
[4070]	Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys		80
[4071]	85	90	95
[4072]	Ala Arg Asp Ile Thr Gly Ser Gly Ser Tyr Gly Trp Phe Asp Pro Trp		
[4073]	100	105	110
[4074]	Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro		
[4075]	115	120	125
[4076]	Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr		
[4077]	130	135	140
[4078]	Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr		
[4079]	145	150	155
[4080]	Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro		
[4081]	165	170	175
[4082]	Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr		
[4083]	180	185	190
[4084]	Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn		
[4085]	195	200	205
[4086]	His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser		
[4087]	210	215	220
[4088]	Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu		
[4089]	225	230	235
[4090]	Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu		
[4091]	245	250	255
[4092]	Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser		
[4093]	260	265	270
[4094]	His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu		
[4095]	275	280	285
[4096]	Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr		
[4097]	290	295	300
[4098]	Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn		
[4099]	305	310	315
[4100]	Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro		
[4101]	325	330	335
[4102]	Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln		
[4103]	340	345	350
[4104]	Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val		
[4105]	355	360	365

[4106]	Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
[4107]	370 375 380
[4108]	Glu Trp Glu Ser Asn Gly Val Pro Glu Leu Asn Val Lys Thr Thr Pro
[4109]	385 390 395 400
[4110]	Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
[4111]	405 410 415
[4112]	Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val
[4113]	420 425 430
[4114]	Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
[4115]	435 440 445
[4116]	Ser Pro Gly
[4117]	450
[4118]	<210> 112
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[4124]	<400> 112
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[4127]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
[4128]	20 25 30
[4129]	Ala Met His Trp Val Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val
[4130]	35 40 45
[4131]	Ser Gly Ile Ser Trp Lys Ser Asn Ile Ile Gly Tyr Ala Asp Ser Val
[4132]	50 55 60
[4133]	Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[4134]	65 70 75 80
[4135]	Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
[4136]	85 90 95
[4137]	Ala Arg Asp Ile Thr Gly Ser Gly Ser Tyr Gly Trp Phe Asp Pro Trp
[4138]	100 105 110
[4139]	Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
[4140]	115 120 125
[4141]	Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
[4142]	130 135 140
[4143]	Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr

[4144]	145	150	155	160
[4145]	Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro			
[4146]	165	170	175	
[4147]	Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr			
[4148]	180	185	190	
[4149]	Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn			
[4150]	195	200	205	
[4151]	His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser			
[4152]	210	215	220	
[4153]	Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala			
[4154]	225	230	235	240
[4155]	Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu			
[4156]	245	250	255	
[4157]	Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser			
[4158]	260	265	270	
[4159]	His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu			
[4160]	275	280	285	
[4161]	Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr			
[4162]	290	295	300	
[4163]	Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn			
[4164]	305	310	315	320
[4165]	Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro			
[4166]	325	330	335	
[4167]	Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln			
[4168]	340	345	350	
[4169]	Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val			
[4170]	355	360	365	
[4171]	Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val			
[4172]	370	375	380	
[4173]	Glu Trp Glu Ser Asn Gly Tyr Gln Glu Asp Asn Tyr Lys Thr Thr Pro			
[4174]	385	390	395	400
[4175]	Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr			
[4176]	405	410	415	
[4177]	Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val			
[4178]	420	425	430	
[4179]	Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu			
[4180]	435	440	445	
[4181]	Ser Pro Gly			
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[4192]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr		
[4193]		20	25 30
[4194]	Ala Met His Trp Val Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val		
[4195]		35	40 45
[4196]	Ser Gly Ile Ser Trp Lys Ser Asn Ile Ile Gly Tyr Ala Asp Ser Val		
[4197]		50	55 60
[4198]	Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr		
[4199]		65	70 75 80
[4200]	Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys		
[4201]		85	90 95
[4202]	Ala Arg Asp Ile Thr Gly Ser Gly Ser Tyr Gly Trp Phe Asp Pro Trp		
[4203]		100	105 110
[4204]	Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro		
[4205]		115	120 125
[4206]	Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr		
[4207]		130	135 140
[4208]	Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr		
[4209]		145	150 155 160
[4210]	Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro		
[4211]		165	170 175
[4212]	Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr		
[4213]		180	185 190
[4214]	Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn		
[4215]		195	200 205
[4216]	His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser		
[4217]		210	215 220
[4218]	Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu		
[4219]		225	230 235 240
[4220]	Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu		
[4221]		245	250 255

[4222]	Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser		
[4223]	260	265	270
[4224]	His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu		
[4225]	275	280	285
[4226]	Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr		
[4227]	290	295	300
[4228]	Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn		
[4229]	305	310	315
[4230]	Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro		
[4231]	325	330	335
[4232]	Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln		
[4233]	340	345	350
[4234]	Val Tyr Thr Leu Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val		
[4235]	355	360	365
[4236]	Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val		
[4237]	370	375	380
[4238]	Glu Trp Glu Ser Asn Gly Tyr Gln Glu Asp Asn Tyr Lys Thr Thr Pro		
[4239]	385	390	395
[4240]	Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr		
[4241]	405	410	415
[4242]	Val Pro Tyr Asp Arg Trp Val Trp Pro Asp Glu Phe Ser Cys Ser Val		
[4243]	420	425	430
[4244]	Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu		
[4245]	435	440	445
[4246]	Ser Pro Gly		
[4247]	450		
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[4254]	<400> 114		
[4255]	Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg		
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[4257]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr		
[4258]	20	25	30
[4259]	Ala Met His Trp Val Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val		
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[4261]	Ser Gly Ile Ser Trp Lys Ser Asn Ile Ile Gly Tyr Ala Asp Ser Val
[4262]	50 55 60
[4263]	Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
[4264]	65 70 75 80
[4265]	Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
[4266]	85 90 95
[4267]	Ala Arg Asp Ile Thr Gly Ser Gly Ser Tyr Gly Trp Phe Asp Pro Trp
[4268]	100 105 110
[4269]	Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
[4270]	115 120 125
[4271]	Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
[4272]	130 135 140
[4273]	Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
[4274]	145 150 155 160
[4275]	Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
[4276]	165 170 175
[4277]	Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
[4278]	180 185 190
[4279]	Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
[4280]	195 200 205
[4281]	His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
[4282]	210 215 220
[4283]	Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala
[4284]	225 230 235 240
[4285]	Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
[4286]	245 250 255
[4287]	Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
[4288]	260 265 270
[4289]	His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
[4290]	275 280 285
[4291]	Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
[4292]	290 295 300
[4293]	Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
[4294]	305 310 315 320
[4295]	Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
[4296]	325 330 335
[4297]	Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
[4298]	340 345 350
[4299]	Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val

[4300]	355	360	365
[4301]	Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val		
[4302]	370	375	380
[4303]	Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro		
[4304]	385	390	395
[4305]	Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr		
[4306]	405	410	415
[4307]	Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val		
[4308]	420	425	430
[4309]	Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu		
[4310]	435	440	445
[4311]	Ser Pro Gly		
[4312]	450		
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[4320]	Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg		
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[4322]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr		
[4323]	20	25	30
[4324]	Ala Met His Trp Val Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Val		
[4325]	35	40	45
[4326]	Ser Gly Ile Ser Trp Lys Ser Asn Ile Ile Gly Tyr Ala Asp Ser Val		
[4327]	50	55	60
[4328]	Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr		
[4329]	65	70	75
[4330]	Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys		
[4331]	85	90	95
[4332]	Ala Arg Asp Ile Thr Gly Ser Gly Ser Tyr Gly Trp Phe Asp Pro Trp		
[4333]	100	105	110
[4334]	Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro		
[4335]	115	120	125
[4336]	Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr		
[4337]	130	135	140
[4338]	Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr		

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[4340]	Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro			
[4341]	165	170	175	
[4342]	Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr			
[4343]	180	185	190	
[4344]	Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn			
[4345]	195	200	205	
[4346]	His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser			
[4347]	210	215	220	
[4348]	Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu			
[4349]	225	230	235	240
[4350]	Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu			
[4351]	245	250	255	
[4352]	Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser			
[4353]	260	265	270	
[4354]	His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu			
[4355]	275	280	285	
[4356]	Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr			
[4357]	290	295	300	
[4358]	Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn			
[4359]	305	310	315	320
[4360]	Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro			
[4361]	325	330	335	
[4362]	Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln			
[4363]	340	345	350	
[4364]	Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val			
[4365]	355	360	365	
[4366]	Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val			
[4367]	370	375	380	
[4368]	Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro			
[4369]	385	390	395	400
[4370]	Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr			
[4371]	405	410	415	
[4372]	Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val			
[4373]	420	425	430	
[4374]	Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu			
[4375]	435	440	445	
[4376]	Ser Pro Gly			
[4377]	450			

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[4384]	<400>	116
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[4387]	Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr	
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[4390]	35 40 45	
[4391]	Tyr Val Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Ser Phe Ser Gly	
[4392]	50 55 60	
[4393]	Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro	
[4394]	65 70 75 80	
[4395]	Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Asn Pro Ile	
[4396]	85 90 95	
[4397]	Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg Thr Val Ala Ala	
[4398]	100 105 110	
[4399]	Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly	
[4400]	115 120 125	
[4401]	Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala	
[4402]	130 135 140	
[4403]	Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln	
[4404]	145 150 155 160	
[4405]	Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser	
[4406]	165 170 175	
[4407]	Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr	
[4408]	180 185 190	
[4409]	Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser	
[4410]	195 200 205	
[4411]	Phe Asn Arg Gly Glu Cys	
[4412]	210	
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[4414]	<211>	447
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[4458]	Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr		
[4459]	305	310	315
[4460]	Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr		
[4461]	325	330	335
[4462]	Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu		
[4463]	340	345	350
[4464]	Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys		
[4465]	355	360	365
[4466]	Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Val Val Glu Trp Glu Ser		
[4467]	370	375	380
[4468]	Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp		
[4469]	385	390	395
[4470]	Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Phe Glu		
[4471]	405	410	415
[4472]	Arg Trp Met Trp Pro Asp Glu Phe Ser Cys Ser Val Met His Glu Ala		
[4473]	420	425	430
[4474]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
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[4485]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ser		
[4486]	20	25	30
[4487]	Trp Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val		
[4488]	35	40	45
[4489]	Ala Trp Ile Ser Pro Tyr Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val		
[4490]	50	55	60
[4491]	Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr		
[4492]	65	70	75
[4493]	Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys		

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[4497]	Leu	Val	Thr	Val	Ser	Ala	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro
[4498]					115					120						125
[4499]	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly
[4500]					130					135						140
[4501]	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn
[4502]	145									150						160
[4503]	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln
[4504]										165						175
[4505]	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser
[4506]										180						190
[4507]	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser
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[4510]										210						220
[4511]	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser
[4512]	225									230						240
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[4514]										245						255
[4515]	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro
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[4517]	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala
[4518]										275						285
[4519]	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val
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[4521]	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr
[4522]	305									310						320
[4523]	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr
[4524]										325						335
[4525]	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu
[4526]										340						350
[4527]	Pro	Pro	Ser	Trp	Asp	Glu	Pro	Trp	Gly	Glu	Asp	Val	Ser	Leu	Thr	Cys
[4528]										355						365
[4529]	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Val	Val	Glu	Trp	Glu	Ser
[4530]										370						380
[4531]	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp
[4532]	385									390						400

[4533]	Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Phe Glu		
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[4535]	Arg Trp Met Trp Pro Asp Glu Phe Ser Cys Ser Val Met His Glu Ala		415
[4536]		420	425
[4537]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		430
[4538]		435	440
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[4549]		20	25
[4550]	Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile		30
[4551]		35	40
[4552]	Tyr Ser Ala Ser Phe Leu Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly		45
[4553]	50	55	60
[4554]	Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro		
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[4556]	Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Leu Phe Thr Pro Pro		80
[4557]		85	90
[4558]	Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala		95
[4559]		100	105
[4560]	Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly		110
[4561]		115	120
[4562]	Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala		125
[4563]		130	135
[4564]	Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln		140
[4565]	145	150	155
[4566]	Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser		160
[4567]		165	170
[4568]	Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr		175
[4569]		180	185
[4570]	Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser		190
[4571]		195	200
			205

[4572]	Phe Asn Arg Gly Glu Cys
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[4574]	<210> 120
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[4580]	<400> 120
[4581]	Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
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[4583]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ser
[4584]	20 25 30
[4585]	Trp Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
[4586]	35 40 45
[4587]	Ala Trp Ile Ser Pro Tyr Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
[4588]	50 55 60
[4589]	Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr
[4590]	65 70 75 80
[4591]	Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
[4592]	85 90 95
[4593]	Ala Arg Arg His Trp Pro Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr
[4594]	100 105 110
[4595]	Leu Val Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
[4596]	115 120 125
[4597]	Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
[4598]	130 135 140
[4599]	Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
[4600]	145 150 155 160
[4601]	Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
[4602]	165 170 175
[4603]	Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
[4604]	180 185 190
[4605]	Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
[4606]	195 200 205
[4607]	Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
[4608]	210 215 220
[4609]	His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser

[4610]	225	230	235	240
[4611]	Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg			
[4612]		245	250	255
[4613]	Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro			
[4614]		260	265	270
[4615]	Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala			
[4616]		275	280	285
[4617]	Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val			
[4618]		290	295	300
[4619]	Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr			
[4620]	305	310	315	320
[4621]	Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr			
[4622]		325	330	335
[4623]	Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu			
[4624]		340	345	350
[4625]	Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys			
[4626]		355	360	365
[4627]	Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ser Val Glu Trp Glu Ser			
[4628]		370	375	380
[4629]	Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp			
[4630]	385	390	395	400
[4631]	Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Phe Glu			
[4632]		405	410	415
[4633]	Arg Trp Met Trp Pro Asp Glu Phe Ser Cys Ser Val Met His Glu Ala			
[4634]		420	425	430
[4635]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly			
[4636]		435	440	445
[4637]	<210> 121			
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[4644]	Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly			
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[4646]	Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ser			
[4647]		20	25	30
[4648]	Trp Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val			

[4649]	35	40	45
[4650]	Ala Trp Ile Ser Pro Tyr Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val		
[4651]	50	55	60
[4652]	Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr		
[4653]	65	70	75
[4654]	Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys		
[4655]	85	90	95
[4656]	Ala Arg Arg His Trp Pro Gly Gly Phe Asp Tyr Trp Gly Gln Gly Thr		
[4657]	100	105	110
[4658]	Leu Val Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser Val Phe Pro		
[4659]	115	120	125
[4660]	Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly		
[4661]	130	135	140
[4662]	Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn		
[4663]	145	150	155
[4664]	Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln		
[4665]	165	170	175
[4666]	Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser		
[4667]	180	185	190
[4668]	Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser		
[4669]	195	200	205
[4670]	Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr		
[4671]	210	215	220
[4672]	His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser		
[4673]	225	230	235
[4674]	Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg		
[4675]	245	250	255
[4676]	Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro		
[4677]	260	265	270
[4678]	Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala		
[4679]	275	280	285
[4680]	Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val		
[4681]	290	295	300
[4682]	Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr		
[4683]	305	310	315
[4684]	Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr		
[4685]	325	330	335
[4686]	Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu		
[4687]	340	345	350

