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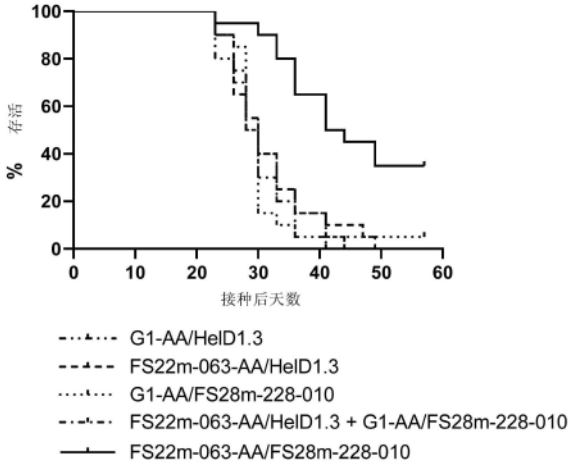
(54)发明名称

抗间皮素抗体

(57)摘要

本申请涉及结合间皮素(MSLN)的抗体分子。抗体分子可用于治疗和诊断疾病和病症,例如癌症。



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1.一种与间皮素(MSLN)结合的抗体分子,其中所述抗体分子为人IgG1分子;并且其中所述抗体分子包含:

(i)如SEQ ID NO: 180所示的VH结构域和如SEQ ID NO: 56所示的VL结构域;

(ii)如SEQ ID NO: 39所示的VH结构域和如SEQ ID NO: 18所示的VL结构域;

(iii)如SEQ ID NO: 109所示的VH结构域和如SEQ ID NO: 93所示的VL结构域;

(iv)如SEQ ID NO: 109所示的VH结构域和如SEQ ID NO: 79所示的VL结构域;

(v)如SEQ ID NO:121所示的VH结构域和如SEQ ID NO: 93所示的VL结构域;

(vi)如SEQ ID NO: 109所示的VH结构域和如SEQ ID NO: 53所示的VL结构域;

(vii)如SEQ ID NO:121所示的VH结构域和如SEQ ID NO: 53所示的VL结构域;

(viii)如SEQ ID NO: 63所示的VH结构域和如SEQ ID NO: 93所示的VL结构域;

(ix)如SEQ ID NO:63所示的VH结构域和如SEQ ID NO: 53所示的VL结构域;

(x)如SEQ ID NO: 115所示的VH结构域和如SEQ ID NO: 79所示的VL结构域;

(xi)如SEQ ID NO: 121所示的VH结构域和如SEQ ID NO: 79所示的VL结构域;或者

(xii)如SEQ ID NO: 69所示的VH结构域和如SEQ ID NO: 79所示的VL结构域。

2.如权利要求1所述的抗体分子,其中所述抗体分子包含如SEQ ID NO: 180所示的VH结构域和如SEQ ID NO: 56所示的VL结构域。

3.如权利要求1所述的抗体分子,其中所述抗体分子包含如SEQ ID NO: 39所示的VH结构域和如SEQ ID NO: 18所示的VL结构域。

4.如权利要求1所述的抗体分子,其中所述抗体分子包含SEQ ID NO:178或176所示的重链和SEQ ID NO:95所示的轻链。

5.如权利要求1所述的抗体分子,其中所述抗体分子包含SEQ ID NO:37或35所示的重链和SEQ ID NO:16所示的轻链。

6.如权利要求1至3中任一项所述的抗体分子,其中所述抗体分子是多特异性抗体分子,并且包含结合CD137的第二抗原结合位点,所述第二抗原结合位点位于CH3结构域。

7.如权利要求6所述的抗体分子,其中所述抗体分子能够在MSLN的存在下激活免疫细胞。

8.如权利要求7所述的抗体分子,其中,所述免疫细胞是T细胞、B细胞、自然杀伤细胞、自然杀伤T细胞或树突细胞。

9.如权利要求6所述的抗体分子,其中所述抗体分子具有CH2结构域,所述CH2结构域包含:

(i)第1.3位的丙氨酸残基;和

(ii)第1.2位的丙氨酸残基;

其中根据IMGT编号方案进行氨基酸残基编号。

10.如权利要求6所述的抗体分子,其中所述抗体分子不结合一种或多种Fcγ受体。

11.一种偶联物,其包含根据权利要求1至10中任一项所述的抗体分子和生物活性分子,所述生物活性分子为细胞因子、细胞因子的配体陷阱、配体、药物或治疗性放射性同位素。

12.一种或多种编码权利要求1至10中任一项所述的抗体分子的核酸分子。

13.一种或多种载体,其包含权利要求12所述的核酸分子。

14.一种重组宿主细胞,其包含权利要求12所述的核酸分子或权利要求13所述的一种或多种载体。

15.一种产生权利要求1至10中任一项所述的抗体分子的方法,其包括在产生所述抗体分子的条件下培养权利要求14所述的重组宿主细胞。

16.一种药物组合物,包含权利要求1至10中任一项所述的抗体分子或权利要求11所述的偶联物和药学上可接受的赋形剂。

17.如权利要求1至10中任一项所述的抗体分子或权利要求11所述的偶联物在制备用于治疗癌症的药物中的用途,所述癌症为结肠癌。

抗间皮素抗体

发明领域

[0001] 本发明涉及结合间皮素(MSLN)的抗体分子。抗体分子可用于治疗和诊断疾病和病症,例如癌症。

[0002] 发明背景

[0003] MSLN在健康个体的胸膜、腹膜和心包膜内膜的间皮细胞上表达相对较低(Hassan等人,2005),但在几种不同的癌症,包括间皮瘤、鳞状细胞癌、胰腺癌、肺癌、胃癌、乳腺癌、子宫内膜癌和卵巢癌中高表达。间皮素的正常生物学功能尚不清楚。在癌症的背景下,MSLN的高表达水平与卵巢癌、胆管癌、肺腺癌和三阴性乳腺癌的预后不良有关。MSLN在正常细胞上的有限表达与在肿瘤细胞上的高表达使其成为使用单克隆抗体的有吸引力的治疗靶标(Hassan等人,2016)。

[0004] MSLN表达为69kDa的前体蛋白(628个氨基酸)。然后,前体蛋白被内切蛋白酶弗林蛋白酶切割以释放分泌的N端区域,称为巨核细胞促进因子(MPF),而40-kDa蛋白成熟的MSLN仍通过糖基磷脂酰肌醇(GPI)接头附着在细胞膜上。人MSLN与MSLN的鼠类和猕猴直系同源物分别具有60%和87%的氨基酸同一性。

[0005] 作为选择性剪接的结果,通过形成缺乏膜锚序列的变体或肿瘤坏死因子α转化酶(TACE)的蛋白酶切割,膜结合的成熟MSLN从细胞上脱落(Sapede等人,2008年,Zhang等人,2011年)。在患者的血清和包括恶性间皮瘤,卵巢癌或高度转移性癌在内的肿瘤基质中均发现可溶性脱落的MSLN。美国食品和药物管理局已批准测量间皮瘤患者血液和积液中的可溶性MSLN水平,以监测患者对治疗和进展的反应(Hollevoet等人,2012;Creany等人,2015)。

[0006] 已开发出几种靶向MSLN的基于抗体的疗法,并已在临床试验中进行了测试,主要用于间皮瘤、胰腺癌和非小细胞肺癌(Hassan等人,2016)。所采用的策略包括通过使用具有抗体依赖性细胞毒性(ADCC)活性的抗MSLN抗体(例如阿莫昔单抗(amatuximab)),以及使用包含与毒素偶联的抗体或抗体片段的抗体药物偶联物(ADC)(例如SS1P-PE38和雷星-阿奈妥单抗(anetumab-ravtansine)),直接杀死肿瘤细胞。另外,抗MSLN结合性Fv片段已用于嵌合抗原受体T细胞疗法中,并且双特异性抗体如ABBV-428正在从临床前研究到临床试验中出现。

[0007] 阿莫昔单抗(Amatuximab)是一种小鼠嵌合IgG1κ单克隆抗体,可阻断MSLN-MUC16相互作用,并依靠ADCC功能消除肿瘤细胞。I期临床试验显示出良好的安全性,但与化疗(吉西他滨或培美曲塞/顺铂)联合使用时,临床疗效有限,恶性间皮瘤的无进展生存率极少/无改善(NCT00738582,Hassan等人,2014年),且与胰腺癌比较者相比,没有总体反应(NCT00570713)。SS1-PE-38是一种重组免疫毒素,包含存在于阿莫昔单抗中的抗MSLN scFv,与蛋白合成抑制剂PE38连接。尽管在I期试验中观察到了很高的抗肿瘤活性(联合化疗时部分反应为77%,NCT01445392),但SS1P的临床应用受到免疫原性和剂量限制性血管渗漏综合征的限制。LMB-100是SS1P-PE38的优化版本,具有较低的体外免疫原性,目前在I和I I期试验中单独,以及与化学疗法联用进行测试(NCT02798536,NCT02810418)。

[0008] 抗MSLN靶向最常用于将细胞毒性药物递送至肿瘤细胞。雷星-阿奈妥单抗

(Anetumab-ravtansine)是与抗有丝分裂剂DM4共价连接的全人源IgG1,在卵巢癌、原发性腹膜癌、输卵管癌和晚期上皮样腹膜间皮瘤的I期试验中显示31％的总反应率(ORR)(NCT01439152)。在间皮瘤中,雷星-阿奈妥单抗与标准化疗剂量组合显示有50％ORR(NCT02639091)。像另一种ADC抗体药物RG7600一样,雷星-阿奈妥单抗是也显示出可耐受的安全性,但在这些研究中已观察到的剂量限制毒性,与针对各个ADC部分的报道一致。迄今为止,尚无法获得来自BMS86148的I期数据。

[0009] 总之,靶向MSLN的未偶联抗体已经显示出良好的安全性,但其治疗功效受到限制,而ADC已经显示出更强的抗肿瘤活性,但与剂量限制性毒性相关。在安全性方面,ADC可能比免疫毒素疗法具有更大的治疗窗口(Zhao等人,2016)。对于许多这些基于抗体的MSLN疗法,正在进行将该疗法与化学疗法或免疫检查点抑制剂(例如PD-1或PD-L1)相结合的II期临床试验。几种旨在与免疫系统结合的双特异性分子也正在开发中,包括靶向MSLN以及共刺激蛋白CD40的ABBV-428,MSLN-CD3双特异性T细胞衔接蛋白(BITE)和MSLN-CD47双特异性分子。

[0010] 发明说明

[0011] 如上所述,已知成熟的MSLN与其他肿瘤相关抗原(TAA)一样,是通过酶切从细胞表面脱落的。然后从肿瘤部位清除MSLN的脱落/可溶部分。这代表了靶向MSLN的治疗剂的挑战,因为脱落/可溶部分可以充当治疗剂的漏槽(sink),在其与肿瘤结合之前将治疗剂从肿瘤部位清除。

[0012] 本发明人进行了广泛的选择程序,以分离抗体分子,其与固定的MSLN的结合比溶液中的MSLN具有更高的亲和力。

[0013] 本文所用的“亲和力(Affinity)”可以指通过K_D测量的抗体分子与其同源抗原之间的结合相互作用的强度。对于本领域技术人员而言显而易见的是,其中抗体分子能够与抗原形成多重结合相互作用(例如,其中抗体分子能够与抗原二价结合并且任选地抗原是二聚体),通过K_D测量的亲和力也可能受到亲合力(avidity)的影响,其中亲合力是指抗体-抗原复合物的整体强度。