[4688]	Pro	Pro	Ser	Trp	Asp	Glu	Pro	Trp	Gly	Glu	Asp	Val	Ser	Leu	Thr	Cys
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[4690]	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ser	Val	Glu	Trp	Glu	Ser
[4691]		370						375					380			
[4692]	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp
[4693]	385					390					395					400
[4694]	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Pro	Phe	Glu
[4695]				405						410					415	
[4696]	Arg	Trp	Met	Trp	Pro	Asp	Glu	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala
[4697]			420						425					430		
[4698]	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	
[4699]		435						440					445			
[4700]	<210> 122															
[4701]	<211> 447															
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[4703]	<213> 人工序列															
[4704]	<220>															
[4705]	<223> 对照PD-L1 mAb S1的氨基酸序列,带有LALA突变重链															
[4706]	<400> 122															
[4707]	Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
[4708]	1			5					10					15		
[4709]	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Asp	Ser
[4710]			20						25					30		
[4711]	Trp	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
[4712]		35						40					45			
[4713]	Ala	Trp	Ile	Ser	Pro	Tyr	Gly	Gly	Ser	Thr	Tyr	Tyr	Ala	Asp	Ser	Val
[4714]	50						55					60				
[4715]	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Ala	Asp	Thr	Ser	Lys	Asn	Thr	Ala	Tyr
[4716]	65					70					75				80	
[4717]	Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
[4718]				85						90				95		
[4719]	Ala	Arg	Arg	His	Trp	Pro	Gly	Gly	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
[4720]			100						105					110		
[4721]	Leu	Val	Thr	Val	Ser	Ala	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro
[4722]			115						120					125		
[4723]	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly
[4724]	130							135					140			
[4725]	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn
[4726]	145					150					155					160

[4727]	Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
[4728]	165 170 175
[4729]	Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
[4730]	180 185 190
[4731]	Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
[4732]	195 200 205
[4733]	Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
[4734]	210 215 220
[4735]	His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
[4736]	225 230 235 240
[4737]	Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
[4738]	245 250 255
[4739]	Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
[4740]	260 265 270
[4741]	Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
[4742]	275 280 285
[4743]	Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
[4744]	290 295 300
[4745]	Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
[4746]	305 310 315 320
[4747]	Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
[4748]	325 330 335
[4749]	Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
[4750]	340 345 350
[4751]	Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
[4752]	355 360 365
[4753]	Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
[4754]	370 375 380
[4755]	Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
[4756]	385 390 395 400
[4757]	Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
[4758]	405 410 415
[4759]	Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
[4760]	420 425 430
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[4762]	435 440 445
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[4766]	<213> 人工序列															
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[4768]	<223> 对照PD-L1 mAb S1重链的氨基酸序列															
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[4773]				20					25					30		
[4774]	Trp	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
[4775]			35					40					45			
[4776]	Ala	Trp	Ile	Ser	Pro	Tyr	Gly	Gly	Ser	Thr	Tyr	Tyr	Ala	Asp	Ser	Val
[4777]		50					55					60				
[4778]	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Ala	Asp	Thr	Ser	Lys	Asn	Thr	Ala	Tyr
[4779]	65					70				75					80	
[4780]	Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
[4781]				85					90					95		
[4782]	Ala	Arg	Arg	His	Trp	Pro	Gly	Gly	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
[4783]				100					105					110		
[4784]	Leu	Val	Thr	Val	Ser	Ala	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro
[4785]			115					120					125			
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[4789]	145					150				155					160	
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[4791]				165					170					175		
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[4793]				180					185					190		
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[4796]	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr
[4797]		210					215					220				
[4798]	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser
[4799]	225					230				235					240	
[4800]	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg
[4801]				245					250					255		
[4802]	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro
[4803]				260					265					270		
[4804]	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala

[4805]	275	280	285
[4806]	Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val		
[4807]	290	295	300
[4808]	Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr		
[4809]	305	310	315
[4810]	Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr		
[4811]	325	330	335
[4812]	Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu		
[4813]	340	345	350
[4814]	Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys		
[4815]	355	360	365
[4816]	Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser		
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[4818]	Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp		
[4819]	385	390	395
[4820]	Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser		
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[4822]	Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala		
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[4824]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
[4825]	435	440	445
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[4829]	<213> 人工序列		
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[4835]	Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Asp Tyr		
[4836]	20	25	30
[4837]	Tyr Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile		
[4838]	35	40	45
[4839]	Gly Glu Ile Asn His Arg Gly Ser Thr Asn Ser Asn Pro Ser Leu Lys		
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[4841]	Ser Arg Val Thr Leu Ser Leu Asp Thr Ser Lys Asn Gln Phe Ser Leu		
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[4843]	Lys Leu Arg Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala		

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[4845]	Phe	Gly	Tyr	Ser	Asp	Tyr	Glu	Tyr	Asn	Trp	Phe	Asp	Pro	Trp	Gly	Gln
[4846]					100					105						110
[4847]	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val
[4848]					115					120						125
[4849]	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala
[4850]					130					135						140
[4851]	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser
[4852]	145									150						160
[4853]	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val
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[4857]	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys
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[4859]	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp
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[4861]	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly
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[4863]	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile
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[4865]	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu
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[4867]	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His
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[4874]					325					330						335
[4875]	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr
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[4877]	Thr	Leu	Pro	Pro	Ser	Arg	Asp	Glu	Leu	Thr	Lys	Asn	Gln	Val	Ser	Leu
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[4879]	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp
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[4881]	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val
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[4885]	Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
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[4887]	Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
[4888]	435 440 445
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[4899]	Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
[4900]	20 25 30
[4901]	Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
[4902]	35 40 45
[4903]	Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
[4904]	50 55 60
[4905]	Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
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[4907]	Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Leu
[4908]	85 90 95
[4909]	Thr Phe Gly Gln Gly Thr Asn Leu Glu Ile Lys Arg Thr Val Ala Ala
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[4911]	Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
[4912]	115 120 125
[4913]	Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
[4914]	130 135 140
[4915]	Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
[4916]	145 150 155 160
[4917]	Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
[4918]	165 170 175
[4919]	Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
[4920]	180 185 190
[4921]	Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser

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[4936]	Trp Ala Gln Glu Gly Ala Pro Ala Gln Leu Pro Cys Ser Pro Thr Ile		
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[4938]	Pro Leu Gln Asp Leu Ser Leu Leu Arg Arg Ala Gly Val Thr Trp Gln		
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[4940]	His Gln Pro Asp Ser Gly Pro Pro Ala Ala Ala Pro Gly His Pro Leu		
[4941]	65	70	75
[4942]	Ala Pro Gly Pro His Pro Ala Ala Pro Ser Ser Trp Gly Pro Arg Pro		
[4943]	85	90	95
[4944]	Arg Arg Tyr Thr Val Leu Ser Val Gly Pro Gly Gly Leu Arg Ser Gly		
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[4946]	Arg Leu Pro Leu Gln Pro Arg Val Gln Leu Asp Glu Arg Gly Arg Gln		
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[4948]	Arg Gly Asp Phe Ser Leu Trp Leu Arg Pro Ala Arg Arg Ala Asp Ala		
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[4950]	Gly Glu Tyr Arg Ala Ala Val His Leu Arg Asp Arg Ala Leu Ser Cys		
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[4952]	Arg Leu Arg Leu Arg Leu Gly Gln Ala Ser Met Thr Ala Ser Pro Pro		
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[4954]	Gly Ser Leu Arg Ala Ser Asp Trp Val Ile Leu Asn Cys Ser Phe Ser		
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[4956]	Arg Pro Asp Arg Pro Ala Ser Val His Trp Phe Arg Asn Arg Gly Gln		
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[4958]	Gly Arg Val Pro Val Arg Glu Ser Pro His His His Leu Ala Glu Ser		
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[4960]	Phe Leu Phe Leu Pro Gln Val Ser Pro Met Asp Ser Gly Pro Trp Gly		

[4961]	225	230	235	240
[4962]	Cys Ile Leu Thr Tyr Arg Asp Gly Phe Asn Val Ser Ile Met Tyr Asn			
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[4964]	Leu Thr Val Leu Gly Leu Glu Pro Pro Thr Pro Leu Thr Val Tyr Ala			
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[4967]		275	280	285
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[4970]	Pro Asp Leu Leu Val Thr Gly Asp Asn Gly Asp Phe Thr Leu Arg Leu			
[4971]	305	310	315	320
[4972]	Glu Asp Val Ser Gln Ala Gln Ala Gly Thr Tyr Thr Cys His Ile His			
[4973]		325	330	335
[4974]	Leu Gln Glu Gln Gln Leu Asn Ala Thr Val Thr Leu Ala Ile Ile Thr			
[4975]		340	345	350
[4976]	Val Thr Pro Lys Ser Phe Gly Ser Pro Gly Ser Leu Gly Lys Leu Leu			
[4977]		355	360	365
[4978]	Cys Glu Val Thr Pro Val Ser Gly Gln Glu Arg Phe Val Trp Ser Ser			
[4979]		370	375	380
[4980]	Leu Asp Thr Pro Ser Gln Arg Ser Phe Ser Gly Pro Trp Leu Glu Ala			
[4981]	385	390	395	400
[4982]	Gln Glu Ala Gln Leu Leu Ser Gln Pro Trp Gln Cys Gln Leu Tyr Gln			
[4983]		405	410	415
[4984]	Gly Glu Arg Leu Leu Gly Ala Ala Val Tyr Phe Thr Glu Leu Ser Ser			
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[4986]	Pro Gly Ala Gln Arg Ser Gly Arg Ala Pro Gly Ala Leu Pro Ala Gly			
[4987]		435	440	445
[4988]	His Leu Leu Leu Phe Leu Ile Leu Gly Val Leu Ser Leu Leu Leu Leu			
[4989]		450	455	460
[4990]	Val Thr Gly Ala Phe Gly Phe His Leu Trp Arg Arg Gln Trp Arg Pro			
[4991]	465	470	475	480
[4992]	Arg Arg Phe Ser Ala Leu Glu Gln Gly Ile His Pro Pro Gln Ala Gln			
[4993]		485	490	495
[4994]	Ser Lys Ile Glu Glu Leu Glu Gln Glu Pro Glu Pro Glu Pro Glu Pro			
[4995]		500	505	510
[4996]	Glu Pro Glu Pro Glu Pro Glu Pro Glu Pro Glu Gln Leu			
[4997]		515	520	525
[4998]	<210> 127			
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[5007]	Glu Ala Pro Val Val Ser Ser Gly Pro Gly Lys Glu Leu Pro Val Val	
[5008]	20 25 30	
[5009]	Trp Ala Gln Glu Gly Ala Pro Val His Leu Pro Cys Ser Leu Lys Ser	
[5010]	35 40 45	
[5011]	Pro Asn Leu Asp Pro Asn Phe Leu Arg Arg Gly Gly Val Ile Trp Gln	
[5012]	50 55 60	
[5013]	His Gln Pro Asp Ser Gly Gln Pro Thr Pro Ile Pro Ala Leu Asp Leu	
[5014]	65 70 75 80	
[5015]	His Gln Gly Met Pro Ser Pro Arg Gln Pro Ala Pro Gly Arg Tyr Thr	
[5016]	85 90 95	
[5017]	Val Leu Ser Val Ala Pro Gly Gly Leu Arg Ser Gly Arg Gln Pro Leu	
[5018]	100 105 110	
[5019]	His Pro His Val Gln Leu Glu Glu Arg Gly Leu Gln Arg Gly Asp Phe	
[5020]	115 120 125	
[5021]	Ser Leu Trp Leu Arg Pro Ala Leu Arg Thr Asp Ala Gly Glu Tyr His	
[5022]	130 135 140	
[5023]	Ala Thr Val Arg Leu Pro Asn Arg Ala Leu Ser Cys Ser Leu Arg Leu	
[5024]	145 150 155 160	
[5025]	Arg Val Gly Gln Ala Ser Met Ile Ala Ser Pro Ser Gly Val Leu Lys	
[5026]	165 170 175	
[5027]	Leu Ser Asp Trp Val Leu Leu Asn Cys Ser Phe Ser Arg Pro Asp Arg	
[5028]	180 185 190	
[5029]	Pro Val Ser Val His Trp Phe Gln Gly Gln Asn Arg Val Pro Val Tyr	
[5030]	195 200 205	
[5031]	Asn Ser Pro Arg His Phe Leu Ala Glu Thr Phe Leu Leu Leu Pro Gln	
[5032]	210 215 220	
[5033]	Val Ser Pro Leu Asp Ser Gly Thr Trp Gly Cys Val Leu Thr Tyr Arg	
[5034]	225 230 235 240	
[5035]	Asp Gly Phe Asn Val Ser Ile Thr Tyr Asn Leu Lys Val Leu Gly Leu	
[5036]	245 250 255	
[5037]	Glu Pro Val Ala Pro Leu Thr Val Tyr Ala Ala Glu Gly Ser Arg Val	
[5038]	260 265 270	

[5039]	Glu Leu Pro Cys His Leu Pro Pro Gly Val Gly Thr Pro Ser Leu Leu		
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[5041]	Ile Ala Lys Trp Thr Pro Pro Gly Gly Gly Pro Glu Leu Pro Val Ala		
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[5043]	Gly Lys Ser Gly Asn Phe Thr Leu His Leu Glu Ala Val Gly Leu Ala		
[5044]	305	310	315 320
[5045]	Gln Ala Gly Thr Tyr Thr Cys Ser Ile His Leu Gln Gly Gln Gln Leu		
[5046]	325	330	335
[5047]	Asn Ala Thr Val Thr Leu Ala Val Ile Thr Val Thr Pro Lys Ser Phe		
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[5049]	Gly Leu Pro Gly Ser Arg Gly Lys Leu Leu Cys Glu Val Thr Pro Ala		
[5050]	355	360	365
[5051]	Ser Gly Lys Glu Arg Phe Val Trp Arg Pro Leu Asn Asn Leu Ser Arg		
[5052]	370	375	380
[5053]	Ser Cys Pro Gly Pro Val Leu Glu Ile Gln Glu Ala Arg Leu Leu Ala		
[5054]	385	390	395 400
[5055]	Glu Arg Trp Gln Cys Gln Leu Tyr Glu Gly Gln Arg Leu Leu Gly Ala		
[5056]	405	410	415
[5057]	Thr Val Tyr Ala Ala Glu Ser Ser Ser Gly Ala His Ser Ala Arg Arg		
[5058]	420	425	430
[5059]	Ile Ser Gly Asp Leu Lys Gly Gly His Leu Val Leu Val Leu Ile Leu		
[5060]	435	440	445
[5061]	Gly Ala Leu Ser Leu Phe Leu Leu Val Ala Gly Ala Phe Gly Phe His		
[5062]	450	455	460
[5063]	Trp Trp Arg Lys Gln Leu Leu Leu Arg Arg Phe Ser Ala Leu Glu His		
[5064]	465	470	475 480
[5065]	Gly Ile Gln Pro Phe Pro Ala Gln Arg Lys Ile Glu Glu Leu Glu Arg		
[5066]	485	490	495
[5067]	Glu Leu Glu Thr Glu Met Gly Gln Glu Pro Glu Pro Glu Pro Glu Pro		
[5068]	500	505	510
[5069]	Gln Leu Glu Pro Glu Pro Arg Gln Leu		
[5070]	515	520	
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[5076]	<223> 食蟹猴LAG-3的氨基酸序列		
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[5078]	Met	Trp	Glu	Ala	Gln	Phe	Leu	Gly	Leu	Leu	Phe	Leu	Gln	Pro	Leu	Trp
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[5080]	Val	Ala	Pro	Val	Lys	Pro	Pro	Gln	Pro	Gly	Ala	Glu	Ile	Ser	Val	Val
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[5082]	Trp	Ala	Gln	Glu	Gly	Ala	Pro	Ala	Gln	Leu	Pro	Cys	Ser	Pro	Thr	Ile
[5083]			35					40					45			
[5084]	Pro	Leu	Gln	Asp	Leu	Ser	Leu	Leu	Arg	Arg	Ala	Gly	Val	Thr	Trp	Gln
[5085]		50					55					60				
[5086]	His	Gln	Pro	Asp	Ser	Gly	Pro	Pro	Ala	Ala	Ala	Pro	Gly	His	Pro	Pro
[5087]	65					70					75				80	
[5088]	Val	Pro	Gly	His	Arg	Pro	Ala	Ala	Pro	Tyr	Ser	Trp	Gly	Pro	Arg	Pro
[5089]				85				90						95		
[5090]	Arg	Arg	Tyr	Thr	Val	Leu	Ser	Val	Gly	Pro	Gly	Gly	Leu	Arg	Ser	Gly
[5091]				100				105						110		
[5092]	Arg	Leu	Pro	Leu	Gln	Pro	Arg	Val	Gln	Leu	Asp	Glu	Arg	Gly	Arg	Gln
[5093]			115					120					125			
[5094]	Arg	Gly	Asp	Phe	Ser	Leu	Trp	Leu	Arg	Pro	Ala	Arg	Arg	Ala	Asp	Ala
[5095]		130					135					140				
[5096]	Gly	Glu	Tyr	Arg	Ala	Thr	Val	His	Leu	Arg	Asp	Arg	Ala	Leu	Ser	Cys
[5097]	145					150				155					160	
[5098]	Arg	Leu	Arg	Leu	Arg	Val	Gly	Gln	Ala	Ser	Met	Thr	Ala	Ser	Pro	Pro
[5099]				165				170						175		
[5100]	Gly	Ser	Leu	Arg	Thr	Ser	Asp	Trp	Val	Ile	Leu	Asn	Cys	Ser	Phe	Ser
[5101]				180				185						190		
[5102]	Arg	Pro	Asp	Arg	Pro	Ala	Ser	Val	His	Trp	Phe	Arg	Ser	Arg	Gly	Gln
[5103]			195					200					205			
[5104]	Gly	Arg	Val	Pro	Val	Gln	Gly	Ser	Pro	His	His	His	Leu	Ala	Glu	Ser
[5105]		210					215					220				
[5106]	Phe	Leu	Phe	Leu	Pro	His	Val	Gly	Pro	Met	Asp	Ser	Gly	Leu	Trp	Gly
[5107]	225					230					235				240	
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[5109]				245				250						255		
[5110]	Leu	Thr	Val	Leu	Gly	Leu	Glu	Pro	Ala	Thr	Pro	Leu	Thr	Val	Tyr	Ala
[5111]			260					265					270			
[5112]	Gly	Ala	Gly	Ser	Arg	Val	Glu	Leu	Pro	Cys	Arg	Leu	Pro	Pro	Ala	Val
[5113]			275					280					285			
[5114]	Gly	Thr	Gln	Ser	Phe	Leu	Thr	Ala	Lys	Trp	Ala	Pro	Pro	Gly	Gly	Gly
[5115]		290					295					300				
[5116]	Pro	Asp	Leu	Leu	Val	Ala	Gly	Asp	Asn	Gly	Asp	Phe	Thr	Leu	Arg	Leu

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[5118]	Glu Asp Val Ser Gln Ala Gln Ala Gly Thr Tyr Ile Cys His Ile Arg			
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[5120]	Leu Gln Gly Gln Gln Leu Asn Ala Thr Val Thr Leu Ala Ile Ile Thr			
[5121]		340	345	350
[5122]	Val Thr Pro Lys Ser Phe Gly Ser Pro Gly Ser Leu Gly Lys Leu Leu			
[5123]		355	360	365
[5124]	Cys Glu Val Thr Pro Ala Ser Gly Gln Glu His Phe Val Trp Ser Pro			
[5125]		370	375	380
[5126]	Leu Asn Thr Pro Ser Gln Arg Ser Phe Ser Gly Pro Trp Leu Glu Ala			
[5127]	385	390	395	400
[5128]	Gln Glu Ala Gln Leu Leu Ser Gln Pro Trp Gln Cys Gln Leu His Gln			
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[5130]	Gly Glu Arg Leu Leu Gly Ala Ala Val Tyr Phe Thr Glu Leu Ser Ser			
[5131]		420	425	430
[5132]	Pro Gly Ala Gln Arg Ser Gly Arg Ala Pro Gly Ala Leu Arg Ala Gly			
[5133]		435	440	445
[5134]	His Leu Pro Leu Phe Leu Ile Leu Gly Val Leu Phe Leu Leu Leu Leu			
[5135]		450	455	460
[5136]	Val Thr Gly Ala Phe Gly Phe His Leu Trp Arg Arg Gln Trp Arg Pro			
[5137]	465	470	475	480
[5138]	Arg Arg Phe Ser Ala Leu Glu Gln Gly Ile His Pro Pro Gln Ala Gln			
[5139]		485	490	495
[5140]	Ser Lys Ile Glu Glu Leu Glu Gln Glu Pro Glu Leu Glu Pro Glu Pro			
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[5142]	Glu Leu Glu Arg Glu Leu Gly Pro Glu Pro Glu Pro Gly Pro Glu Pro			
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[5144]	Glu Pro Glu Gln Leu			
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[5155]	Asn Ala Phe Thr Val Thr Val Pro Lys Asp Leu Tyr Val Val Glu Tyr			

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[5157]	Gly	Ser	Asn	Met	Thr	Ile	Glu	Cys	Lys	Phe	Pro	Val	Glu	Lys	Gln	Leu			
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[5159]	Asp	Leu	Ala	Ala	Leu	Ile	Val	Tyr	Trp	Glu	Met	Glu	Asp	Lys	Asn	Ile			
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[5161]	Ile	Gln	Phe	Val	His	Gly	Glu	Glu	Asp	Leu	Lys	Val	Gln	His	Ser	Ser			
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[5163]	Tyr	Arg	Gln	Arg	Ala	Arg	Leu	Leu	Lys	Asp	Gln	Leu	Ser	Leu	Gly	Asn			
[5164]				85					90				95						
[5165]	Ala	Ala	Leu	Gln	Ile	Thr	Asp	Val	Lys	Leu	Gln	Asp	Ala	Gly	Val	Tyr			
[5166]			100					105				110							
[5167]	Arg	Cys	Met	Ile	Ser	Tyr	Gly	Gly	Ala	Asp	Tyr	Lys	Arg	Ile	Thr	Val			
[5168]			115					120				125							
[5169]	Lys	Val	Asn	Ala	Pro	Tyr	Asn	Lys	Ile	Asn	Gln	Arg	Ile	Leu	Val	Val			
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[5171]	Asp	Pro	Val	Thr	Ser	Glu	His	Glu	Leu	Thr	Cys	Gln	Ala	Glu	Gly	Tyr			
[5172]	145					150				155						160			
[5173]	Pro	Lys	Ala	Glu	Val	Ile	Trp	Thr	Ser	Ser	Asp	His	Gln	Val	Leu	Ser			
[5174]				165					170				175						
[5175]	Gly	Lys	Thr	Thr	Thr	Thr	Asn	Ser	Lys	Arg	Glu	Glu	Lys	Leu	Phe	Asn			
[5176]			180						185				190						
[5177]	Val	Thr	Ser	Thr	Leu	Arg	Ile	Asn	Thr	Thr	Thr	Asn	Glu	Ile	Phe	Tyr			
[5178]			195						200				205						
[5179]	Cys	Thr	Phe	Arg	Arg	Leu	Asp	Pro	Glu	Glu	Asn	His	Thr	Ala	Glu	Leu			
[5180]		210						215				220							
[5181]	Val	Ile	Pro	Glu	Leu	Pro	Leu	Ala	His	Pro	Pro	Asn	Glu	Arg	Thr	His			
[5182]	225					230				235						240			
[5183]	Leu	Val	Ile	Leu	Gly	Ala	Ile	Leu	Leu	Cys	Leu	Gly	Val	Ala	Leu	Thr			
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[5185]	Phe	Ile	Phe	Arg	Leu	Arg	Lys	Gly	Arg	Met	Met	Asp	Val	Lys	Lys	Cys			
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[5187]	Gly	Ile	Gln	Asp	Thr	Asn	Ser	Lys	Lys	Gln	Ser	Asp	Thr	His	Leu	Glu			
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[5204]	Asp Leu Leu Ala Leu Val Val Tyr Trp Glu Lys Glu Asp Glu Gln Val	
[5205]	50 55 60	
[5206]	Ile Gln Phe Val Ala Gly Glu Glu Asp Leu Lys Pro Gln His Ser Asn	
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[5208]	Phe Arg Gly Arg Ala Ser Leu Pro Lys Asp Gln Leu Leu Lys Gly Asn	
[5209]	85 90 95	
[5210]	Ala Ala Leu Gln Ile Thr Asp Val Lys Leu Gln Asp Ala Gly Val Tyr	
[5211]	100 105 110	
[5212]	Cys Cys Ile Ile Ser Tyr Gly Gly Ala Asp Tyr Lys Arg Ile Thr Leu	
[5213]	115 120 125	
[5214]	Lys Val Asn Ala Pro Tyr Arg Lys Ile Asn Gln Arg Ile Ser Val Asp	
[5215]	130 135 140	
[5216]	Pro Ala Thr Ser Glu His Glu Leu Ile Cys Gln Ala Glu Gly Tyr Pro	
[5217]	145 150 155 160	
[5218]	Glu Ala Glu Val Ile Trp Thr Asn Ser Asp His Gln Pro Val Ser Gly	
[5219]	165 170 175	
[5220]	Lys Arg Ser Val Thr Thr Ser Arg Thr Glu Gly Met Leu Leu Asn Val	
[5221]	180 185 190	
[5222]	Thr Ser Ser Leu Arg Val Asn Ala Thr Ala Asn Asp Val Phe Tyr Cys	
[5223]	195 200 205	
[5224]	Thr Phe Trp Arg Ser Gln Pro Gly Gln Asn His Thr Ala Glu Leu Ile	
[5225]	210 215 220	
[5226]	Ile Pro Glu Leu Pro Ala Thr His Pro Pro Gln Asn Arg Thr His Trp	
[5227]	225 230 235 240	
[5228]	Val Leu Leu Gly Ser Ile Leu Leu Phe Leu Ile Val Val Ser Thr Val	
[5229]	245 250 255	
[5230]	Leu Leu Phe Leu Arg Lys Gln Val Arg Met Leu Asp Val Glu Lys Cys	
[5231]	260 265 270	
[5232]	Gly Val Glu Asp Thr Ser Ser Lys Asn Arg Asn Asp Thr Gln Phe Glu	
[5233]	275 280 285	

[5234]	Glu Thr															
[5235]	290															
[5236]	<210> 131															
[5237]	<211> 290															
[5238]	<212> PRT															
[5239]	<213> 人工序列															
[5240]	<220>															
[5241]	<223> 食蟹猴PD-L1的氨基酸序列															
[5242]	<400> 131															
[5243]	Met	Arg	Ile	Phe	Ala	Val	Phe	Ile	Phe	Thr	Ile	Tyr	Trp	His	Leu	Leu
[5244]	1				5					10					15	
[5245]	Asn	Ala	Phe	Thr	Val	Thr	Val	Pro	Lys	Asp	Leu	Tyr	Val	Val	Glu	Tyr
[5246]				20					25					30		
[5247]	Gly	Ser	Asn	Met	Thr	Ile	Glu	Cys	Lys	Phe	Pro	Val	Glu	Lys	Gln	Leu
[5248]			35				40					45				
[5249]	Asp	Leu	Thr	Ser	Leu	Ile	Val	Tyr	Trp	Glu	Met	Glu	Asp	Lys	Asn	Ile
[5250]		50					55				60					
[5251]	Ile	Gln	Phe	Val	His	Gly	Glu	Glu	Asp	Leu	Lys	Val	Gln	His	Ser	Asn
[5252]	65					70				75						80
[5253]	Tyr	Arg	Gln	Arg	Ala	Gln	Leu	Leu	Lys	Asp	Gln	Leu	Ser	Leu	Gly	Asn
[5254]					85					90					95	
[5255]	Ala	Ala	Leu	Arg	Ile	Thr	Asp	Val	Lys	Leu	Gln	Asp	Ala	Gly	Val	Tyr
[5256]				100					105					110		
[5257]	Arg	Cys	Met	Ile	Ser	Tyr	Gly	Gly	Ala	Asp	Tyr	Lys	Arg	Ile	Thr	Val
[5258]			115					120					125			
[5259]	Lys	Val	Asn	Ala	Pro	Tyr	Asn	Lys	Ile	Asn	Gln	Arg	Ile	Leu	Val	Val
[5260]		130					135				140					
[5261]	Asp	Pro	Val	Thr	Ser	Glu	His	Glu	Leu	Thr	Cys	Gln	Ala	Glu	Gly	Tyr
[5262]	145					150					155					160
[5263]	Pro	Lys	Ala	Glu	Val	Ile	Trp	Thr	Ser	Ser	Asp	His	Gln	Val	Leu	Ser
[5264]					165					170					175	
[5265]	Gly	Lys	Thr	Thr	Thr	Thr	Asn	Ser	Lys	Arg	Glu	Glu	Lys	Leu	Leu	Asn
[5266]				180					185					190		
[5267]	Val	Thr	Ser	Thr	Leu	Arg	Ile	Asn	Thr	Thr	Ala	Asn	Glu	Ile	Phe	Tyr
[5268]			195					200					205			
[5269]	Cys	Ile	Phe	Arg	Arg	Leu	Asp	Pro	Glu	Glu	Asn	His	Thr	Ala	Glu	Leu
[5270]		210					215					220				
[5271]	Val	Ile	Pro	Glu	Leu	Pro	Leu	Ala	Leu	Pro	Pro	Asn	Glu	Arg	Thr	His
[5272]	225					230					235					240