[0014] 具体地,人们认为本发明的抗体分子以高亲合力结合MSLN,并因此在抗体能够结合两个MSLN分子的情况下更牢固地结合MSLN,如抗原的多个拷贝固定在表面上一样,与MSLN呈单体形式的情况相比,MSLN在溶液中的情况也有望如此。不希望受到理论的束缚,据认为由于抗体对单体MSLN的亲和力低,因此本发明的抗体分子将不会在体内的溶液中保持与脱落MSLN的结合,因此不会很快从肿瘤部位清除,因此通过在肿瘤细胞表面结合MSLN,将有更长的时间发挥治疗作用。先前已经报道了膜结合的MSLN的优选靶向,尽管所讨论的分子是使用与本发明人所采用的不同的方法分离的。具体而言,已经报道了通过分离靶向MSLN不同区域的分子来优先靶向结合膜的MSLN(Asgarov等人,2017;Tang等人,2013)。例如,已经报道了与人Fc融合的单结构域(仅VH结构域)抗体SD1-Fc,其靶向靠近细胞膜的表位以促进CDC活性(Tang等人,2013)。然而,尚不清楚这些表位在不同的癌症环境中如何暴露。此外,据报道,MSLN-CD3双特异性T细胞衔接蛋白(BITE)优先结合细胞结合的MSLN。但是,这些分子都不是完整的IgG分子,也不能够与MSLN二价结合,因为两者都与靶标单价结合(通过SD1-Fc中的VH结构域或BITE的scFv)。

[0015] 由本发明人分离的抗体分子结合MSLN上的不同表位/区域。从某些抗体分子能够

阻断配体MUC16与MSLN的结合而其他抗体不能阻断的事实中可以明显看出这一点。认为将MUC16阻断至MSLN对于抑制表达MUC16的癌细胞向胸膜和腹膜中表达MSLN的表面的转移是有利的(Chen等人,2013)。其他更靠近细胞膜的结合区域可能促进ADCC和CDC活性。

[0016] 已经显示本发明的抗MSLN抗体分子具有ADCC活性,因此有望在癌症治疗中找到应用。具体而言,已显示抗体分子能够靶向在其细胞表面上包含MSLN的肿瘤细胞并通过ADCC介导肿瘤细胞的杀伤。

[0017] 本发明的抗体分子还可用于制备包含本发明的抗体分子和生物活性分子(例如毒素)ADC。通过将生物活性分子靶向递送至肿瘤细胞,此类分子也有望用于治疗在其细胞表面上包含MSLN的癌症。

[0018] 本发明人已经认识到,本发明的抗MSLN抗体可以用于制备多特异性抗体,例如双特异性分子,除MSLN外还结合第二抗原。优选地,多特异性分子双价结合第二抗原。具体地,本发明人已经制备了抗MSLN抗体分子,其在抗体分子的每个CH3结构域中包含能够二价结合第二抗原的额外的抗原结合位点。

[0019] 抗体分子结合的第二抗原可以是免疫细胞抗原,例如肿瘤坏死因子受体超家族(TNFRSF)的成员。肿瘤坏死因子(TNF)受体需要聚集才能激活。具体而言,TNF受体配体与其受体的初始连接会引发一系列事件,导致TNF受体三聚化,然后受体聚集,激活NFkB细胞内信号传导途径和随后的免疫细胞激活。为了治疗剂有效地激活TNFR受体,因此需要以模仿三聚体配体的方式将几种TNF受体单体桥接在一起。许多抗TNF受体激动剂抗体要么需要通过Fcγ受体进行交联才能发挥其激动活性,要么在没有交联的情况下表现出激动活性。在这两种情况下,抗体的激动活性均不限于特定位点,因为在整个人体中都发现了Fcγ受体。

[0020] 预期包含针对免疫细胞抗原的恒定结构域结合位点的双特异性抗MSLN抗体分子能够在存在MSLN的情况下有条件地激活免疫细胞抗原,而无需例如常规抗体分子所需的Fcγ受体介导的交联。认为抗体分子与MSLN的结合将引起抗体分子在MSLN位点的交联,这继而将导致免疫细胞表面上的免疫细胞抗原聚集和激活。因此,预期抗体分子的激动活性取决于存在的免疫细胞抗原和MSLN。换句话说,预期激动活性是有条件的。另外,认为在MSLN存在下抗体的交联有助于通过抗体分子的恒定域抗原结合位点结合的免疫细胞抗原的聚集。由于MSLN是肿瘤抗原,因此预期抗体分子能够以疾病依赖的方式,例如在肿瘤微环境中激活免疫细胞。预期免疫细胞的这种靶向激活将有助于避免脱靶副作用。本发明人已经表明,在小鼠肿瘤模型中,在不存在Fcγ受体结合的情况下,包含抗MSLN和抗CD137结合位点的双特异性抗体分子能够抑制肿瘤生长并增加存活。

[0021] 包含对第二抗原具有特异性的抗MSLN Fab和CH3结构域结合位点的抗体分子二价结合MSLN和第二抗原。在第二抗原是免疫细胞抗原的情况下,两个靶标的二价结合有望使表达免疫细胞抗原的免疫细胞和MSLN之间的桥接更稳定,从而延长免疫细胞位于特定部位,例如肿瘤微环境的时间,并且可以对疾病,例如肿瘤起作用。这与绝大多数常规的双特异性抗体形式不同,后者是异二聚体并通过一个Fab臂单价结合每个靶抗原。预期这种单价相互作用不仅不稳定,而且在许多情况下首先不足以诱导免疫细胞抗原例如TNF受体的聚集。

[0022] 包含对第二抗原具有特异性的CH3结构域结合位点的本发明的抗MSLN抗体分子的另一个特征是,MSLN和第二抗原的两个抗原结合位点均包含在抗体结构本身内。具体地,抗

体分子不需要经由接头或其他手段将其他蛋白质与抗体分子融合以产生与两个靶标均二价结合的分子。这具有许多优点。具体地,可以使用与用于产生标准抗体的方法相似的方法来产生抗体分子,因为它们不包含任何额外的融合部分。由于接头可能随时间降解,导致抗体分子的异质群体,因此该结构也有望提高抗体的稳定性。仅具有一种融合蛋白的群体中的那些抗体可能无法像具有两种融合蛋白的抗体一样有效地诱导免疫细胞抗原(例如TNF受体)的条件性激动。连接物的裂解/降解可以在向患者施用治疗剂之前或之后进行(例如,通过酶切或患者体内pH),从而导致其在患者体内循环时的有效性降低。由于抗体分子中没有接头,因此预期抗体分子在给药之前和之后均保留相同数目的结合位点。此外,从分子的免疫原性的观点来看,抗体分子的结构也是优选的,因为当将分子施用于患者时,融合蛋白或接头或两者的引入可诱导免疫原性,导致治疗效果降低。

[0023] 因此,本发明提供:[1]与间皮素(MSLN)结合的抗体分子,其中所述抗体分子的抗原结合位点包含抗体的互补决定区(CDR)1-6:

[0024] (i)分别如SEQ ID NO:98、73、99、20、21和44所示的FS28-256-271;

[0025] (ii)分别如SEQ ID NO:10、11、41、20、21和22所示的FS28-024-052;

[0026] (iii)分别如SEQ ID NO:98、73、99、20、21和34所示的FS28-256-021;

[0027] (iv)分别如SEQ ID NO:98、73、99、20、21和25所示的FS28-256-012;

[0028] (v)分别如SEQ ID NO:101、73、103、20、21和34所示的FS28-256-023;

[0029] (vi)分别如SEQ ID NO:98、73、99、20、21和43所示的FS28-256-024;

[0030] (vii)分别如SEQ ID NO:101、73、103、20、21和43所示的FS28-256-026;

[0031] (viii)分别如SEQ ID NO:98、73、99、20、21和44所示的FS28-256-027;

[0032] (ix)分别如SEQ ID NO:85、73、75、20、21和34所示的FS28-256-001;

[0033] (x)分别如SEQ ID NO:85、73、75、20、21和43所示的FS28-256-005;

[0034] (xi)分别如SEQ ID NO:111、73、113、20、21和25所示的FS28-256-014;

[0035] (xii)分别如SEQ ID NO:101、73、103、20、21和25所示的FS28-256-018;

[0036] (xiii)分别如SEQ ID NO:71、73、75、20、21和25所示的FS28-256;

[0037] (xiv)分别如SEQ ID NO:10、11、32、20、21和22所示的FS28-024-051;

[0038] (xv)分别如SEQ ID NO:10、11、51、20、21和22所示的FS28-024-053;或者

[0039] (xvi)分别如SEQ ID NO:10、11、12、20、21和22所示的FS28-024;和

[0040] 其中CDR序列是根据ImMunoGeneTics(IMGT)编号方案定义的。

[0041] [2]与MSLN结合的抗体分子,其中该分子的抗原结合位点包含抗体的CDR1-6:

[0042] (i)分别如SEQ ID NO:97、182、100、23、24和44所示的FS28-256-271;

[0043] (ii)分别如SEQ ID NO:13、14、42、23、24和22所示的FS28-024-052;

[0044] (iii)分别如SEQ ID NO:97、74、100、23、24和34所示的FS28-256-021;

[0045] (iv)分别如SEQ ID NO:97、74、100、23、24和25所示的FS28-256-012;

[0046] (v)分别如SEQ ID NO:102、74、104、23、24和34所示的FS28-256-023;

[0047] (vi)分别如SEQ ID NO:97、74、100、23、24和43所示的FS28-256-024;

[0048] (vii)分别如SEQ ID NO:102、74、104、23、24和43所示的FS28-256-026;

[0049] (viii)分别如SEQ ID NO:97、74、100、23、24和44所示的FS28-256-027;

[0050] (ix)分别如SEQ ID NO:86、74、76、23、24和34所示的FS28-256-001;

[0051] (x)分别如SEQ ID NO:86、74、76、23、24和43所示的FS28-256-005;

[0052] (xi)分别如SEQ ID NO:112、74、114、23、24和25所示的FS28-256-014;

[0053] (xii)分别如SEQ ID NO:102、74、104、23、24和25所示的FS28-256-018;

[0054] (xiii)分别如SEQ ID NO:72、74、76、23、24和25所示的FS28-256;

[0055] (xiv)分别如SEQ ID NO:13、14、33、23、24和22所示的FS28-024-051;

[0056] (xiv)分别如SEQ ID NO:13、14、52、23、24和22所示的FS28-024-053;或者

[0057] (xvi)分别如SEQ ID NO:13、14、15、23、24和22所示的FS28-024;和

[0058] 其中CDR序列是根据Kabat编号方案定义的。

[0059] [3]如[1]或[2]所述的抗体分子,其中所述抗体分子包含重链可变(VH)结构域和/或轻链可变(VL)结构域,优选VH结构域和VL结构域。

[0060] [4]如[1]至[3]中任一项所述的抗体分子,其中所述抗体分子包含免疫球蛋白重链和/或免疫球蛋白轻链,优选免疫球蛋白重链和免疫球蛋白轻链。

[0061] [5]如[3]至[4]中任一项所述的抗体分子,其中所述抗体分子包含抗体的VH结构域和/或VL结构域,优选抗体的VH结构域和VL结构域:

[0062] (i)分别如SEQ ID NO:180和56所示的FS28-256-271;

[0063] (ii)分别如SEQ ID NO:39和18所示的FS28-024-052;

[0064] (iii)分别如SEQ ID NO:109和93所示的FS28-256-021;

[0065] (iv)分别如SEQ ID NO:109和79所示的FS28-256-012;

[0066] (v)分别如SEQ ID NO:121和93所示的FS28-256-023;

[0067] (vi)分别如SEQ ID NO:109和53所示的FS28-256-024;

[0068] (vii)分别如SEQ ID NO:121和53所示的FS28-256-026;

[0069] (viii)分别如SEQ ID NO:109和56所示的FS28-256-027;

[0070] (ix)分别如SEQ ID NO:63和93所示的FS28-256-001;

[0071] (x)分别如SEQ ID NO:63和53所示的FS28-256-005;

[0072] (xi)分别如SEQ ID NO:115和79所示的FS28-256-014;

[0073] (xii)分别如SEQ ID NO:121和79所示的FS28-256-018;

[0074] (xiii)分别如SEQ ID NO:69和79所示的FS28-256;

[0075] (xiv)分别如SEQ ID NO:30和18所示的FS28-024-051;

[0076] (xv)分别如SEQ ID NO:49和18所示的FS28-024-053;或者

[0077] (xvi)分别如SEQ ID NO:8和18所示的FS28-024。

[0078] [6]如[1]至[5]中任一项所述的抗体分子,其中所述抗体分子包含抗体的重链[无LALA]和轻链:

[0079] (i)分别如SEQ ID NO:176和95所示的FS28-256-271;

[0080] (ii)分别如SEQ ID NO:35和16所示的FS28-024-052;

[0081] (iii)分别如SEQ ID NO:105和83所示的FS28-256-021;

[0082] (iv)分别如SEQ ID NO:105和77所示的FS28-256-012;

[0083] (v)分别如SEQ ID NO:123和83所示的FS28-256-023;

[0084] (vi)分别如SEQ ID NO:105和90所示的FS28-256-024;

[0085] (vii)分别如SEQ ID NO:123和90所示的FS28-256-026;

[0086] (viii)分别如SEQ ID NO:105和95所示的FS28-256-027;

[0087] (ix)分别如SEQ ID NO:81和83所示的FS28-256-001;

[0088] (x)分别如SEQ ID NO:87和90所示的FS28-256-005;

[0089] (xi)分别如SEQ ID NO:117和77所示的FS28-256-014;

[0090] (xii)分别如SEQ ID NO:123和77所示的FS28-256-018;

[0091] (xiii)分别如SEQ ID NO:65和77所示的FS28-256;

[0092] (xiv)分别如SEQ ID NO:26和16所示的FS28-024-051;

[0093] (xv)分别如SEQ ID NO:45和16所示的FS28-024-053;或者

[0094] (xvi)分别如SEQ ID NO:4和16所示的FS28-024。

[0095] [7]如[1]至[5]中任一项所述的抗体分子,其中所述抗体分子包含抗体的重链[具有LALA]和轻链:

[0096] (i)分别如SEQ ID NO:178和95所示的FS28-256-271;

[0097] (ii)分别如SEQ ID NO:37和16所示的FS28-024-052;

[0098] (iii)分别如SEQ ID NO:107和83所示的FS28-256-021;

[0099] (iv)分别如SEQ ID NO:107和77所示的FS28-256-012;

[0100] (v)分别如SEQ ID NO:125和83所示的FS28-256-023;

[0101] (vi)分别如SEQ ID NO:107和90所示的FS28-256-024;

[0102] (vii)分别如SEQ ID NO:125和90所示的FS28-256-026;

[0103] (viii)分别如SEQ ID NO:107和95所示的FS28-256-027;

[0104] (ix)分别如SEQ ID NO:89和83所示的FS28-256-001;

[0105] (x)分别如SEQ ID NO:89和90所示的FS28-256-005;

[0106] (xi)分别如SEQ ID NO:119和77所示的FS28-256-014;

[0107] (xii)分别如SEQ ID NO:125和77所示的FS28-256-018;

[0108] (xiii)分别如SEQ ID NO:67和77所示的FS28-256;

[0109] (xiv)分别如SEQ ID NO:28和16中所示的FS28-024-051;

[0110] (xv)分别如SEQ ID NO:47和16所示的FS28-024-053;或者

[0111] (xvi)分别如SEQ ID NO 5和16所示的FS28-024。

[0112] [8]如[1]至[7]中任一项所述的抗体分子,其中所述抗体分子包含抗体FS28-256-271的CDR 1-6、VH结构域、VL结构域、轻链和/或重链。

[0113] [9]如[1]至[7]中任一项所述的抗体分子,其中所述抗体分子包含抗体FS28-024-052的CDR 1-6、VH结构域、VL结构域、轻链和/或重链。

[0114] [10]如[1]至[9]中任一项所述的抗体分子,其中所述MSLN是细胞表面结合的MSLN。

[0115] [11]如[10]所述的抗体分子,其中所述抗体分子以比溶液中的MSLN更高的亲和力与固定的MSLN结合。

[0116] [12]如[11]所述的抗体分子,其中所述抗体分子以8nM的亲和力(kD)或更高的亲和力结合至固定的MSLN。

[0117] [13]如[11]或[12]所述的抗体分子,其中所述抗体分子以15nM的亲和力(kD)或更低的亲和力与溶液中的MSLN结合。

[0118] [14]如[1]至[13]中任一项所述的抗体分子,其中所述MSLN是人MSLN。

[0119] [15]如[14]所述的抗体分子,其中所述MSLN由SEQ ID NO:169所示的序列组成或包含SEQ ID NO:169所示的序列。

[0120] [16]如[1]至[13]中任一项所述的抗体分子,其中所述MSLN是猕猴MSLN。

[0121] [17]如[16]所述的抗体分子,其中所述MSLN由SEQ ID NO:170所示的序列组成或包含SEQ ID NO:170所示的序列。

[0122] [18]如[1]至[17]中任一项所述的抗体分子,其中所述抗体分子包含抗体FS28-024-051、FS28-024-052、FS28-024-053或FS28-024的CDR 1-6、VH结构域、VL结构域、轻链和/或重链,其中所述抗体阻断MUC16与MSLN的结合。

[0123] [19]如[1]至[17]中任一项所述的抗体分子,其中所述抗体分子包含抗体FS28-256-271、FS28-256-021、FS28-256-012、FS28-256-023、FS28-256-024、FS28-256-026或FS28-256-027、FS28-256-001、FS28-256-005、FS28-256-014、FS28-256-018或FS28-256的CDR 1-6、VH结构域、VL结构域、轻链和/或重链,其中抗体不阻断MUC16与MSLN的结合。

[0124] [20]如[18]或[19]所述的抗体分子,其中所述MUC16是人MUC16。

[0125] [21]如[1]至[20]中任一项所述的抗体分子,其中所述抗体分子是多特异性抗体分子,并且包含与第二抗原结合的第二抗原结合位点。

[0126] [22]如[21]所述的抗体分子,其中所述抗体分子是双特异性、三特异性或四特异性抗体分子。

[0127] [23]如[22]所述的抗体分子,其中所述抗体分子是双特异性分子。

[0128] [24]如[21]至[23]中任一项所述的抗体分子,其中所述第二抗原结合位点位于所述抗体分子的恒定结构域中。

[0129] [25]如[21]至[24]中任一项所述的抗体分子,其中所述第二抗原是免疫细胞抗原。

[0130] [26]如[25]所述的抗体分子,其中所述免疫细胞抗原是肿瘤坏死因子受体超家族(TNFRSF)的成员。

[0131] [27]如[26]所述的抗体分子,其中所述TNFRSF的成员是OX40或CD137。

[0132] [28]如[21]至[27]中任一项所述的抗体分子,其中所述第二抗原结合位点包含第一序列、第二序列和/或第三序列,其中所述第一序列、第二序列和第三序列分别位于恒定结构域的AB结构环、CD结构环和EF结构环中。

[0133] [29]如[24]至[28]中任一项所述的抗体分子,其中所述恒定结构域是CH3结构域。

[0134] [30]如[26]至[29]中任一项所述的抗体分子,其中所述抗体分子在存在肿瘤细胞表面结合的MSLN的情况下能够激活免疫细胞上的TNFRSF成员。

[0135] [31]如[26]至[30]中任一项所述的抗体分子,其中所述抗体分子与TNFRSF成员和与肿瘤细胞表面结合的MSLN的结合引起免疫细胞表面上TNFRSF成员的聚集。

[0136] [32]如[30]或[31]所述的抗体分子,其中所述免疫细胞是T细胞、B细胞、自然杀伤(NK)细胞、自然杀伤T(NKT)细胞或树突状细胞(DC)。

[0137] [33]如[32]所述的抗体分子,其中所述免疫细胞是T细胞。

[0138] [34]如[1]至[33]中任一项所述的抗体分子,其中所述抗体分子具有或能够引发抗体依赖性细胞毒性(ADCC)。

[0139] [35]如[1]至[33]中任一项所述的抗体分子,其中所述抗体分子已被修饰以减少或消除抗体分子的CH2结构域与一种或多种Fcγ受体的结合。

[0140] [36]如[1]至[33]或[35]中任一项所述的抗体分子,其中所述抗体分子不结合Fcγ受体。

[0141] [37]如[35]或[36]所述的抗体分子,其中所述Fcγ受体选自下组:FcγRI、FcγRIIa、FcγRIIb和FcγRI II。

[0142] [38]一种偶联物,其包含[1]至[37]中任一项所述的抗体分子和生物活性分子。

[0143] [39]一种偶联物,其包含[1]至[37]中任一项所述的抗体分子和可检测标记。

[0144] [40]一种编码[1]至[37]中任一项所述的抗体分子的一种或多种核酸分子。

[0145] [41]如[40]所述的一种或多种核酸分子,其中所述一种或多种核酸分子包含抗体的VH结构域和/或VL结构域核酸序列:

[0146] (i)分别如SEQ ID NO:181和57所示的FS28-256-271;

[0147] (ii)分别如SEQ ID NO:40和19所示的FS28-024-052;

[0148] (iii)分别如SEQ ID NO:110和94所示的FS28-256-021;

[0149] (iv)分别如SEQ ID NO:110和80所示的FS28-256-012;

[0150] (v)分别如SEQ ID NO:122和94所示的FS28-256-023;

[0151] (vi)分别如SEQ ID NO:110和54所示的FS28-256-024;

[0152] (vii)分别如SEQ ID NO:122和54所示的FS28-256-026;

[0153] (viii)分别如SEQ ID NO:110和57所示的FS28-256-027;

[0154] (ix)分别如SEQ ID NO:64和94所示的FS28-256-001;

[0155] (x)分别如SEQ ID NO:64和54所示的FS28-256-005;

[0156] (xi)分别如SEQ ID NO:116和80所示的FS28-256-014;

[0157] (xii)分别如SEQ ID NO:122和80所示的FS28-256-018;