[5273]	Leu Val Ile Leu Gly Ala Ile Phe Leu Leu Leu Gly Val Ala Leu Thr
[5274]	245 250 255
[5275]	Phe Ile Phe Tyr Leu Arg Lys Gly Arg Met Met Asp Met Lys Lys Cys
[5276]	260 265 270
[5277]	Gly Ile Arg Val Thr Asn Ser Lys Lys Gln Arg Asp Thr Gln Leu Glu
[5278]	275 280 285
[5279]	Glu Thr
[5280]	290
[5281]	<210> 132
[5282]	<211> 447
[5283]	<212> PRT
[5284]	<213> 人工序列
[5285]	<220>
[5286]	<223> 抗小鼠LAG-3/FITC mAb2 FS18-7-108-29/4420的重链的氨基酸序列,包括 LALA突变
[5287]	<400> 132
[5288]	Glu Val Lys Leu Asp Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Arg
[5289]	1 5 10 15
[5290]	Pro Met Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Tyr
[5291]	20 25 30
[5292]	Trp Met Asn Trp Val Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val
[5293]	35 40 45
[5294]	Ala Gln Ile Arg Asn Lys Pro Tyr Asn Tyr Glu Thr Tyr Tyr Ser Asp
[5295]	50 55 60
[5296]	Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser
[5297]	65 70 75 80
[5298]	Val Tyr Leu Gln Met Asn Asn Leu Arg Val Glu Asp Met Gly Ile Tyr
[5299]	85 90 95
[5300]	Tyr Cys Thr Gly Ser Tyr Tyr Gly Met Asp Tyr Trp Gly Gln Gly Thr
[5301]	100 105 110
[5302]	Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
[5303]	115 120 125
[5304]	Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
[5305]	130 135 140
[5306]	Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
[5307]	145 150 155 160
[5308]	Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
[5309]	165 170 175
[5310]	Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser

[5311]	180	185	190
[5312]	Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser		
[5313]	195	200	205
[5314]	Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr		
[5315]	210	215	220
[5316]	His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser		
[5317]	225	230	235
[5318]	Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg		
[5319]	245	250	255
[5320]	Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro		
[5321]	260	265	270
[5322]	Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala		
[5323]	275	280	285
[5324]	Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val		
[5325]	290	295	300
[5326]	Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr		
[5327]	305	310	315
[5328]	Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr		
[5329]	325	330	335
[5330]	Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu		
[5331]	340	345	350
[5332]	Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys		
[5333]	355	360	365
[5334]	Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Val Val Glu Trp Glu Ser		
[5335]	370	375	380
[5336]	Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp		
[5337]	385	390	395
[5338]	Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Phe Glu		
[5339]	405	410	415
[5340]	Arg Trp Met Trp Pro Asp Glu Phe Ser Cys Ser Val Met His Glu Ala		
[5341]	420	425	430
[5342]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
[5343]	435	440	445
[5344]	<210> 133		
[5345]	<211> 447		
[5346]	<212> PRT		
[5347]	<213> 人工序列		
[5348]	<220>		
[5349]	<223> 抗小鼠LAG-3/FITC mAb2 FS18-7-108-35/4420的重链的氨基酸序列,包括		

LALA突变

[5350] <400> 133

[5351] Glu Val Lys Leu Asp Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Arg

[5352] 1 5 10 15

[5353] Pro Met Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Tyr

[5354] 20 25 30

[5355] Trp Met Asn Trp Val Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val

[5356] 35 40 45

[5357] Ala Gln Ile Arg Asn Lys Pro Tyr Asn Tyr Glu Thr Tyr Tyr Ser Asp

[5358] 50 55 60

[5359] Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser

[5360] 65 70 75 80

[5361] Val Tyr Leu Gln Met Asn Asn Leu Arg Val Glu Asp Met Gly Ile Tyr

[5362] 85 90 95

[5363] Tyr Cys Thr Gly Ser Tyr Tyr Gly Met Asp Tyr Trp Gly Gln Gly Thr

[5364] 100 105 110

[5365] Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro

[5366] 115 120 125

[5367] Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly

[5368] 130 135 140

[5369] Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn

[5370] 145 150 155 160

[5371] Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln

[5372] 165 170 175

[5373] Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser

[5374] 180 185 190

[5375] Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser

[5376] 195 200 205

[5377] Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr

[5378] 210 215 220

[5379] His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser

[5380] 225 230 235 240

[5381] Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg

[5382] 245 250 255

[5383] Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro

[5384] 260 265 270

[5385] Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala

[5386] 275 280 285

[5387] Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val

[5388]	290	295	300
[5389]	Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr		
[5390]	305	310	315
[5391]	Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr		
[5392]	325	330	335
[5393]	Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu		
[5394]	340	345	350
[5395]	Pro Pro Ser Trp Asp Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys		
[5396]	355	360	365
[5397]	Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ser Val Glu Trp Glu Ser		
[5398]	370	375	380
[5399]	Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp		
[5400]	385	390	395
[5401]	Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Pro Phe Glu		
[5402]	405	410	415
[5403]	Arg Trp Met Trp Pro Asp Glu Phe Ser Cys Ser Val Met His Glu Ala		
[5404]	420	425	430
[5405]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
[5406]	435	440	445
[5407]	<210> 134		
[5408]	<211> 447		
[5409]	<212> PRT		
[5410]	<213> 人工序列		
[5411]	<220>		
[5412]	<223> 抗小鼠LAG-3/FITC mAb2 FS18-7-108-29/4420的重链的氨基酸序列		
[5413]	<400> 134		
[5414]	Glu Val Lys Leu Asp Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Arg		
[5415]	1	5	10
[5416]	Pro Met Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Tyr		
[5417]	20	25	30
[5418]	Trp Met Asn Trp Val Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val		
[5419]	35	40	45
[5420]	Ala Gln Ile Arg Asn Lys Pro Tyr Asn Tyr Glu Thr Tyr Tyr Ser Asp		
[5421]	50	55	60
[5422]	Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser		
[5423]	65	70	75
[5424]	Val Tyr Leu Gln Met Asn Asn Leu Arg Val Glu Asp Met Gly Ile Tyr		
[5425]	85	90	95
[5426]	Tyr Cys Thr Gly Ser Tyr Tyr Gly Met Asp Tyr Trp Gly Gln Gly Thr		

[5427]		100		105		110											
[5428]	Ser	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	
[5429]		115		120		125											
[5430]	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	
[5431]		130		135		140											
[5432]	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	
[5433]	145			150		155										160	
[5434]	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	
[5435]				165		170										175	
[5436]	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	
[5437]				180		185										190	
[5438]	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	
[5439]		195		200		205											
[5440]	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	
[5441]		210		215		220											
[5442]	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	
[5443]	225			230		235										240	
[5444]	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	
[5445]				245		250										255	
[5446]	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	
[5447]				260		265										270	
[5448]	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	
[5449]		275		280		285											
[5450]	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	
[5451]		290		295		300											
[5452]	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	
[5453]	305			310		315										320	
[5454]	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	
[5455]				325		330										335	
[5456]	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	
[5457]				340		345										350	
[5458]	Pro	Pro	Ser	Trp	Asp	Glu	Pro	Trp	Gly	Glu	Asp	Val	Ser	Leu	Thr	Cys	
[5459]				355		360										365	
[5460]	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Val	Val	Glu	Trp	Glu	Ser	
[5461]		370		375		380											
[5462]	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	
[5463]	385			390		395										400	
[5464]	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Pro	Phe	Glu	
[5465]				405		410										415	

[5466]	Arg Trp Met Trp Pro Asp Glu Phe Ser Cys Ser Val Met His Glu Ala
[5467]	420 425 430
[5468]	Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
[5469]	435 440 445
[5470]	<210> 135
[5471]	<211> 107
[5472]	<212> PRT
[5473]	<213> 人工序列
[5474]	<220>
[5475]	<223> 包括C-末端赖氨酸的Fcab FS18-7-9 CH3结构域的氨基酸序列
[5476]	<400> 135
[5477]	Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Trp Asp
[5478]	1 5 10 15
[5479]	Glu Pro Trp Gly Glu Asp Val Ser Leu Thr Cys Leu Val Lys Gly Phe
[5480]	20 25 30
[5481]	Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
[5482]	35 40 45
[5483]	Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
[5484]	50 55 60
[5485]	Phe Leu Tyr Ser Lys Leu Thr Val Pro Tyr Asp Arg Trp Val Trp Pro
[5486]	65 70 75 80
[5487]	Asp Glu Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
[5488]	85 90 95
[5489]	Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
[5490]	100 105
[5491]	<210> 136
[5492]	<211> 5
[5493]	<212> PRT
[5494]	<213> 人工序列
[5495]	<220>
[5496]	<223> 抗PD-L1抗体84G09的CDR的氨基酸序列(根据Kabat) HCDR1
[5497]	<400> 136
[5498]	Asp Tyr Ala Met His
[5499]	1 5
[5500]	<210> 137
[5501]	<211> 17
[5502]	<212> PRT
[5503]	<213> 人工序列
[5504]	<220>

[5505] <223> 抗PD-L1抗体84G09的CDR的氨基酸序列(根据Kabat) HCDR2
[5506] <400> 137
[5507] Gly Ile Ser Trp Lys Ser Asn Ile Ile Gly Tyr Ala Asp Ser Val Lys
[5508] 1 5 10 15
[5509] Gly
[5510] <210> 138
[5511] <211> 13
[5512] <212> PRT
[5513] <213> 人工序列
[5514] <220>
[5515] <223> 抗PD-L1抗体84G09的CDR的氨基酸序列(根据Kabat) HCDR3
[5516] <400> 138
[5517] Asp Ile Thr Gly Ser Gly Ser Tyr Gly Trp Phe Asp Pro
[5518] 1 5 10
[5519] <210> 139
[5520] <211> 11
[5521] <212> PRT
[5522] <213> 人工序列
[5523] <220>
[5524] <223> 抗PD-L1抗体84G09的CDR的氨基酸序列(根据Kabat) LCDR1
[5525] <400> 139
[5526] Arg Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn
[5527] 1 5 10
[5528] <210> 140
[5529] <211> 7
[5530] <212> PRT
[5531] <213> 人工序列
[5532] <220>
[5533] <223> 抗PD-L1抗体84G09的CDR的氨基酸序列(根据Kabat) LCDR2
[5534] <400> 140
[5535] Val Ala Ser Ser Leu Gln Ser
[5536] 1 5
[5537] <210> 141
[5538] <211> 9
[5539] <212> PRT
[5540] <213> 人工序列
[5541] <220>
[5542] <223> 抗PD-L1抗体84G09的CDR的氨基酸序列(根据Kabat) LCDR3
[5543] <400> 141

[5544] Gln Gln Ser Tyr Ser Asn Pro Ile Thr
[5545] 1 5
[5546] <210> 142
[5547] <211> 318
[5548] <212> DNA
[5549] <213> 人工序列
[5550] <220>
[5551] <223> Fcab FS18-7-9 CH3结构域的CH0密码子优化的核苷酸序列
[5552] <400> 142
[5553] ggccagcccc gggaacccca ggtgtacaca ctgcctccat cctgggatga gccctggggc 60
[5554] gaggatgtgt ctctgacctg tctcgtgaaa ggcttctacc cctccgatat cgccgtggaa 120
[5555] tgggagagca acggccagcc cgagaacaac tacaagacca cccccctgt gctggactcc 180
[5556] gacggctcat tcttctgtga cagcaagctg acagtgcct acgacagatg ggtgtggccc 240
[5557] gacgagttct cctgctcctg gatgcacgag gccctgcaca accactacac ccagaagtcc 300
[5558] ctgtccctga gccccggc 318

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CH3																																								CH3																																																																																																																							
AB																				CD																				EF																				CH3																																																																																																			
1.4	1.3	1.2	1.1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	35	36	37	38	39	40	41	42	43	44	45	45.1	45.2	45.3	45.4	77	78	79	80																																																																																																											
FS18-7-9	G	Q	P	R	E	P	Q	V	Y	T	L	P	P	S	W	D	E	P	W	G	E	D	V	S	L	T	C	L	V	K	G	F	Y	P	S	D	I	A	V	E	W	E	S	N	G	Q	P	E	N	Y	K	T																																																																																																											
FS18-7-32																																																																																																																																																															
FS18-7-33																																																																																																																																																															
FS18-7-36																																																																																																																																																															
FS18-7-58																																																																																																																																																															
FS18-7-62																																																																																																																																																															
FS18-7-65																																																																																																																																																															
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FS18-7-88																																																																																																																																																															
FS18-7-95																																																																																																																																																															
FS18-7-9	T	P	P	V	L	D	S	D	G	S	F	F	L	Y	S	K	L	T	V	P	Y	D	R	W	V	W	P	D	E	F	S	C	S	V	M	H	E	A	L	H	N	Y	T	Q	K	S	L	S	P	G																																																																																																													
FS18-7-32	81	82	83	84	84.1	84.2	84.3	84.4	85.3	85.2	85.1	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	106	107	108	109	110	112	113	114	115	116	117	118	119	120	121	122	123	124	125	129																																																																																																											
FS18-7-33																																																																																																																																																															
FS18-7-36										Y																																																																																																																																																					
FS18-7-58																																																																																																																																																															
FS18-7-62																																																																																																																																																															
FS18-7-65																																																																																																																																																															
FS18-7-78																																																																																																																																																															
FS18-7-88																																																																																																																																																															
FS18-7-95																																																																																																																																																															

图1

Fcab	对FS18-7-9的同 一性 ₊
FS18-7-32	99.1%
FS18-7-33	99.1%
FS18-7-36	99.1%
FS18-7-58	96.2%
FS18-7-62	98.1%
FS18-7-65	97.2%
FS18-7-78	97.2%
FS18-7-88	97.2%
FS18-7-95	97.2%