[0158] (xiiii)分别如SEQ ID NO 70和80所示的FS28-256;

[0159] (xiv)分别如SEQ ID NO:31和19所示的FS28-024-051;

[0160] (xv)分别如SEQ ID NO:50和19所示的FS28-024-053;或者

[0161] (xvi)分别如SEQ ID NO:9和19所示的FS28-024。

[0162] [42]如[40]或[41]所述的一种或多种核酸分子,其中所述一种或多种核酸分子包含:

[0163] (i)如SEQ ID NO:179或177所示的抗体FS28-256-271的重链核酸序列,和/或如SEQ ID NO:96所示的抗体FS28-256-271的轻链核酸序列;

[0164] (ii)如SEQ ID NO:38或36所示的抗体FS28-024-052的重链核酸序列和/或如SEQ ID NO:17所示的抗体FS28-024-052的轻链核酸序列;

[0165] (iii)如SEQ ID NO:108或106所示的抗体FS28-256-021的重链核酸序列,和/或如SEQ ID NO:92所示的抗体FS28-256-021的轻链核酸序列;

[0166] (iv)如SEQ ID NO:108或106所示的抗体FS28-256-012的重链核酸序列和/或如SEQ ID NO:78所示的抗体FS28-256-012的轻链核酸序列;

[0167] (v)如SEQ ID NO:126或124所示的抗体FS28-256-023的重链核酸序列,和/或如SEQ ID NO:92所示的抗体FS28-256-023的轻链核酸序列;

[0168] (vi)如SEQ ID NO:108或106所示的抗体FS28-256-024的重链核酸序列,和/或如SEQ ID NO:91所示的抗体FS28-256-024的轻链核酸序列;

[0169] (vii)如SEQ ID NO:126或124所示的抗体FS28-256-026的重链核酸序列和/或如SEQ ID NO:91所示的抗体FS28-256-026的轻链核酸序列;

[0170] (viii)如SEQ ID NO:108或106所示的抗体FS28-256-027的重链核酸序列和/或如SEQ ID NO:96所示的抗体FS28-256-027的轻链核酸序列;

[0171] (ix)如SEQ ID NO:84或82所示的抗体FS28-256-001的重链核酸序列,和/或如SEQ ID NO:92所示的抗体FS28-256-001的轻链核酸序列;

[0172] (x)如SEQ ID NO:84或88所示的抗体FS28-256-005的重链核酸序列,和/或如SEQ ID NO:91所示的抗体FS28-256-005的轻链核酸序列;

[0173] (xi)如SEQ ID NO:120或118所示的抗体FS28-256-014的重链核酸序列,和/或如SEQ ID NO:78所示的抗体FS28-256-014的轻链核酸序列;

[0174] (xii)如SEQ ID NO:126或124所示的抗体FS28-256-018的重链核酸序列,和/或如SEQ ID NO:78所示的抗体FS28-256-018的轻链核酸序列;

[0175] (xiii)如SEQ ID NO:68或66所示的抗体FS28-256的重链核酸序列,和/或如SEQ ID NO:78所示的抗体FS28-256的轻链核酸序列;

[0176] (xiv)如SEQ ID NO:29或27所示的抗体FS28-024-051的重链核酸序列和/或如SEQ ID NO:17所示的抗体FS28-024-051的轻链核酸序列;

[0177] (xv)如SEQ ID NO:48或46所示的抗体FS28-024-053的重链核酸序列,和/或如SEQ ID NO:17所示的抗体FS28-024-053的轻链核酸序列;或者

[0178] (xvi)如SEQ ID NO:7或6所示的抗体FS28-024的重链核酸序列,和/或SEQ ID NO:17所示的抗体FS28-024的轻链核酸序列。

[0179] [43]一种或多种载体,其包含[40]至[42]中任一项所述的一种或多种核酸分子。

[0180] [44]一种重组宿主细胞,其包含根据[40]至[42]中任一项所述的一种或多种核酸分子或[43]所述的一种或多种载体。

[0181] [45]一种如[1]至[37]中任一项所述的抗体分子的生产方法,包括在用于生产抗体分子的条件下培养[44]的重组宿主细胞。

[0182] [46]如[45]所述的方法,其进一步包括分离和/或纯化所述抗体分子。

[0183] [47]一种药物组合物,其包含[1]至[39]中任一项所述的抗体分子或偶联物和药学上可接受的赋形剂。

[0184] [48]如[1]至[39]中任一项所述的抗体分子或偶联物在治疗个体中的癌症的方法中的用途。

[0185] [49]一种在个体中治疗癌症的方法,其包括向所述个体施用治疗有效量的如[1]至[39]中任一项所述的抗体分子或偶联物。

[0186] [50]如[1]至[39]中任一项所述的抗体分子或偶联物在制备用于治疗癌症的药物中的用途。

[0187] [51]如[48]至[50]中任一项所述的抗体分子或偶联物的用途、所述方法或所述用途,其中所述癌症细胞在其细胞表面上表达MSLN。

[0188] [52]如[48]至[50]中任一项所述的抗体分子或偶联物的用途、所述方法或所述用

途,其中所述癌症选自下组:间皮瘤,胰腺癌,卵巢癌和肺癌。

[0189] [53]如[48]所述的抗体分子或偶联物的用途,其中所述治疗方法包括与第二治疗剂组合向个体施用抗体分子或偶联物。

[0190] [54]如[49]所述的方法,其中所述方法进一步包括向所述个体施用治疗有效量的第二治疗剂。

[0191] [55]如[1]至[37]或[39]中任一项所述的抗体分子或偶联物在检测,诊断,预后或监测个体癌症预后的方法中的用途。

[0192] [56]一种检测,诊断,预后或监测个体中癌症的预后的方法,该方法包括使用如[1]至[37]或[39]中任一项所述的抗体分子或偶联物。

[0193] [57]如[1]至[37]或[39]中任一项所述的抗体分子或偶联物在制备用于检测,诊断,预后或监测个体癌症预后的诊断产品中的用途。

[0194] [58]一种在检测,诊断,预后或监测个体癌症预后的方法中所用的试剂盒,该试剂盒包含根据[1]至[37]或[39]中任一项所述的抗体分子或偶联物。

[0195] [59]如[55]至[58]中任一项所述的抗体分子或偶联物的用途、所述方法、所述用途或所述试剂盒,其中所述癌症选自下组:间皮瘤,胰腺癌,卵巢癌和肺癌。

[0196] 附图简要说明

[0197] 图1显示了抗MSLN mAb与NCI-H226细胞的结合。抗人MSLN单克隆抗体FS28-024,FS28-026,FS28-091,FS28-185和FS28-256(均为IgG1LALA形式)显示出与NCI-H226细胞的剂量依赖性结合。FS28-024,FS28-026和FS28-091以低纳摩尔EC_{50}值显示出与细胞表面MSLN的高亲和力结合,类似于阳性对照抗MSLN mAb SS1。与FS28-024,FS28-026和FS28-091相比,单抗FS28-185和FS28-256与细胞表面MSLN的结合较弱,EC_{50}值超过30nM,E_{max}值较低。

[0198] 图2显示了抗MSLNmAb 2的ADCC活性。抗人MSLN mAb 2FS28-024-052和FS28-256-271以及阳性对照抗体SS1以hIgG1LALA形式(无效应子功能)和具有效应子功能的主链hIgG1进行了测试。FS28-024-052具有测试抗体中最高的ADCC活性,而FS28-256-271具有与对照抗体相当的ADCC活性。在所有情况下,如预期的那样,将LALA突变引入IgG1骨架完全消除了任何ADCC活性。

[0199] 图3显示了在用(A)G1-AA/HelD1.3(人IgG1对照),(B)FS22m-063-AA/HelD1.3(mAb^2形式的抗小鼠CD137Fcab);(C)FS22m-063-AA/HelD1.3和G1-AA/FS28m-228-010(抗小鼠CD137Fcab加上抗小鼠MSLN Fab)的组合,(D)FS22m-063-AA/FS28m-228-010(抗小鼠CD137/MSLNmAb^2) (E)FS22m-063-AA/4420(mAb^2形式的抗小鼠CD137Fcab)和(F)G1-AA/FS28m-228-010(抗小鼠MSLN Fab)处理的CT26.G10同系肿瘤模型中的个体肿瘤体积测量结果,与同种型对照以及其他处理组相比,FS22m-063-AA/FS28m-228-010显示出肿瘤生长减少。

[0200] 图4显示了用G1-AA/HelD1.3(IgG对照),FS22m-063-AA/HelD1.3(mAb^2形式的抗小鼠CD137Fcab),FS22m-063-AA/4420(mAb^2形式的抗小鼠CD137Fcab),G1-AA/FS28m-228-010(抗小鼠MSLN Fab),FS22m-063-AA/HelD1.3和G1-AA/FS28m-228-010(抗小鼠CD137Fcab加抗小鼠MSLN Fab)和FS22m-063-AA/FS28m-228-010(抗小鼠CD137/MSLN mAb^2)处理的CT26.G10同系肿瘤模型的Kaplan Meier生存曲线。结果表明,与用同种型对照处理的小鼠或其他处理组相比,FS22m-063-AA/FS28m-228-010处理可显著提高存活率。

[0201] 详述

[0202] 本发明涉及结合MSLN的抗体分子。抗体分子优选结合人MSLN,更优选结合人和猕猴MSLN。本发明的抗体分子优选能够结合在细胞表面上表达的MSLN。该细胞优选是肿瘤细胞。

[0203] 抗体分子优选与MSLN特异性结合。术语“特异性”可以指这样的情况,其中抗体分子将不显示与除其特异性结合伴侣(在本文为MSLN)以外的分子的任何显著结合。术语“特异性”也适用于抗体分子对由许多抗原携带的特定表位(例如MSLN上的表位)具有特异性的情况,在这种情况下,抗体分子将能够与携带表位的各种抗原结合。抗体分子优选不与参与细胞粘附的其他分子,例如CEACAM-5,E-钙粘蛋白,血栓调节蛋白和/或EpCAM结合或不显示任何显著结合。

[0204] 如上文背景部分所述,成熟的MSLN从肿瘤细胞中脱落,并从肿瘤部位清除。该脱落的MSLN可以充当抗MSLN结合分子的漏槽(sink),该MSLN结合分子在与脱落的MSLN结合后也从肿瘤部位清除。为了选择优先结合存在于肿瘤细胞表面的MSLN的分子,本发明人选择了对MSLN具有高亲合力的抗体分子。具体地,本发明人选择了以比溶液中的MSLN更高的亲合力与固定的MSLN结合的抗体分子。以高亲合力结合MSLN的抗体分子被认为优先与存在于肿瘤细胞上的MSLN结合,而预期会存在多个拷贝的MSLN,并且可用于抗体分子的二价结合,与肿瘤细胞释放的间皮素相反,后者预期将以单体形式存在。不希望受到理论的束缚,因此预期本发明的抗体分子从肿瘤部位清除的速度较慢,因此具有更长的时间窗可发挥其治疗作用。

[0205] 抗体分子优选以比溶液中的MSLN更高的亲和力与固定的MSLN结合。固定的MSLN可以是固定在诸如用于表面等离子体共振的芯片之类的表面上的MSLN。溶液中的MSLN在本文中也称为可溶性MSLN,并且没有被固定。可溶性MSLN优选为单体形式,即单体间皮素。

[0206] 抗体对其同源抗原的亲和力可以表示为抗体结合所述抗原的平衡解离常数(K_D)。K_D值越高,抗体分子对抗原的亲和力越低。

[0207] 抗体分子优选以至少9nM,8nM,7nM或6nM的亲和力(K_D)或更高的亲和力与固定的MSLN结合。优选地,抗体分子以至少7nM,6nM或更高的亲和力与固定的MSLN结合。

[0208] 抗体分子优选以15nM的亲和力(KD)或更低的亲和力与固定的MSLN结合。更优选地,抗体分子以16nM,17nM或18nM的亲和力(K_D)或更低的亲和力与固定的MSLN结合。

[0209] 在一个优选的实施方式中,抗体分子以6nM的亲和力(K_D)或更高的亲和力结合固定的MSLN,并以18nM的亲和力(K_D)或更低的亲和力结合溶液中的MSLN。

[0210] 抗体分子对包含表面结合的MSLN的细胞的结合亲和力可以通过确定实现抗体分子与细胞的半数最大结合(EC_{50})所需的抗体分子的浓度来测量。确定实现抗体分子与细胞的半数最大结合所需的抗体分子浓度的合适方法是本领域已知的,并在本发明实施例中公开(参见例如实施例4)。如上所述,考虑到在肿瘤环境中存在脱落的MSLN,与包含表面结合的MSLN的肿瘤细胞的结合不受到或较少受可溶性间皮素的影响的抗体分子是优选的。因此,在优选的实施方式中,在可溶性MSLN存在下,使抗体与包含表面结合的MSLN的细胞(例如肿瘤细胞)达到半数最大结合(EC_{50})所需的抗体分子的浓度比在不存在可溶性MSLN的情况下实现抗体与细胞半数最大结合(EC_{50})所需的抗体分子浓度小于20倍,小于15倍,小于10倍,小于9倍,小于8倍,小于7倍,小于6倍,小于5倍,小于4倍或小于3倍。

[0211] 已经显示,不阻断MUC16与MSLN结合的抗体分子与包含细胞结合的MSLN的细胞的结合受可溶性MSLN的存在的影响较小。因此,不能或不会阻断MUC16与MSLN结合的抗体分子可能是优选的。

[0212] 或者,抗体分子可以阻断MUC16与MSLN的结合。

[0213] 固定的MSLN可以具有SEQ ID NO:169所示的序列。溶液中的MSLN可以具有SEQ ID NO:169所示的序列。

[0214] 还已经显示出本发明的抗体分子结合猕猴MSLN。与猕猴MSLN以及人MSLN的结合被认为有利于用猕猴中的抗体分子进行功效和毒性研究,这可以预测抗体分子在人体内的功效和毒性。

[0215] 抗体分子可以以相似的亲和力结合至固定的人MSLN和固定的猕猴MSLN。另外,抗体分子可以以相似的亲和力结合溶液中的人MSLN和溶液中的猕猴MSLN。认为这对于确保用猕猴中的抗体分子进行的功效和毒性研究预测该抗体分子在人中的功效和毒性是有益的。

[0216] 因此,在一个优选的实施方式中,抗体分子与固定化的猕猴MSLN的亲和力比抗体分子与固定化的人MSLN结合的亲和力低或高不超过10倍,优选不超过5倍,更优选不超过2倍。另外,抗体分子优选以低于或高于抗体分子结合溶液中人MSLN的亲和力的不超过10倍,优选不超过5倍,更优选不超过2倍的亲和力与溶液中的猕猴MSLN结合。

[0217] 可以通过表面等离振子共振(SPR),例如Biacore来确定抗体分子与同源抗原,例如人或猕猴MSLN的结合亲和力。

[0218] 抗体分子可以是嵌合的,人源化的或人的。优选地,抗体分子是人抗体分子。

[0219] 抗体分子优选是单克隆的。在没有污染物的意义上,可以分离抗体分子,例如能够结合其他多肽和/或血清成分的抗体。

[0220] 抗体分子可以是天然的或部分或全部合成产生的。例如,抗体分子可以是重组抗体分子。

[0221] 抗体分子包含一个或多个MSLN的基于CDR的抗原结合位点。

[0222] 抗体分子可以是免疫球蛋白或其抗原结合片段。例如,抗体分子可以是IgG,IgA,IgE或IgM分子,优选为IgG分子,例如IgG1,IgG2,IgG3或IgG4分子,更优选为IgG1或IgG2分子,最优选为IgG1分子,或其片段。在一个优选的实施方式中,抗体分子是完整的免疫球蛋白分子。

[0223] 在其他实施方式中,抗体分子可以是包含MSLN的基于CDR的抗原结合位点的抗原结合片段。例如,抗原结合片段可以是抗原结合片段(Fab),IgGΔCH2,F(ab')$_2$,单链Fab(scFab),二硫键稳定的可变片段(dsFv),单链可变片段(scFv),(scFv)$_2$,scFv-CH3(微型抗体),scFv-Fc,scFv拉链(scFv-zipper),双链抗体,三链抗体,四链抗体或单域抗体(sdAb),例如V_HH结构域或纳米抗体。优选的抗原结合片段包含多于一个的MSLN的基于CDR的抗原结合位点,即它们可以是多价的。因此,抗原结合片段可以优选是IgGΔCH2,F(ab′)$_2$,双链抗体,三链抗体或四链抗体。(Brinkmann和Kontermann(2017)和Powers等人(2012))。

[0224] 抗体及其构建和使用方法在本领域中是众所周知的,例如,在Holl iger和Hudson,2005中进行了描述。可以采用单克隆抗体和其他抗体,也可以使用重组DNA技术生产其他抗体或保留原始抗体特异性的嵌合分子。此类技术可能涉及将一个抗体分子的CDR或可变区引入不同的抗体分子(EP-A-184187,GB2188638A和EP-A-239400)。

[0225] 基于CDR的抗原结合位点是抗体可变区中的抗原结合位点。基于CDR的抗原结合位点可以由三个CDR形成,例如三个轻链可变域(VL)CDR或三个重链可变域(VH)CDR。优选地,基于CDR的抗原结合位点由六个CDR,即三个VL CDR和三个VH CDR形成。不同的CDR对抗原结合的贡献可以在不同的抗原结合位点中变化。

[0226] 抗原结合位点的三个VH结构域CDR可以位于免疫球蛋白VH结构域内,并且三个VL结构域CDR可以位于免疫球蛋白VL结构域内。例如,基于CDR的抗原结合位点可以位于抗体可变区中。

[0227] 抗体分子具有针对MSLN的一个或优选多于一个,例如两个,基于CDR的抗原结合位点。因此,抗体分子可包含一个VH和一个VL结构域,但优选包含两个VH和两个VL结构域,即两个VH/VL结构域对,例如在天然存在的IgG分子中的情况。

[0228] 基于CDR的抗原结合位点可以包含抗体FS28-256-271,FS28-024-052,FS28-256-021,FS28-256-012,FS28-256-023,FS28-256-024,FS28-256-026,FS28-256-027,FS28-256-001,FS28-256-005,FS28-256-014,FS28-256-018,FS28-256,FS28-024-051,FS28-024-053或FS28-024,优选抗体FS28-256-271或FS28-024-052,最优选抗体FS28-256-271的三个VH CDR或三个VL CDR,优选三个VH CDR和三个VL CDR。

[0229] CDR的序列可以使用常规技术容易地从抗体分子的VH和VL结构域序列确定。如本文所述,抗体FS28-256-271,FS28-024-052,FS28-256-021,FS28-256-012,FS28-256-023,FS28-256-024,FS28-256-026,FS28-256-027,FS28-256-001,FS28-256-005,FS28-256-014,FS28-256-018,FS28-256,FS28-024-051,FS28-024-053和FS28-024的VH和VL结构域序列,并且可以从所述序列确定所述抗体的三个VH和三个VL结构域CDR。CDR序列可以例如根据Kabat等人,1991或国际ImMunoGeneTics信息系统(IMGT)(Lefranc等人,2015)确定。

[0230] 根据IMGT编号的抗体分子的VH结构域CDR1,CDR2和CDR3序列可以分别是位于抗体分子的VH结构域的27-38位、56-65位和105-117位的序列。

[0231] 根据Kabat编号的抗体分子的VH结构域CDR1,CDR2和CDR3序列可以分别是位于VH结构域的31-35、50-65和95-102位的序列。

[0232] 根据IMGT编号的抗体分子的VL结构域CDR1,CDR2和CDR3序列可以分别是位于VL结构域的27-38、56-65和105-117位的序列。

[0233] 根据Kabat编号的抗体分子的VL结构域CDR1,CDR2和CDR3序列可以分别是位于VL结构域的24-34、50-56和89-97位的序列。

[0234] 例如,VH结构域CDR1,CDR2和CDR3的序列:

[0235] (i)FS28-256-271可以分别如SEQ ID NO:98、73和99所示;

[0236] (ii)FS28-024-052可以分别如SEQ ID NO:10、11和41所示;

[0237] (iii)FS28-256-021可以分别如SEQ ID NO:98、73和99所示;

[0238] (iv)FS28-256-012可以分别如SEQ ID NO:98、73和99所示;

[0239] (v)FS28-256-023可以分别如SEQ ID NO:101、73和103所示;

[0240] (vi)FS28-256-024可以分别如SEQ ID NO:98、73和99所示;

[0241] (vii)FS28-256-026可以分别如SEQ ID NO:101、73和103所示;

[0242] (viii)FS28-256-027可以分别如SEQ ID NO:98、73和99所示;

[0243] (ix)FS28-256-001可以分别如SEQ ID NO:85、73和75所示;

[0244] (x)FS28-256-005可以分别如SEQ ID NO:85、73和75所示;

[0245] (xi)FS28-256-014可以分别如SEQ ID NO:111、73和113所示;

[0246] (xii)FS28-256-018可以分别如SEQ ID NO:101、73和103所示;

[0247] (xiii)FS28-256可以分别如SEQ ID NO:71、73和75所示;

[0248] (xiv)FS28-024-051可以分别如SEQ ID NO:10、11和32所示;

[0249] (xv)FS28-024-053可以分别如SEQ ID NO:10、11和51所示;和

[0250] (xvi)FS28-024可以分别如SEQ ID NO:10、11和12所示;

[0251] 其中,CDR序列是根据IMGT编号方案定义的。

[0252] VL结构域CDR1,CDR2和CDR3的序列:

[0253] (i)FS28-256-271可以分别如SEQ ID NO:20、21和44所示;

[0254] (ii)FS28-024-052可以分别如SEQ ID NO:20、21和22所示;

[0255] (iii)FS28-256-021可以分别如SEQ ID NO:20、21和34所示;

[0256] (iv)FS28-256-012可以分别如SEQ ID NO:20、21和25所示;

[0257] (v)FS28-256-023可以分别如SEQ ID NO:20、21和34所示;

[0258] (vi)FS28-256-024可以分别如SEQ ID NO:20、21和43所示;

[0259] (vii)FS28-256-026可以分别如SEQ ID NO:20、21和43所示;

[0260] (viii)FS28-256-027可以分别如SEQ ID NO:20、21和44所示;