B

图1续

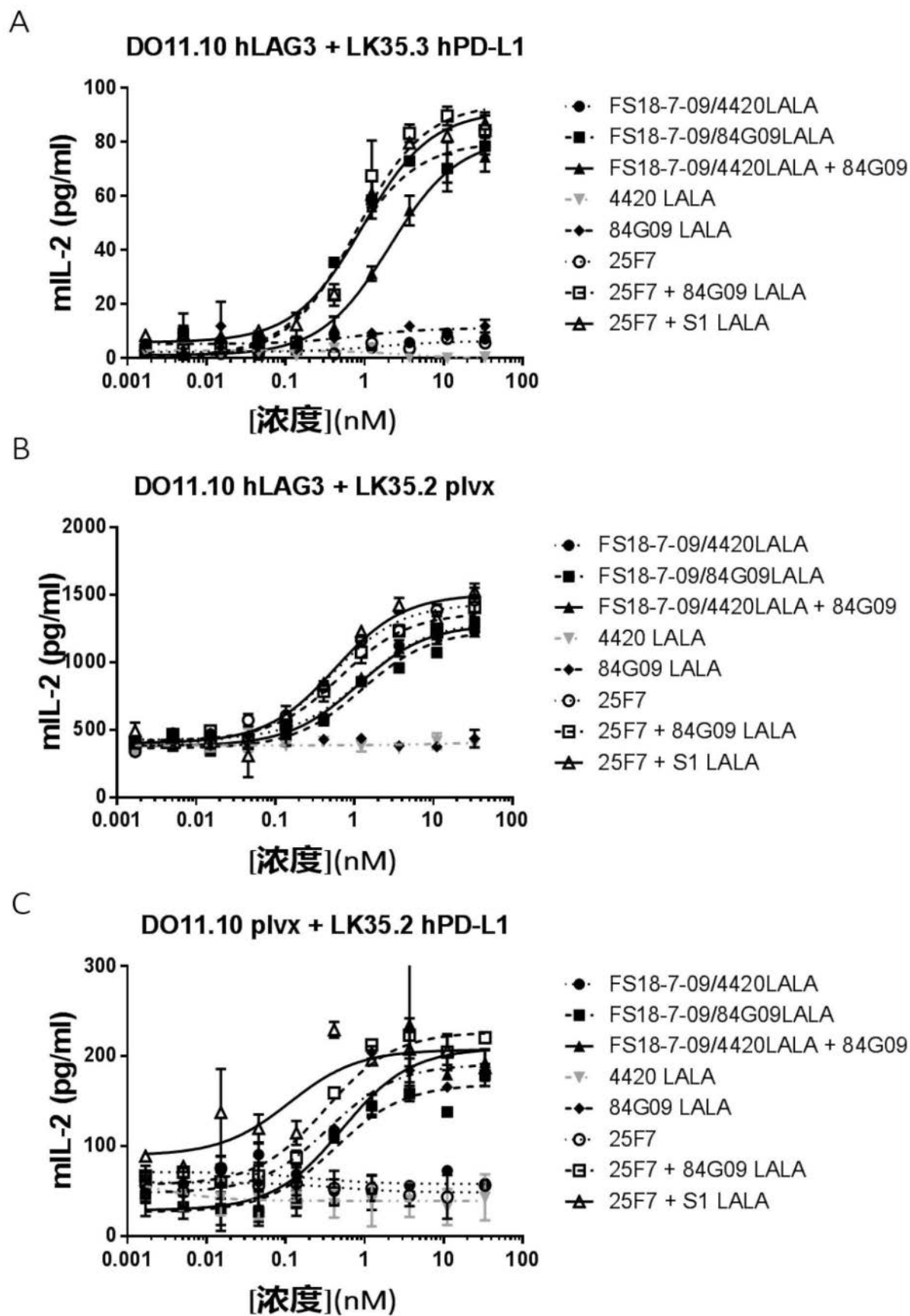
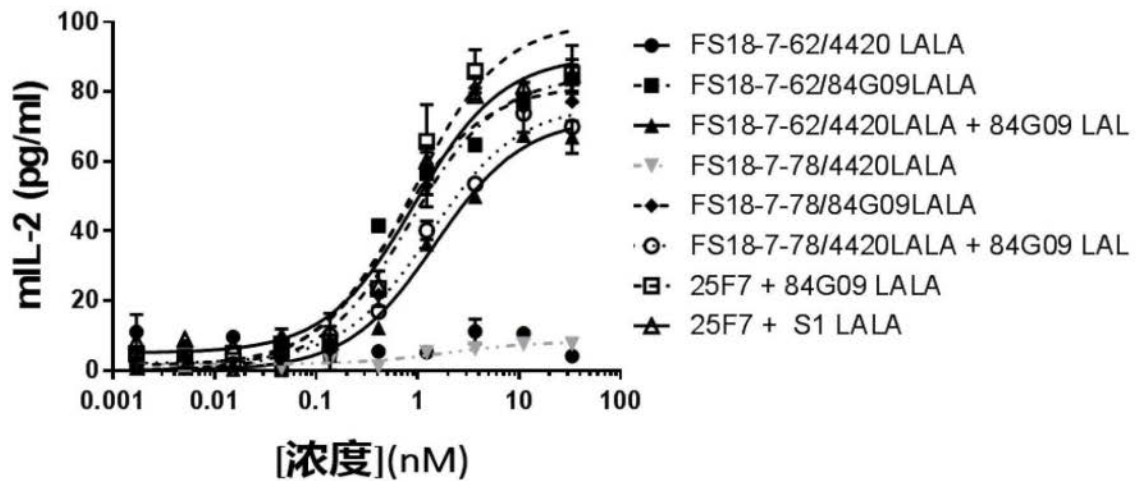