[0261] (ix)FS28-256-001可以分别如SEQ ID NO:20、21和34所示;

[0262] (x)FS28-256-005可以分别如SEQ ID NO:20、21和43所示;

[0263] (xi)FS28-256-014可以分别如SEQ ID NO:20、21和25所示;

[0264] (xii)FS28-256-018可以分别如SEQ ID NO:20、21和25所示;

[0265] (xiii)FS28-256可以分别如SEQ ID NO:20、21和25所示;

[0266] (xiv)FS28-024-051可以分别如SEQ ID NO:20、21和22所示;

[0267] (xv)FS28-024-053可以分别如SEQ ID NO:20、21和22所示;和

[0268] (xvi)FS28-024可以分别如SEQ ID NO:20、21和22所示;

[0269] 其中,CDR序列是根据IMGT编号方案定义的。

[0270] 例如,VH结构域CDR1,CDR2和CDR3的序列:

[0271] (i)FS28-256-271可以分别如SEQ ID NO:97、182和100所示;

[0272] (ii)FS28-024-052可以分别如SEQ ID NO:13、14和42所示;

[0273] (iii)FS28-256-021可以分别如SEQ ID NO:97、74和100所示;

[0274] (iv)FS28-256-012可以分别如SEQ ID NO:97、74和100所示;

[0275] (v)FS28-256-023可以分别如SEQ ID NO:102、74和104所示;

[0276] (vi)FS28-256-024可以分别如SEQ ID NO:97、74和100所示;

[0277] (vii)FS28-256-026可以分别如SEQ ID NO:102、74和104所示;

[0278] (viii)FS28-256-027可以分别如SEQ ID NO:97、74和100所示;

[0279] (ix)FS28-256-001可以分别如SEQ ID NO:86、74和76所示;

[0280] (x)FS28-256-005可以分别如SEQ ID NO:86、74和76所示;

[0281] (xi)FS28-256-014可以分别如SEQ ID NO:112、74和114所示;

[0282] (xii)FS28-256-018可以分别如SEQ ID NO:102、74和104所示;

[0283] (xiii)FS28-256可以分别如SEQ ID NO:72、74和76所示;

[0284] (xiv)FS28-024-051可以分别如SEQ ID NO:13、14和33所示;

[0285] (xv)FS28-024-053可以分别如SEQ ID NO:13、14和52所示;和

[0286] (xvi)FS28-024可以分别如SEQ ID NO:13、14和15所示;

[0287] 其中CDR序列是根据Kabat编号方案定义的。

[0288] VL结构域CDR1,CDR2和CDR3的序列:

[0289] (i)FS28-256-271可以分别如SEQ ID NO:23、24和44所示;

[0290] (ii)FS28-024-052可以分别如SEQ ID NO:23、24和22所示;

[0291] (iii)FS28-256-021可以分别如SEQ ID NO:23、24和34所示;

[0292] (iv)FS28-256-012可以分别如SEQ ID NO:23、24和25所示;

[0293] (v)FS28-256-023可以分别如SEQ ID NO:23、24和34所示;

[0294] (vi)FS28-256-024可以分别如SEQ ID NO:23、24和43所示;

[0295] (vii)FS28-256-026可以分别如SEQ ID NO:23、24和43所示;

[0296] (viii)FS28-256-027可以分别如SEQ ID NO:23、24和44所示;

[0297] (ix)FS28-256-001可以分别如SEQ ID NO:23、24和34所示;

[0298] (x)FS28-256-005可以分别如SEQ ID NO:23、24和43所示;

[0299] (xi)FS28-256-014可以分别如SEQ ID NO:23、24和25所示;

[0300] (xii)FS28-256-018可以分别如SEQ ID NO:23、24和25所示;

[0301] (xiii)FS28-256可以分别如SEQ ID NO:23、24和25所示;

[0302] (xiv)FS28-024-051可以分别如SEQ ID NO:23、24和22所示;

[0303] (xv)FS28-024-053可以分别如SEQ ID NO:23、24和22所示;和

[0304] (xvi)FS28-024可以分别如SEQ ID NO:23、24和22所示;

[0305] 其中CDR序列是根据Kabat编号方案定义的。

[0306] 基于CDR的抗原结合位点可包含VH或VL结构域,优选抗体FS28-256-271,FS28-024-052,FS28-256-021,FS28-256-012,FS28-256-023,FS28-256-024,FS28-256-026,FS28-256-027,FS28-256-001,FS28-256-005,FS28-256-014,FS28-256-018,FS28-256,FS28-024-051,FS28-024-053或FS28-024,优选抗体FS28-256-271或FS28-024-052,最优选抗体FS28-256-271的VH或VL结构域。

[0307] 抗体FS28-256-271,FS28-024-052,FS28-256-021,FS28-256-012,FS28-256-023,FS28-256-024,FS28-256-026,FS28-256-027,FS28-256-001,FS28-256-005,FS28-256-014,FS28-256-018,FS28-256,FS28-024-051,FS28-024-053和FS28-024的VH结构域可具有分别如SEQ ID NO:180、39、109、109、121、109、121、109、63、63、115、121、69、30、49和8所示的序列。

[0308] 抗体FS28-256-271,FS28-024-052,FS28-256-021,FS28-256-012,FS28-256-023,FS28-256-024,FS28-256-026,FS28-256-027,FS28-256-001,FS28-256-005,FS28-256-014,FS28-256-018,FS28-256,FS28-024-051,FS28-024-053和FS28-024的VL结构域可具有分别如SEQ ID NO:56、18、93、79、93、53、53、56、93、53、79、79、79、18、18和18所示的序列。

[0309] 抗体分子可包含重链或轻链,优选抗体FS28-256-271,FS28-024-052,FS28-256-021,FS28-256-012,FS28-256-023,FS28-256-024,FS28-256-026,FS28-256-027,FS28-

256-001,FS28-256-005,FS28-256-014,FS28-256-018,FS28-256,FS28-024-051,FS28-024-053或FS28-024,优选抗体FS28-256-271或FS28-024-052,最优选抗体FS28-256-271的重链或轻链。

[0310] 抗体FS28-256-271,FS28-024-052,FS28-256-021,FS28-256-012,FS28-256-023,FS28-256-024,FS28-256-026,FS28-256-027,FS28-256-001,FS28-256-005,FS28-256-014,FS28-256-018,FS28-256,FS28-024-051,FS28-024-053和FS28-024的重链(具有LALA突变)可分别具有如SEQ ID NO:178、37、107、107、125、107、125、107、89、89、119、125、67、28、47、5所示的序列。

[0311] 抗体FS28-256-271,FS28-024-052,FS28-256-021,FS28-256-012,FS28-256-023,FS28-256-024,FS28-256-026,FS28-256-027,FS28-256-001,FS28-256-005,FS28-256-014,FS28-256-018,FS28-256,FS28-024-051,FS28-024-053和FS28-024的重链(不具有LALA突变)可分别具有如SEQ IDNO:176、35、105、105、123、105、123、105、81、87、117、123、65、26、45和4所示的序列。

[0312] 抗体FS28-256-271,FS28-024-052,FS28-256-021,FS28-256-012,FS28-256-023,FS28-256-024,FS28-256-026,FS28-256-027,FS28-256-001,FS28-256-005,FS28-256-014,FS28-256-018,FS28-256,FS28-024-051,FS28-024-053和FS28-024的轻链可具有分别如SEQ ID NO:95、16、83、77、83、90、90、95、83、90、77、77、77、16、16和16所示的序列。

[0313] 抗体分子还可包含本文所述的CDR,VH结构域,VL结构域,重链或轻链序列的变体。合适的变体可以通过序列改变或突变以及筛选的方法获得。在一个优选的实施方式中,包含一个或多个这样的变体序列的抗体分子保留了亲本抗体分子的一个或多个功能特征,例如对MSLN,优选人和/或猕猴MSLN的结合特异性和/或结合亲和力。例如,包含一个或多个变体序列的抗体分子优选以与(亲本)抗体分子相同的亲和力或更高的亲和力结合MSLN。亲本抗体分子是不包含已被掺入变体抗体分子中的氨基酸取代,缺失和/或插入的抗体分子。

[0314] 包含抗体FS28-256-021,FS28-256-012,FS28-256-023,FS28-256-024,FS28-256-026,FS28-256-027,FS28-256-001,FS28-256-005,FS28-256-014,FS28-256-018或FS28-256的CDR 1-6,VH结构域和/或重链的抗体分子可以在VH结构域的55或57位上包含氨基酸取代,其中氨基酸残基编号是根据IMGT编号方案进行的。

[0315] 例如,抗体分子可包含抗体FS28-256-027的CDR 1-6,VH结构域和/或重链,其中抗体分子在VH结构域的55位包含氨基酸取代,其中氨基酸残基编号是根据IMGT编号方案进行的。

[0316] 本发明的抗体分子可以包含VH结构域,VL结构域,重链或轻链,其与抗体FS28-256-271,FS28-024-052,FS28-256-021,FS28-256-012,FS28-256-023,FS28-256-024,FS28-256-026,FS28-256-027,FS28-256-001,FS28-256-005,FS28-256-014,FS28-256-018,FS28-256,FS28-024-051,FS28-024-053或FS28-024,优选抗体FS28-256-271或FS28-024-052,最优选抗体FS28-256-271的VH结构域,VL结构域,重链或轻链具有至少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。

[0317] 通常参考算法GAP(威斯康星州GCG软件包,Accelerys有限公司,美国圣地亚哥)来

定义序列同一性。GAP使用Needleman和Wunsch算法比对两个完整序列,从而最大化地增加匹配数并最小化地减少缺口数。通常,使用默认参数,缺口产生罚分等于12并且缺口延伸罚分等于4。GAP的使用可能是优选的,但是也可以使用其他算法,例如,BLAST(使用Altschul等人,1990年,FASTA的方法(使用Pearson和Lipman,1988年的方法),或Smith-Waterman算法(Smith和Waterman,1981年),或Altschul等人的TBLASTN程序,1990年,同上,通常采用默认参数,特别是可以使用psi-Blast算法(Altschul等人,1997)。

[0318] 抗体分子可包含VH CDR1,VH CDR2,VH CDR3,VL CDR1,VL CDR2和/或VLCDR3,与抗体FS28-256-271,FS28-024-052,FS28-256-021,FS28-256-012,FS28-256-023,FS28-256-024,FS28-256-026,FS28-256-027,FS28-256-001,FS28-256-005,FS28-256-014,FS28-256-018,FS28-256,FS28-024-051,FS28-024-053或FS28-024,优选抗体FS28-256-271或FS28-024-052,最优选抗体FS28-256-271的VH CDR1,VH CDR2,VH CDR3,VL CDR1,VL CDR2和/或VL CDR3相比,其具有一个或多个氨基酸序列改变(氨基酸残基的添加,缺失,取代和/或插入),优选3个或更少,2个或更少或1个改变。