图2

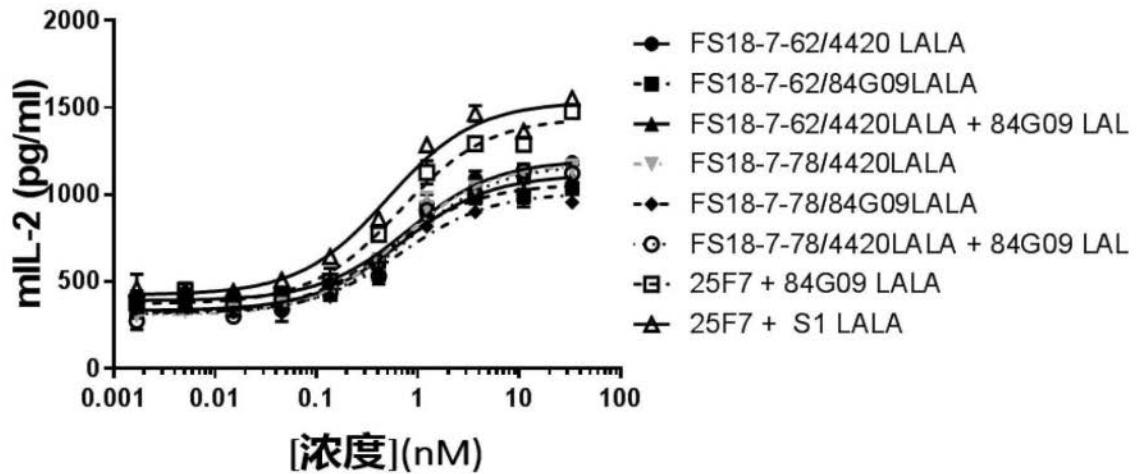
D

DO11.10 hLAG3 + LK35.2 hPD-L1



E

DO11.10 hLAG3 + LK35.2 plvx



F

DO11.10 plvx + LK35.2 hPD-L1

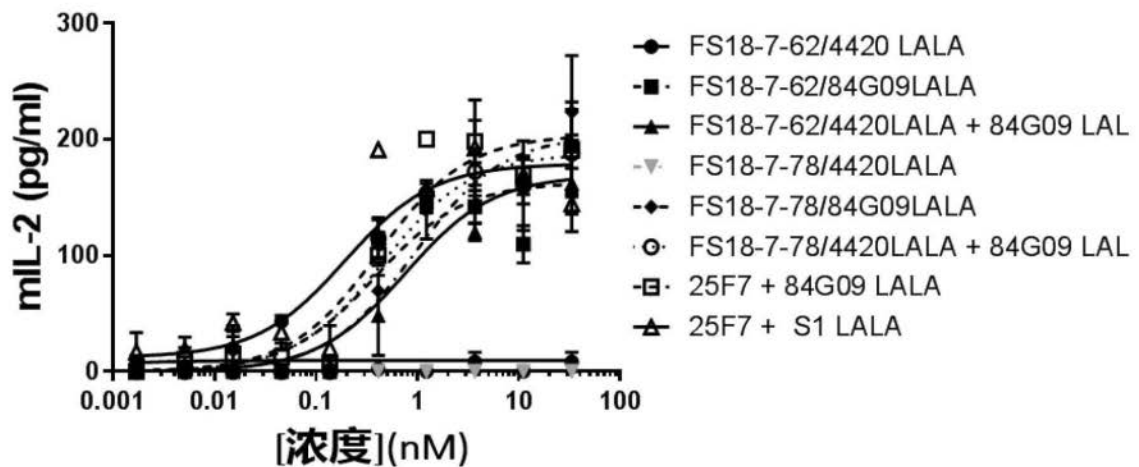


图2续

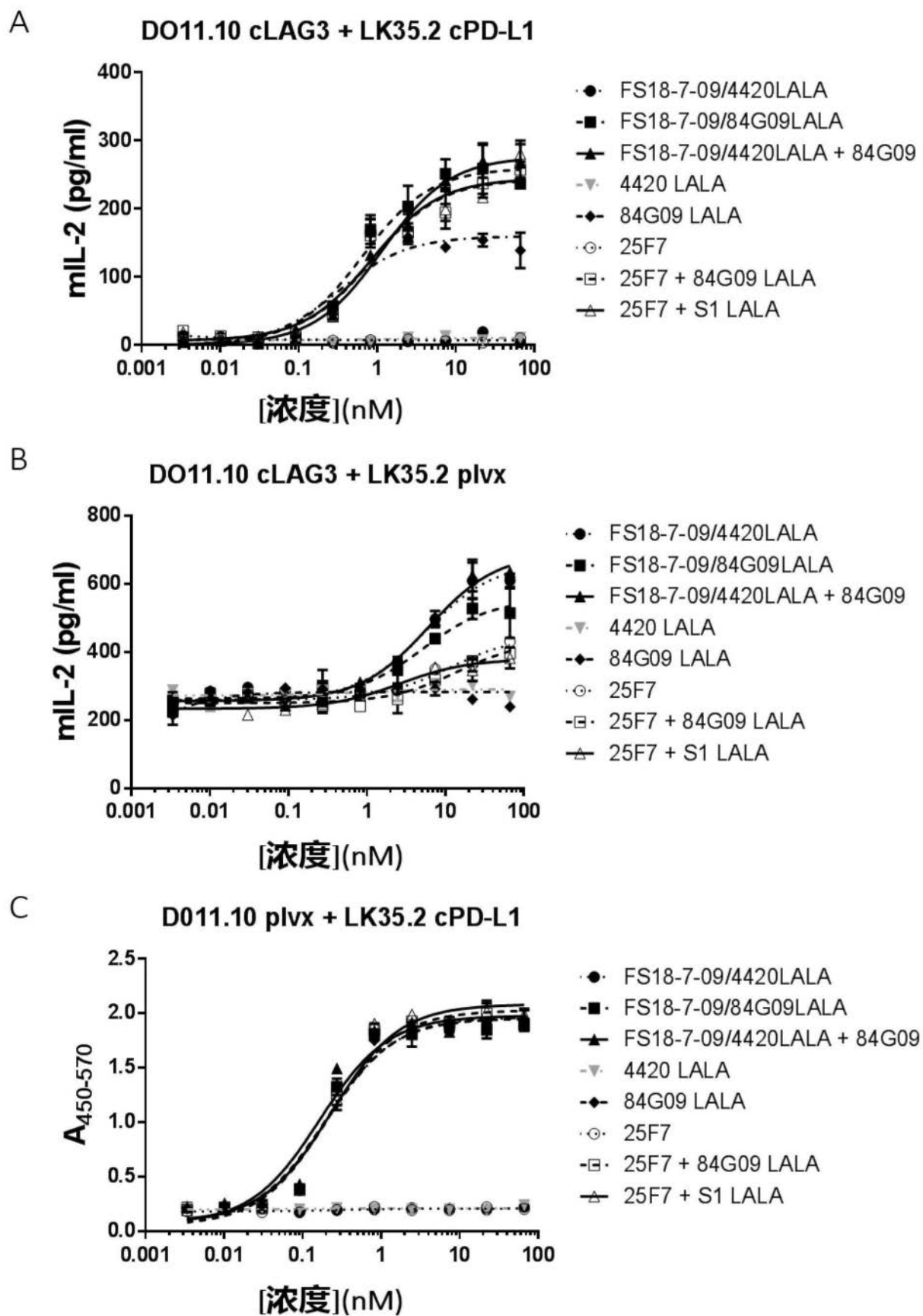


图3

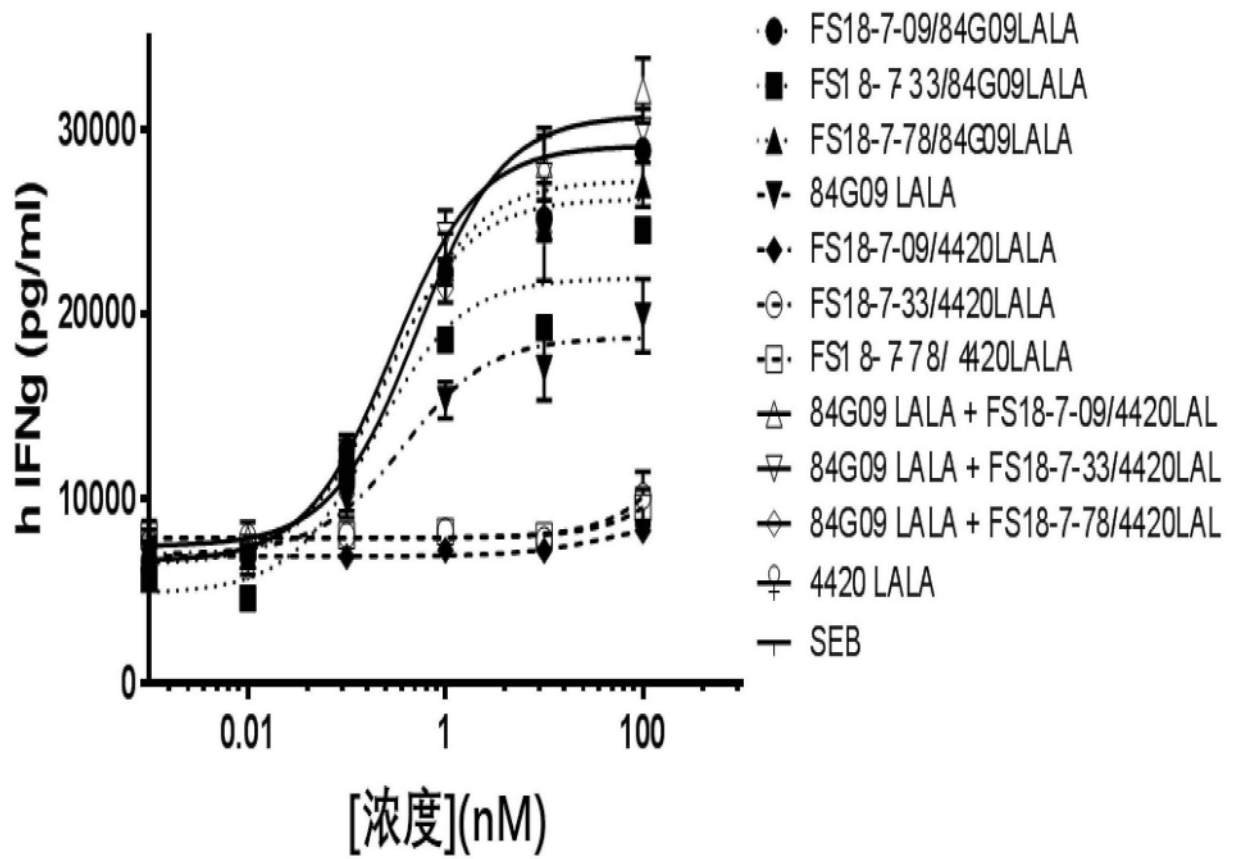