[0319] 抗体分子可包含VH结构域,VL结构域,重链或轻链,与抗体FS28-256-271,FS28-024-052,FS28-256-021,FS28-256-012,FS28-256-023,FS28-256-024,FS28-256-026,FS28-256-027,FS28-256-001,FS28-256-005,FS28-256-014,FS28-256-018,FS28-256,FS28-024-051,FS28-024-053或FS28-024,优选抗体FS28-256-271或FS28-024-052,最优选抗体FS28-256-271的VH结构域,VL结构域,重链或轻链相比,其具有一个或多个氨基酸序列改变(氨基酸残基的添加,缺失,取代和/或插入),优选20个或更少,15个或更少,10个或更少,5个或更少,4个或更少,3个或更少,2个或更少或1个改变。具体地,氨基酸序列改变可以位于抗体分子的一个或多个框架区,例如抗体分子的重链和/或轻链的一个或多个框架区。

[0320] 在一个或多个氨基酸被另一种氨基酸取代的优选实施方式中,该取代可以是保守取代,例如如下表所示。在一些实施方式中,中间一列中相同类别的氨基酸被互相取代,即,例如,非极性氨基酸被另一种非极性氨基酸取代。在一些实施方式中,最右边一列中同一行中的氨基酸被互相取代。

[0321]

脂肪族	非极性	G A P
		I L V
	极性－不带电	C S T M
		N Q
	极性－带电	D E
		K R
芳香族		H F W Y

[0322] 在一些实施方式中,取代可以在功能上是保守的。即,在一些实施方式中,与等效的未取代的抗体分子相比,该取代可能不影响(或可能基本上不影响)包含该取代的抗体分子的一种或多种功能性质(例如结合亲和力)。

[0323] 抗体分子的重链可以任选地在重链CH3结构域序列的直接C末端包含另外的赖氨酸残基(K)。

[0324] 已知CH2结构域结合Fcγ受体和补体。CH2结构域与Fcγ受体的结合是抗体依赖性细胞介导的细胞毒性(ADCC)所必需的,而与补体的结合是补体依赖性细胞毒性(CDC)所必需的。如果抗体分子用于治疗癌症而不是ADC形式,则ADCC活性有望导致癌细胞的杀伤,因此优选被保留。然而,在抗体分子为ADC形式并与生物活性分子偶联的情况下,预期降低或

消除ADCC活性的突变将有利于避免在生物活性分子被递送至细胞之前通过ADCC杀死靶癌细胞。另外,在抗体分子包含如本文所述的免疫细胞抗原的第二抗原结合位点的情况下,预期降低或消除ADCC和/或CDC活性的突变将是有用的,应避免ADCC和/或CDC介导的抗体分子结合免疫细胞的杀伤。

[0325] 抗体分子的CH2结构域因此可以包含一种或多种突变,其减少或消除CH2结构域与一种或多种Fcγ受体如FcγRI,FcγRIIa,FcγRI Ib,FcγRII I和/或补体的结合。发明人推测减少或消除与Fcγ受体的结合将减少或消除抗体分子介导的ADCC。类似地,预期减少或消除与补体的结合将减少或消除抗体分子介导的CDC。减少或消除CH2结构域与一种或多种Fcγ受体和/或补体结合的突变是本领域已知的(Wang等人,2018)。这些突变包括在Bruhns等人(2009年)和Hezareh等人(2001年)中描述的“LALA突变”,这涉及用丙氨酸(L1.3A和L1.2A)取代CH2结构域的1.3和1.2位的亮氨酸残基。或者,已知将CH2结构域84.4位的天冬酰胺(N)突变为丙氨酸,甘氨酸或谷氨酰胺(N84.4A,N84.4G或N84.4Q),通过保守的N-连接的糖基化位点的突变产生a-糖基抗体会降低IgG1效应子功能(Wang等人,2018)。作为另一种选择,已知补体激活(C1q结合)和ADCC可通过将CH2结构域第114位的脯氨酸突变为丙氨酸或甘氨酸(P114A或P114G)而降低(Idusogie等人,2000;Klein等人,2016)。也可以组合这些突变,以产生具有进一步降低的ADCC或CDC活性或没有ADCC或CDC活性的抗体分子。

[0326] 因此,抗体分子可包含CH2结构域,其中CH2结构域优选包含:

[0327] (i)1.3和1.2位的丙氨酸残基;和/或

[0328] (ii)114位的丙氨酸或甘氨酸;和/或

[0329] (iii)84.4位的丙氨酸,谷氨酰胺或甘氨酸;

[0330] 其中根据IMGT编号方案进行氨基酸残基编号。

[0331] 在一个优选的实施方式中,抗体分子包含CH2结构域,其中CH2结构域包含:

[0332] (i)1.3位的丙氨酸残基;和

[0333] (ii)1.2位的丙氨酸残基;

[0334] 其中根据IMGT编号方案进行氨基酸残基编号。

[0335] 例如,CH2结构域可包含LALA突变,并具有如SEQ ID NO:173所示的序列。

[0336] 在一个替代的优选实施方式中,抗体分子包含CH2结构域,其中CH2结构域包含:

[0337] (i)1.3位的丙氨酸残基;

[0338] (ii)1.2位的丙氨酸残基;和

[0339] (iii)114位的丙氨酸;

[0340] 其中根据IMGT编号方案进行氨基酸残基编号。

[0341] 例如,CH2结构域可包含LALA-PA突变,并具有如SEQ ID NO:174所示的序列。

[0342] 还考虑了这样的抗体分子,其包含针对MSLN的基于CDR的抗原结合位点,并且与本文所述的抗体分子竞争,或者与本文所述的抗体分子结合在MSLN上相同的表位。用于确定两种抗体竞争抗原的方法是本领域已知的。例如,两种抗体与抗原结合的竞争可以通过表面等离振子共振来确定,例如使用Biacore仪器。类似地已知用于定位与抗体结合的表位的方法。

[0343] 据报道,MSLN的N末端区域与MUC16相互作用。据报道,这种相互作用可能在癌细胞

粘附中起作用。

[0344] 已经显示抗体分子对配体结合具有活性范围。例如,抗体分子可能能够阻断或可能不能阻断MUC16与MSLN的结合。或者,抗体分子可能能够增强MUC16与MSLN的结合。例如,抗体分子可以包含抗体FS28-024-051,FS28-024-052,FS28-024-053或FS28-024的CDR 1-6,VH结构域,VL结构域,重链和/或轻链,或其变体,其中抗体分子阻断MUC16与MSLN的结合。

[0345] 在一个优选的实施方式中,抗体分子不阻断MUC16与MSLN的结合。例如,抗体分子可包含抗体FS28-256-271,FS28-256-021,FS28-256-012,FS28-256-023,FS28-256-024,FS28-256-026,FS28-256-027,FS28-256-001,FS28-256-005,FS28-256-014,FS28-256-018,FS28-256的CDR 1-6,VH结构域,VL结构域,重链和/或轻链,或其变体,其中抗体分子不阻断MUC16与MSLN的结合。

[0346] 适用于确定抗体分子阻断MUC16与MSLN结合的能力的方法是本领域已知的,包括ELISA和基于细胞的测定,例如一种抗体竞争与MUC16的结合以与表达MSLN的细胞(例如NCI-H226细胞)结合的实验。

[0347] 在优选的实施方式中,除了针对MSLN的基于CDR的抗原结合位点之外,抗体分子还可包含一个或多个其他抗原结合位点,这些位点与一种或多种其他抗原结合。一个或多个其他的抗原结合位点优选特异性地结合其同源抗原。

[0348] 一个或多个其他的抗原结合位点优选不结合MSLN。抗体分子因此可以是多特异性的,例如双特异性,三特异性或四特异性分子,优选双特异性分子。在一个优选的实施方式中,抗体分子能够同时结合MSLN和一种或多种其他抗原。

[0349] 已知抗体分子具有包含离散结构域的模块结构,其可以以多种不同方式组合以产生多特异性,例如双特异性,三特异性或四特异性抗体形式。示例性的多特异性抗体形式在例如,Spiess等人(2015)和Kontermann(2012)中描述。本发明的抗体分子可以以这种多特异性形式使用。

[0350] 例如,本发明的抗体分子可以是异二聚抗体分子,例如异二聚完整免疫球蛋白分子或其片段。在这种情况下,抗体分子的一部分将具有如本文所述的一个或多个序列。例如,在本发明的抗体分子是双特异性异二聚抗体分子的情况下,抗体分子可包含如本文所述的重链和轻链,分别与包含VH结构域和VL结构域的重链和轻链配对,结合MSLN以外的抗原或另外结合MSLN上的另一个表位。制备异二聚抗体的技术是本领域已知的,并且包括钮扣结构(knobs-into-holes)(KIH)技术,该技术涉及对抗体分子的CH3域进行改造以产生“钮”或“扣”以促进链异二聚化。或者,可以通过将电荷对引入抗体分子中来制备异二聚抗体,以避免由于静电排斥而使CH3结构域同二聚化,并通过静电吸引来指导异二聚化。异二聚体抗体形式的实例包括CrossMab,mAb-Fv,SEED抗体(SEED-body)和Kih IgG。

[0351] 或者,多特异性抗体分子可包含完整的免疫球蛋白分子或其片段以及另外的一个或多个抗原结合部分。抗原结合部分可以是例如Fv,scFv或单域抗体,并且可以与完整的免疫球蛋白分子或其片段融合。包含与完整免疫球蛋白分子融合的其他抗原结合部分的多特异性抗体分子的实例包括DVD-IgG,DVI-IgG,scFv4-IgG,IgG-scFv和scFv-IgG分子(Spiess等人,2015年;图1)。包含与免疫球蛋白片段融合的另外的抗原结合部分的多特异性抗体分子的实例包括例如BiTE分子,双链抗体和DART分子(Spiess等人,2015;图1)。其他合适的形式对于技术人员将是显而易见的。

[0352] 在一个优选的实施方式中,抗体分子包含结合第二抗原的第二抗原结合位点,其中第二抗原结合位点位于抗体分子的恒定结构域中。例如,抗体分子可以是mAb^2(™)双特异性抗体。如本文所指,mAb^2双特异性抗体是IgG免疫球蛋白,其在其可变区的每个可变区中包括基于CDR的抗原结合位点,并且在抗体分子的恒定结构域中包括至少一个抗原结合位点。

[0353] 在一个优选的实施方式中,该抗体是结合MSLN和第二抗原的抗体分子,该抗体分子包括:

[0354] (i)针对MSLN的两个基于CDR的抗原结合位点,分别由免疫球蛋白VH结构域和免疫球蛋白VL结构域形成;和

[0355] (ii)结合位于抗体分子的两个CH3结构域中的第二抗原的两个抗原结合位点。

[0356] 在一个更优选的实施方式中,该抗体是完整的免疫球蛋白分子,例如,与MSLN和第二抗原结合的完整IgG1分子,该抗体分子包含:

[0357] (i)针对MSLN的两个基于CDR的抗原结合位点,分别由免疫球蛋白VH结构域和免疫球蛋白VL结构域形成;和

[0358] (ii)结合位于抗体分子的两个CH3结构域中的第二抗原的两个抗原结合位点;和

[0359] 其中免疫球蛋白分子进一步包含CH1,CH2和CL结构域。

[0360] 第二抗原的抗原结合位点可以位于抗体分子的任何恒定结构域中。例如,第二抗原的抗原结合位点可以位于CH4,CH3,CH2,CH1或CL结构域中的一个或多个中,优选CH3或CH2结构域,最优选CH3结构域。