图4

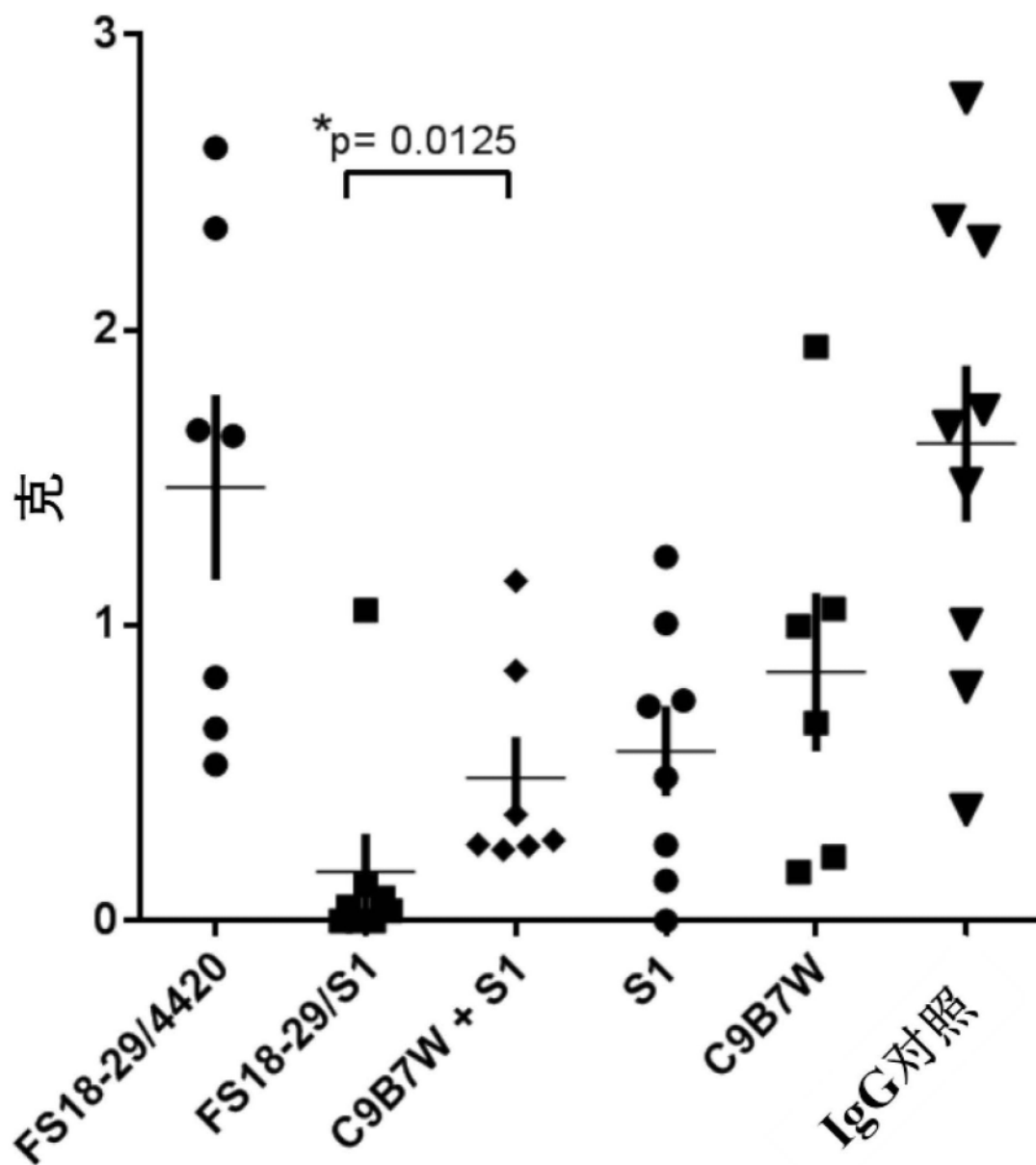


图5

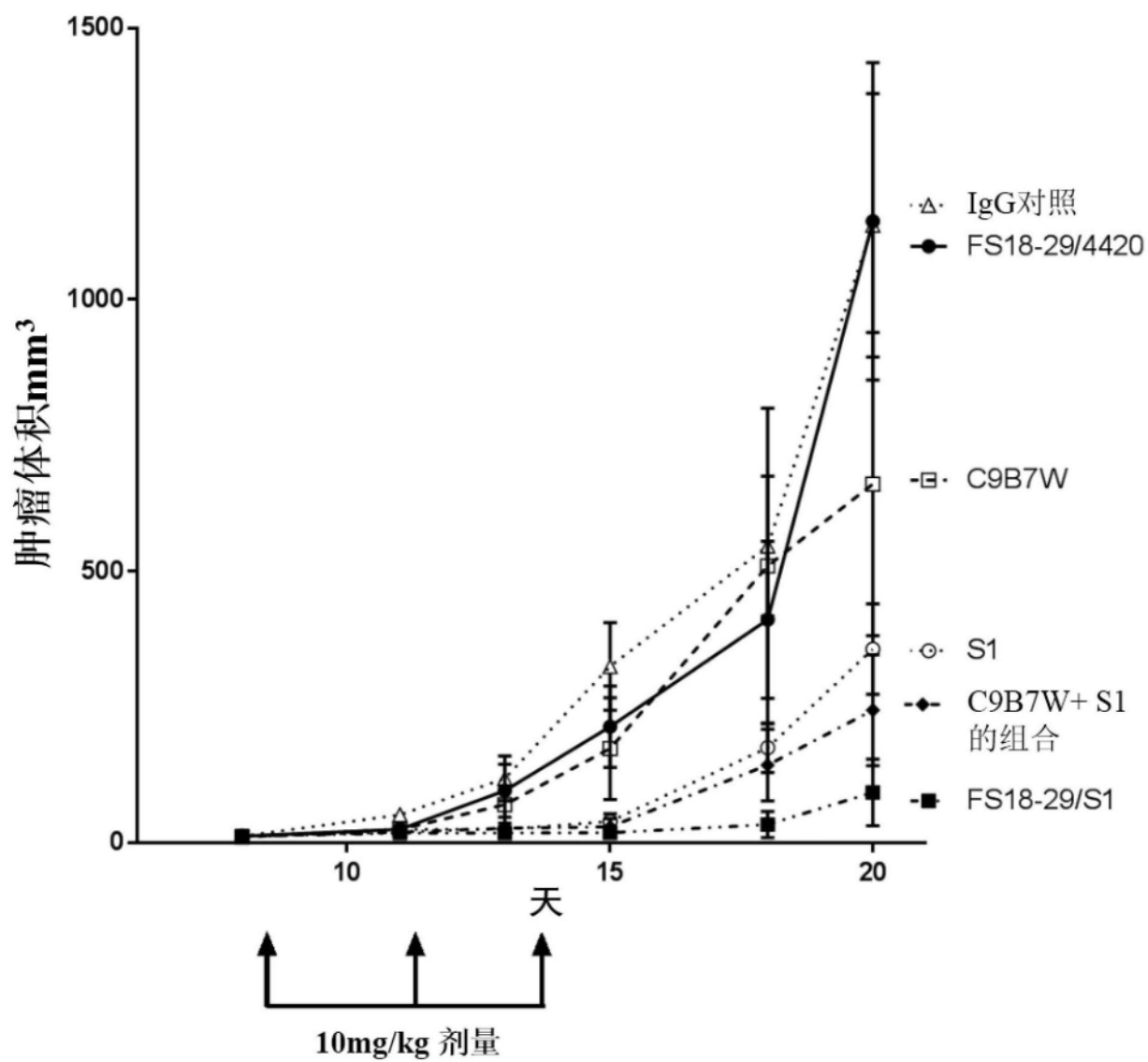


图6

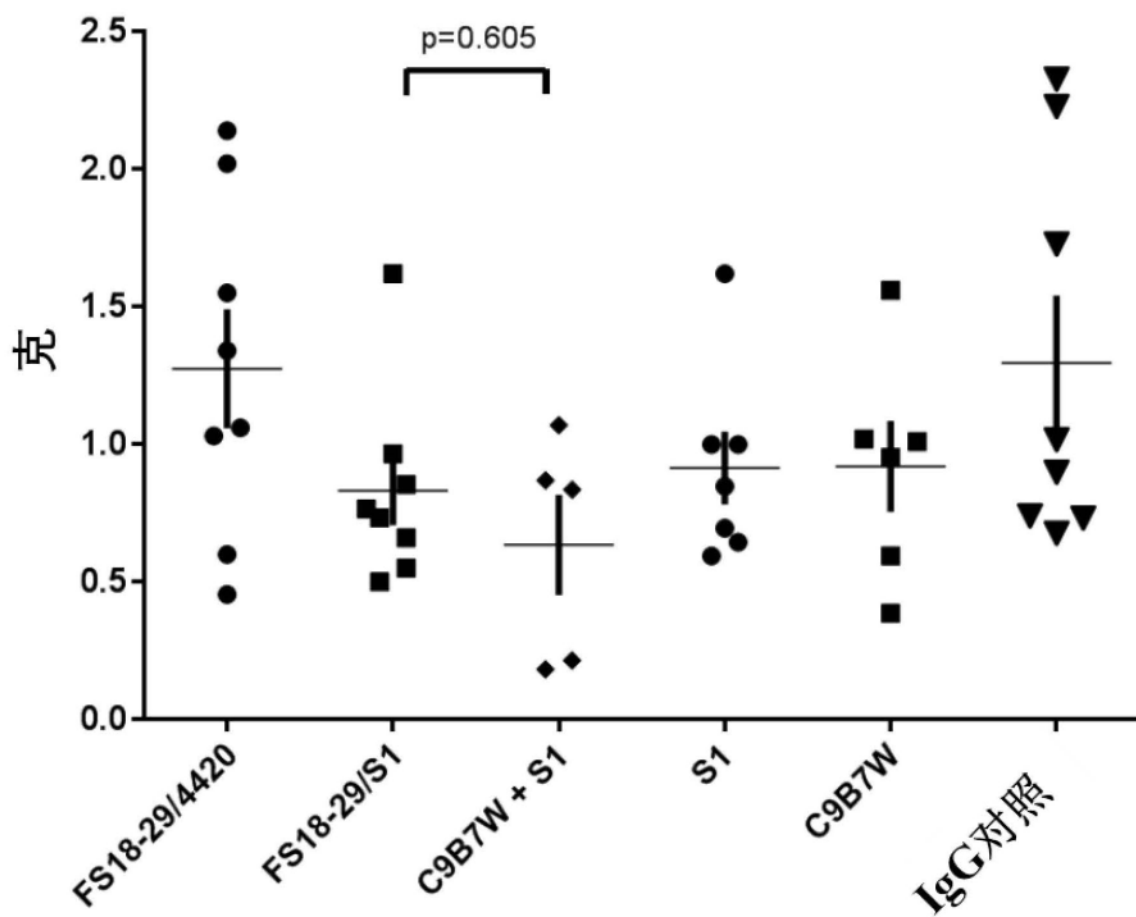


图7

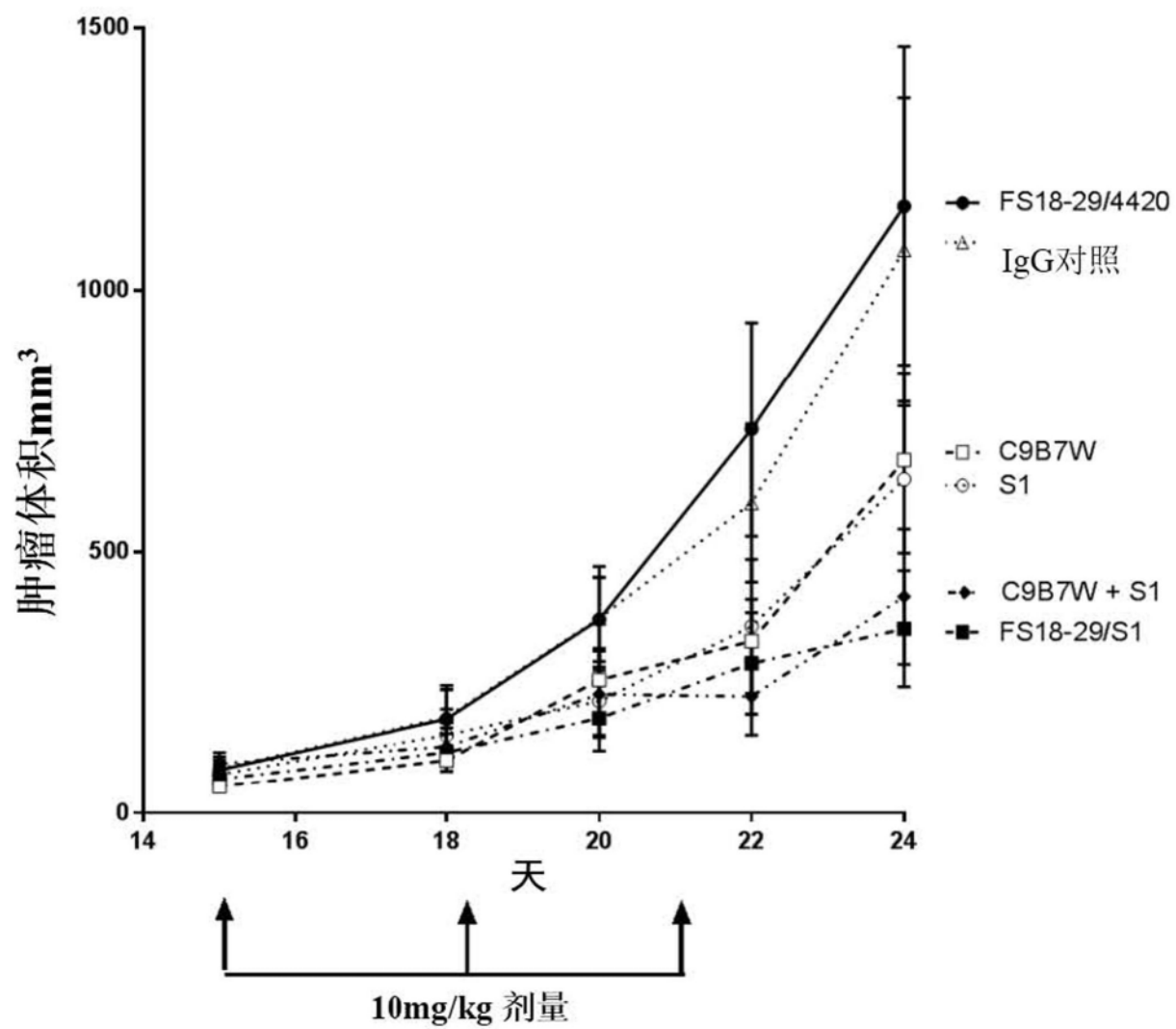


图8

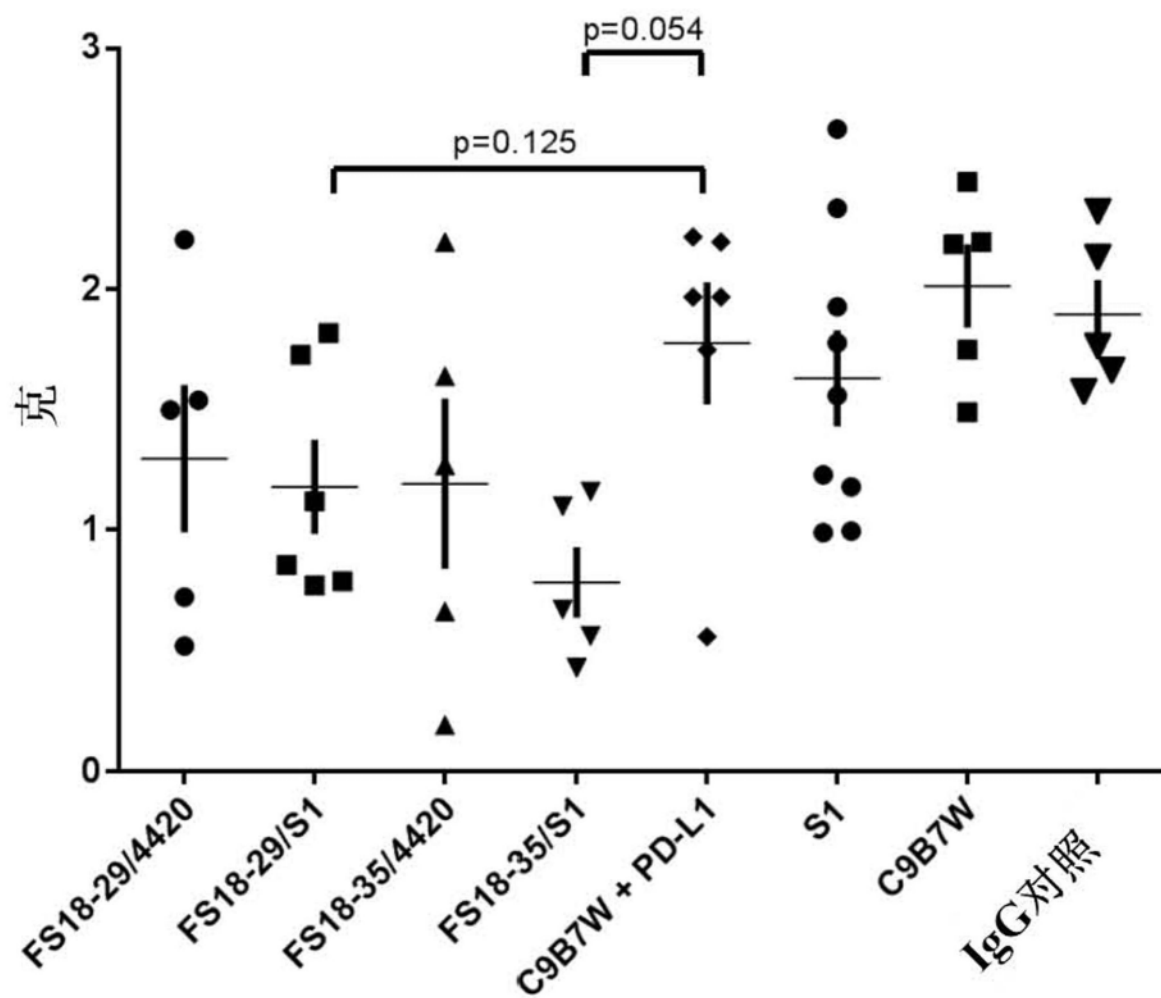


图9

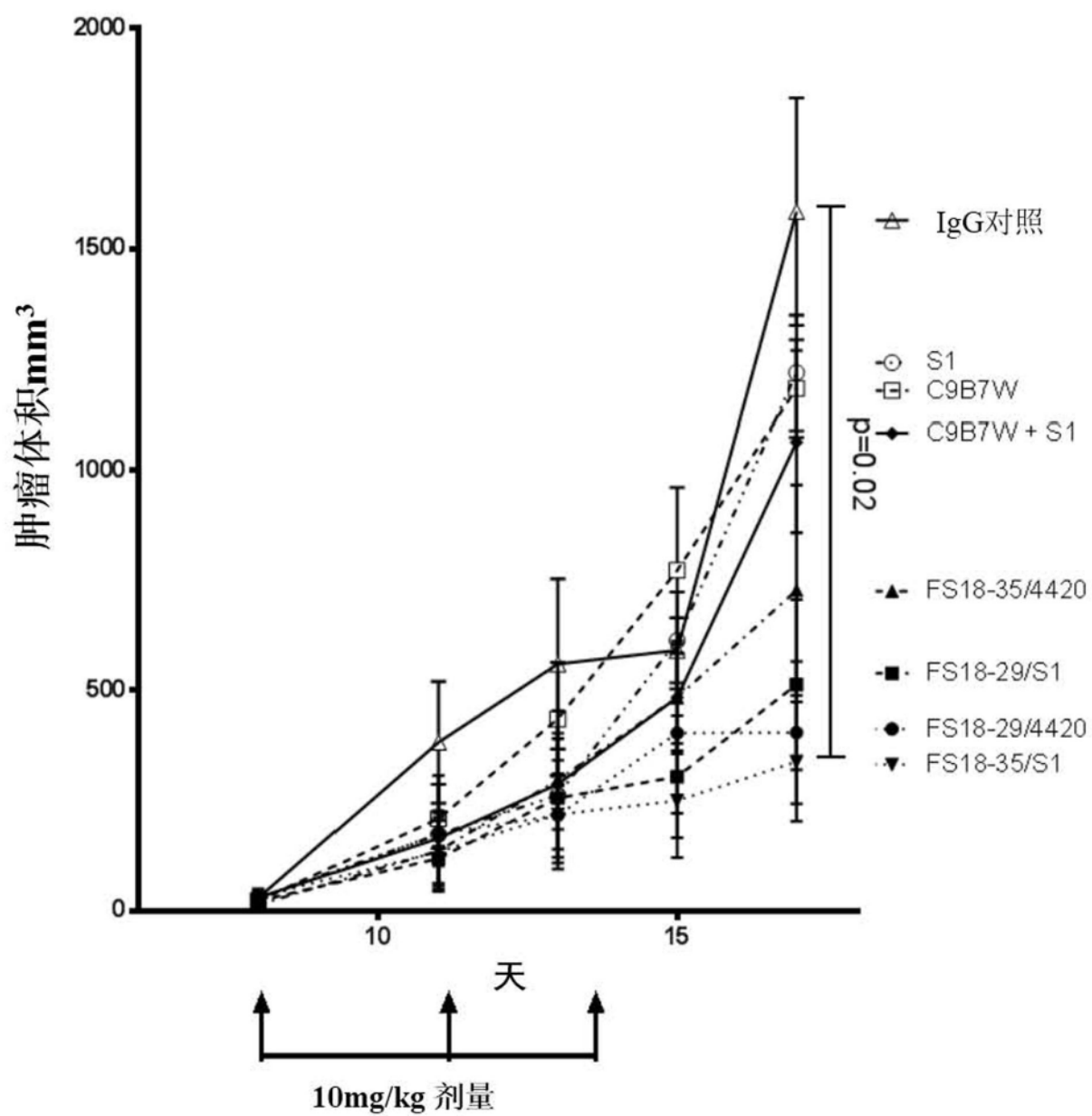


图10

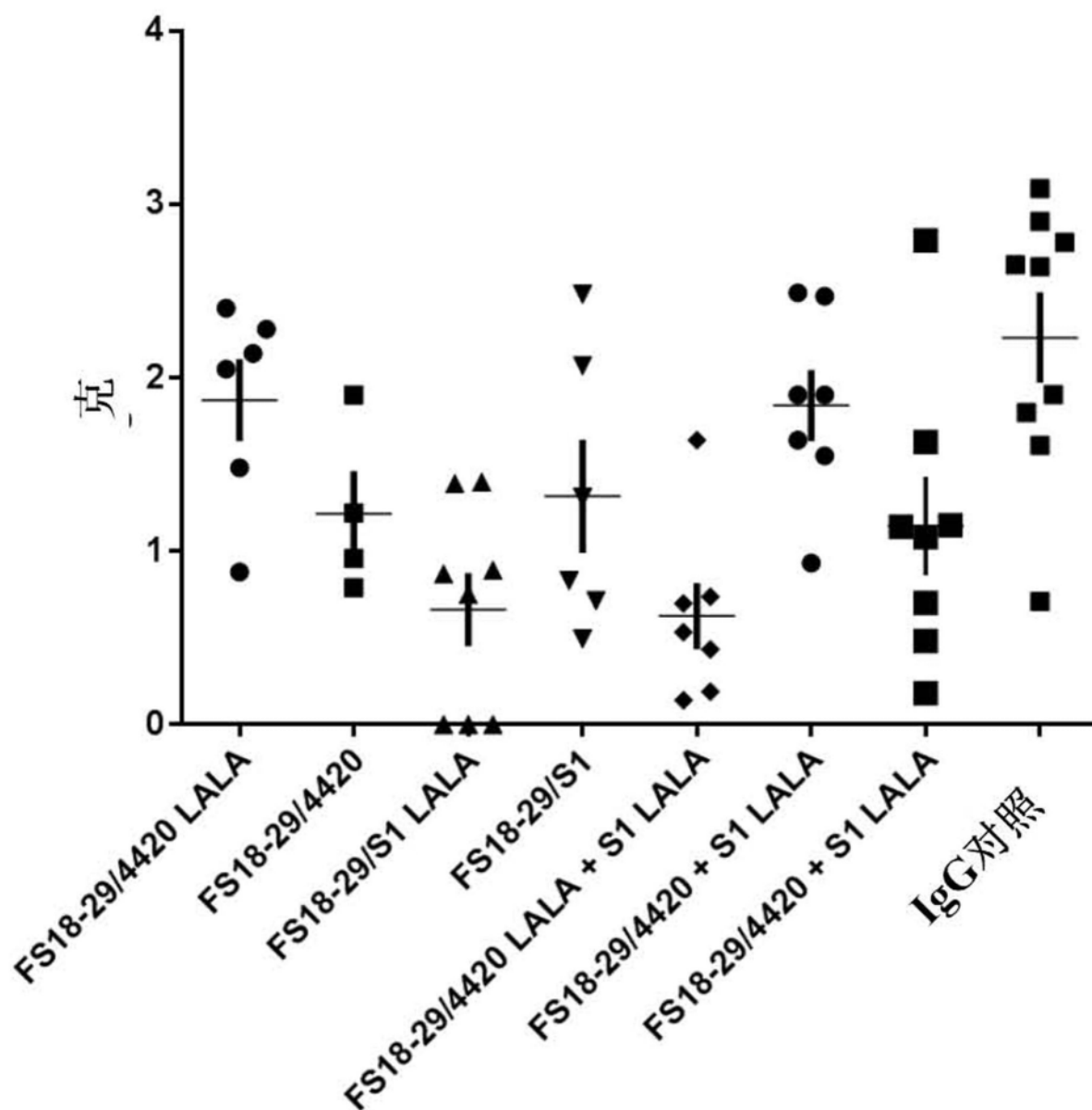


图11

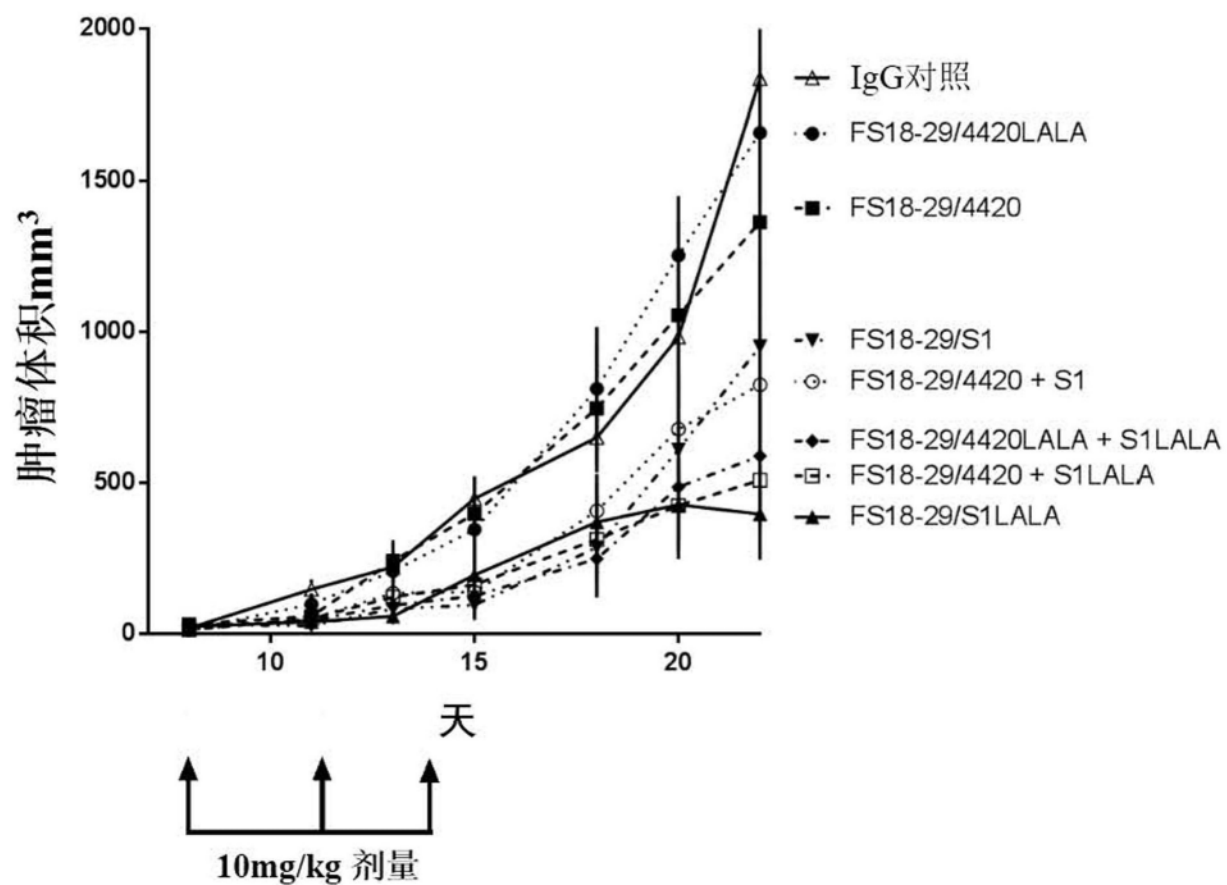


图12

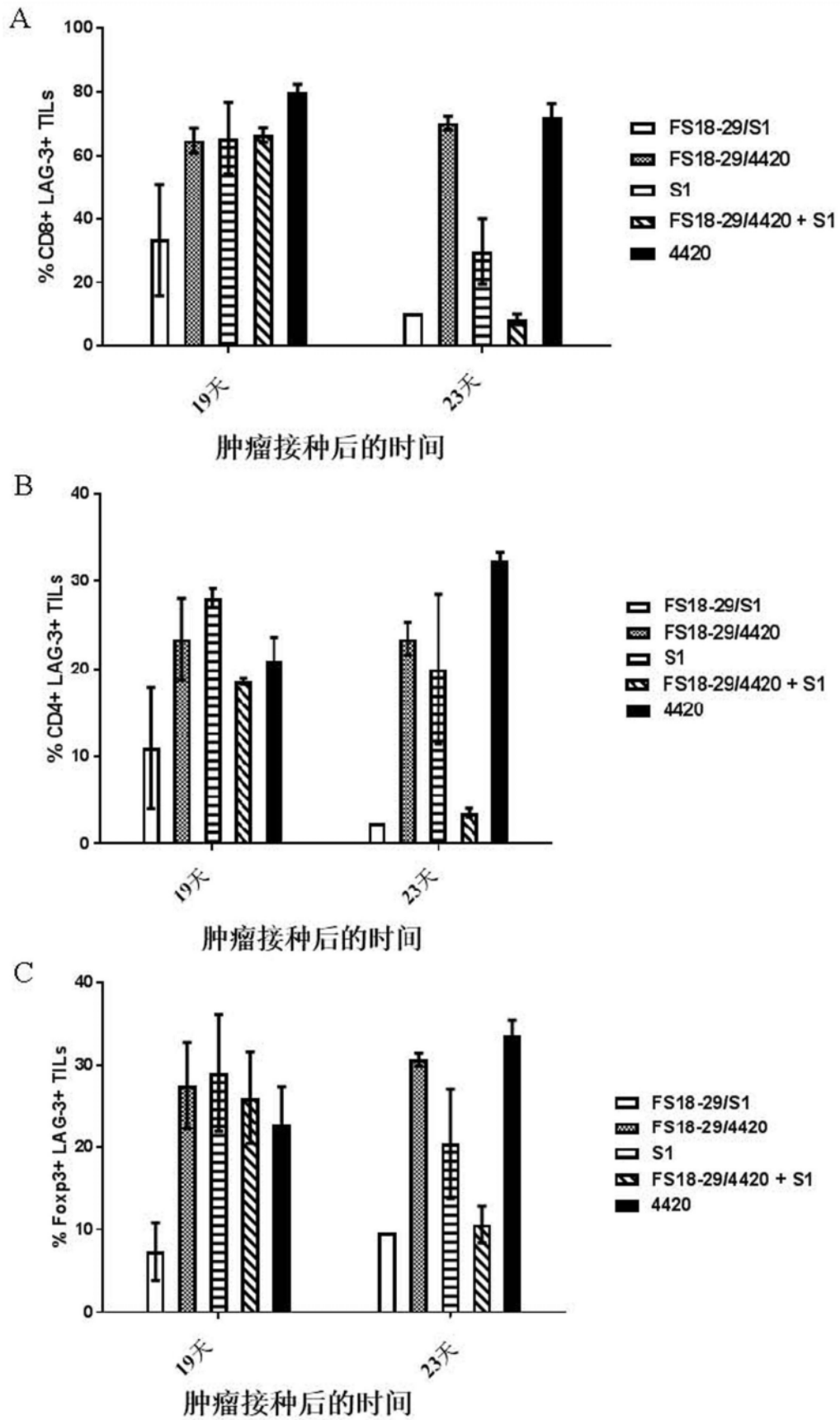


图13

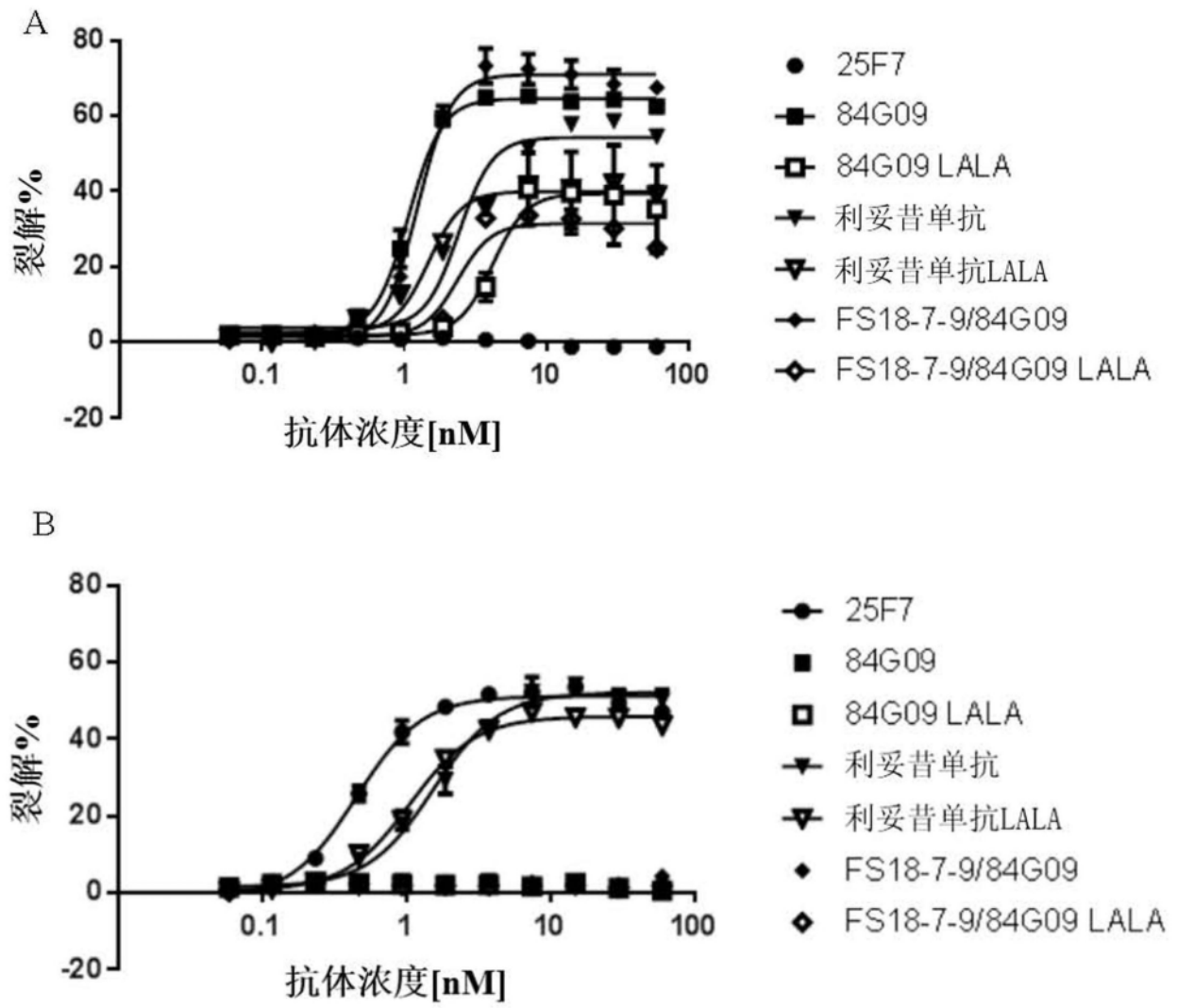


图14

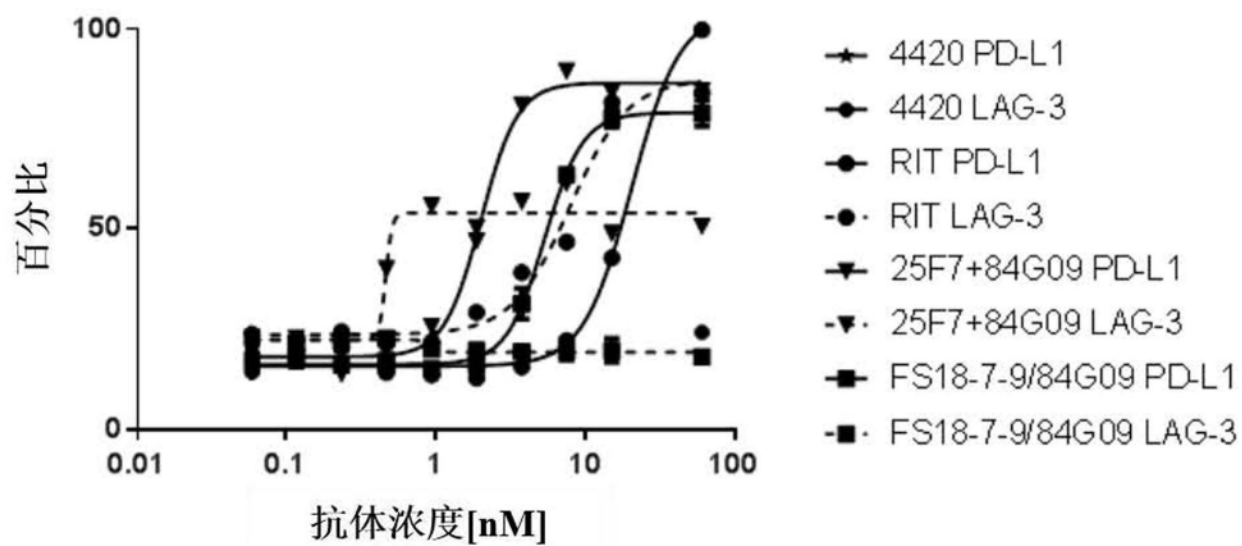


图15

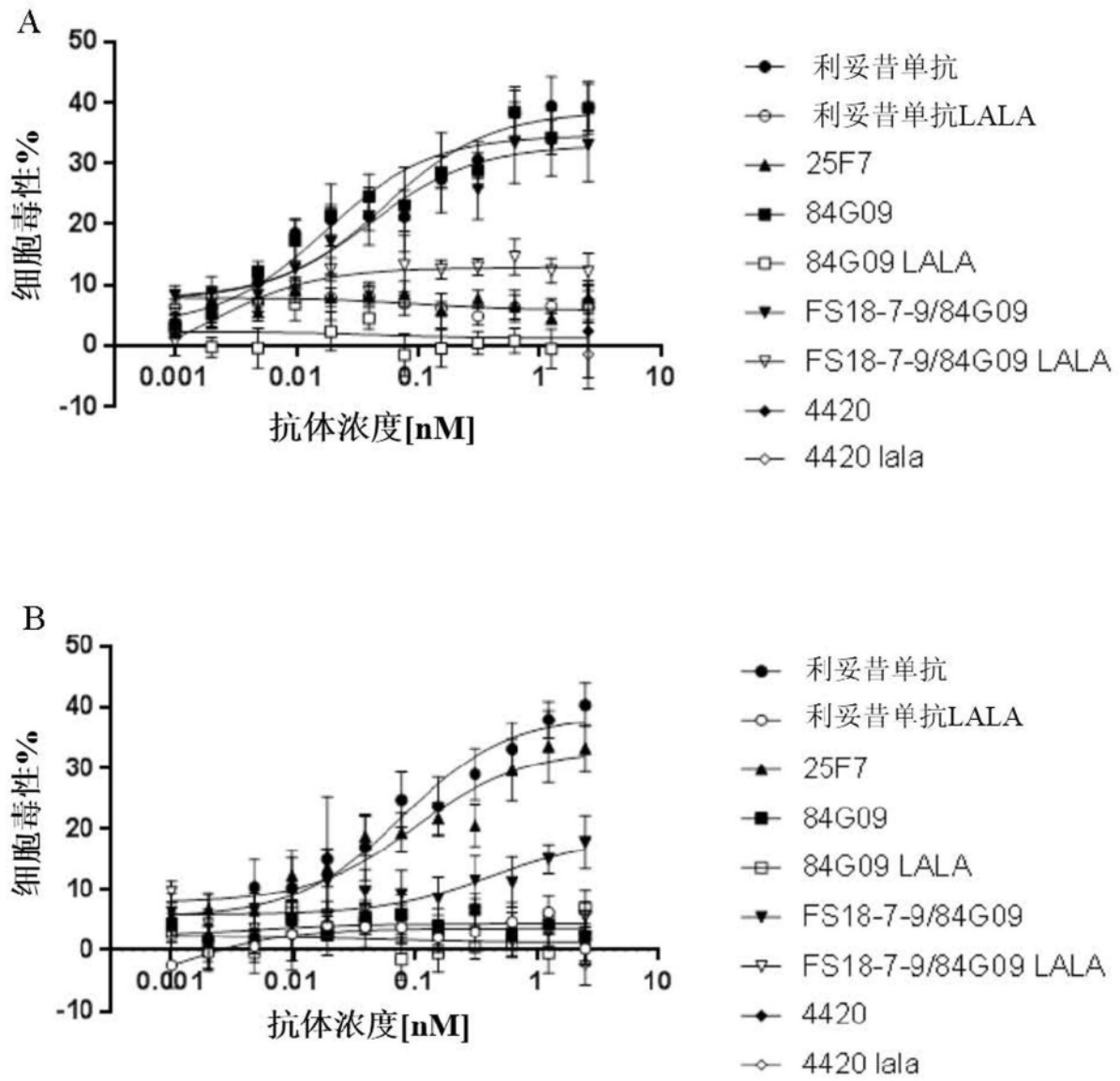


图16