[0361] 抗原结合位点可以由抗体分子恒定结构域的一个或多个,例如一个,两个,三个或更多个结构环组成。

[0362] 抗体恒定结构域的结构环包括AB,BC,CD,DE,EF和FG结构环。抗原结合位点可包含恒定结构域的AB,BC,CD,DE,EF和FG结构环中的两个或更多个,优选AB和EF结构环,或AB,CD和EF结构环。

[0363] 抗体恒定结构域中结构环的位置是本领域众所周知的。例如,CH3结构域的结构环位于CH3结构域的10和19位(AB环),28和39位(BC环),42和79位(CD环),82和85位(DE环),91和102位(EF环)和106和117位(FG环)之间,其中残基根据IMGT编号方案进行编号。可以容易地确定其他恒定结构域中结构环位置的定位。

[0364] 恒定结构域的结构环可包含一个或多个氨基酸修饰,以便形成第二抗原的抗原结合位点。一种或多种氨基酸修饰可包括氨基酸取代,添加或缺失。将氨基酸修饰引入抗体恒定域的结构环区域以产生靶抗原的抗原结合位点是本领域众所周知的,并且例如在Wozniak-Knopp G等人,2010,WO2006/072620和WO2009/132876中进行了描述。恒定结构域结合位点的实例在下面提供。

[0365] 在一个优选的实施方式中,抗体分子在AB,CD和/或EF结构环,优选AB和EF结构环或AB,CD和EF结构环中包含一个或多个氨基酸修饰(取代,添加和/或缺失)。例如,抗体分子可在CH3结构域的11-18位、43-78位和/或92-101位处,优选在CH3结构域的11-18位和92—101位处或在11-18、43-78和92-101位处包含一个或多个氨基酸修饰(取代,添加和/或缺失),以提供第二抗原的抗原结合位点,如本文所述。更优选地,抗体分子在CH3结构域的12-18、45.1至78、92至94和/或97-98位处包含一个或多个氨基酸修饰(取代,添加和/或缺失)。

更优选在CH3结构域的12-18、92至94和97-98位,或12-18、45.1至78、92至94和97-98位为如本文所述的第二抗原提供抗原结合位点。未修饰的CH3结构域优选包含SEQ ID NO:172所示的序列或由其组成。残基编号是根据IMGT编号方案进行的。

[0366] 被抗体分子的第二抗原结合位点结合的第二抗原可以是免疫细胞抗原,优选是肿瘤坏死因子受体超家族(TNFRSF)的成员。TNFRSF受体是膜结合的细胞因子受体,其包含结合肿瘤坏死因子超家族(TNFSF)的一个或多个配体的细胞外富含半胱氨酸的结构域。

[0367] TNFRSF受体优选位于免疫细胞如T细胞,抗原呈递细胞(APC),NK细胞和/或B细胞,优选T细胞的表面上。在结合TNFRSF配体后,TNFRSF受体在免疫细胞表面上形成簇,从而激活免疫细胞。例如,结合配体的TNFRSF受体可以形成多聚体,例如三聚体或多聚体簇。配体结合的TNFRSF受体簇的存在刺激了激活免疫细胞的细胞内信号传导途径。

[0368] 不希望被理论所束缚,人们认为通过使肿瘤细胞表面上的MSLN和免疫细胞表面上的TNFRSF受体结合,抗体分子将通过与MSLN结合而交联,从而驱动TNFRSF受体的聚集和活化,因此激活免疫细胞。换句话说,当两个靶标都结合时,抗体分子将充当TNFRSF受体激动剂。然后,活化的免疫细胞可以启动,促进或参与针对表达细胞表面结合的MSLN的癌症的免疫应答。Chen和Mellman(2013)概述了免疫系统在识别和消除癌细胞中的作用。

[0369] 抗体分子可以通过与Fcγ受体结合而交联,但这既效率低下又不能靶向特定的位置,例如,疾病的部位,因为表达Fcγ受体的细胞遍布整个人体。在一个优选的实施方式中,包含针对TNFRSF受体的第二抗原结合位点的抗体分子因此包含一个或突变,以减少或消除与本文所述的一个或多个Fcγ受体的结合。

[0370] 本发明人已经显示了使用包含针对MSLN和TNFRSF受体的结合位点的双特异性分子,特别是包含针对TNFRSF受体的两个恒定结构域结合位点和针对MSLN的两个基于CDR的抗原结合位点的mAb^2分子,这些抗体分子既与MSLN也与TNFRSF受体结合,可诱导或增强T细胞活化。

[0371] 包含针对TNFRSF受体的第二抗原结合位点的抗体分子,仅在与MSLN和TNFRSF受体结合时才激活T细胞等免疫细胞,或者在与MSLN和TNFRSF结合时增强其免疫细胞激活活性,也称为条件激动剂。这种免疫细胞激活活性独立于抗体分子与Fcγ受体和/或外部交联剂(例如蛋白A或G或二级抗体)的结合,因此可以将抗体分子的条件激动剂活性靶向到同时存在MSLN和TNFRSF的部位。由于MSLN是肿瘤抗原,因此抗体分子可以选择性地在肿瘤部位而不是个体的其他部位激活免疫细胞,例如T细胞。

[0372] 与依靠其他机制(例如外部交联剂或通过Fcγ受体相互作用进行交联)进行交联的抗体分子相比,仅在与MSLN和TNFRSF受体结合时才激活免疫细胞(例如T细胞)的抗体分子可能具有增强的免疫细胞激活活性。因为TNFRSF受体的活化是更有效的,所以相对于其他抗TNFRSF抗体分子,本文所述的抗体分子的浓度较低时可以实现免疫细胞的活化。

[0373] 当本发明的抗体分子包含存在于T细胞上的TNFRSF受体的第二抗原结合位点时,当抗体分子被交联时,例如通过与MSLN结合进行交联时,与不交联的抗体分子相比,该抗体分子优选诱导免疫细胞(如T细胞)增强的活化。

[0374] 可以使用T细胞活化测定法来测量抗体分子活化T细胞的能力。T细胞在激活时释放IL-2。因此,T细胞活化测定可以测量IL-2的释放,以确定抗体分子诱导的T细胞活化的水平。

[0375] 例如,当抗体分子交联时,可以通过测量在T细胞活化测定中T细胞实现IL-2的半数最大释放所需的抗体分子的浓度来确定抗体分子活化T细胞的能力。这也称为抗体分子的EC_{50}。较低的EC_{50}表示需要较低的抗体分子浓度以实现T细胞活化测定中的T细胞IL-2的半数最大释放,因此该抗体分子具有较高的T细胞活化活性。可以使用例如抗CH2抗体来使抗体分子交联。

[0376] 另外或可替代地,抗体分子激活T细胞的能力可以通过在存在抗体分子的情况下通过在T细胞活化测定中测量由T细胞释放的IL-2的最大浓度来确定,其中抗体分子是交联的。

[0377] 在一个优选的实施方式中,当交联时,例如,抗体分子(例如,包含FcabFS22-172-003的mAb^2形式)通过与NCI-H226细胞结合,在T细胞活化试验中的EC_{50}为在FS22-172-003-AA/FS28-256-271在同一测定中的EC_{50}的50倍,40倍,30倍,20倍,10倍或5倍之内,其中FS22-172-003-AA/FS28-256-271由SEQ ID NO:187的重链和SEQ ID NO:188的轻链组成。

[0378] 例如,当进行交联时,抗体分子在原代T细胞活化试验中的EC_{50}可能为交联时的30nM或以下,25nM或以下,20nM或以下,14nM或以下,10nM或以下,5nM或以下,4nM以下,3nM以下,2nM以下,1.5nM,1nM或0.5nM以下,优选为1.5nM以下,更优选为1nM,最优选为0.5nM以下。

[0379] 另外或可替代地,可以通过在存在交联抗体分子的情况下在T细胞活化测定中测量由T细胞释放的IL-2的最大浓度来确定抗体分子活化T细胞的能力。

[0380] 在一个优选的实施方式中,在抗体交联,例如,通过与NCI-H226细胞结合的情况下,在存在抗体分子(例如,包含Fcab FS22-172-003的mAb^2形式)的T细胞活化测定中,T细胞释放的IL-2的最大浓度为在同一试验中,在存在FS22-172-003-AA/FS28-256-271时的T细胞释放的IL-2的最大浓度的20%或10%以内,FS22-172-003-AA/FS28-256-271由SEQ ID NO:187的重链和SEQ ID NO:188的轻链组成。

[0381] 例如,取决于第二抗原结合位点结合的TNFRSF受体,T细胞测定可以是pan-T细胞活化测定或CD8+T活化细胞测定。例如,当TNFRSF受体是OX40时,pan-T细胞测定是合适的,而当TNFRSF受体是CD137时,CD8+T细胞测定是合适的。

[0382] 例如,pan-T细胞活化测定法可以包括从白细胞耗竭锥体中分离人PBMC。分离PBMC的方法是本领域已知的。然后可以从PBMC分离T细胞。从PBMC中分离T细胞的方法在本领域中也是已知的。

[0383] T细胞活化测定法可包括例如在合适的培养基,例如T细胞培养基中制备所需数量的T细胞。可以以1.0×10^6细胞/ml的浓度制备所需数量的T细胞。然后可以使用合适的T细胞活化试剂刺激T细胞,该试剂提供T细胞活化所需的信号。例如,T细胞活化试剂可以是包含CD3和CD28的试剂,例如包含CD3和CD28的珠。分离的T细胞可以与T细胞活化试剂一起孵育过夜以活化T细胞。此后,可以洗涤活化的T细胞以将T细胞从T细胞活化试剂分离,并以合适的浓度例如2.0×10^6细胞/ml重悬于T细胞培养基中。然后可以将活化的T细胞添加到涂有抗人CD3抗体的板上。

[0384] 可以制备每种测试抗体分子的合适稀释液并将其添加到孔中。然后可以将T细胞与测试抗体在37℃,5%CO_2下孵育24小时。可以收集上清液并进行测定以确定上清液中IL-2的浓度。用于确定溶液中IL-2浓度的方法是本领域已知的,并且在本实施例中进行了描

述。可以将人IL-2的浓度与抗体分子的对数浓度作图。可以使用对数(激动剂)对响应方程拟合得到曲线。

[0385] 例如,CD8+T细胞活化测定法可包括从白细胞耗竭锥分离人PBMC。分离PBMC的方法是本领域已知的。然后可以从PBMC中分离出CD8+T细胞。从PBMC中分离CD8+T细胞的方法在本领域中也是已知的。

[0386] 然后可以将CD8+T细胞添加到涂有抗人CD3抗体的多层板中。可以制备每种测试抗体分子的合适稀释液并将其添加到孔中。然后可以将T细胞与测试抗体在37℃,5%CO_2下孵育24小时。可以收集上清液并进行测定以确定上清液中IL-2的浓度。用于确定溶液中IL-2浓度的方法是本领域已知的,并且在本实施例中进行了描述。可以将人IL-2的浓度对抗体分子的对数浓度作图。可以使用对数(激动剂)对响应方程拟合得到曲线。

[0387] TNFRSF受体包括CD27、CD40、EDA2R、EDAR、FAS、LTBR、RELT、TNFRSF1A、TNFRSF1B、TNFRSF4(OX40)、TNFRSF6B、TNFRSF8、TNFRSF9(CD137)、TNFRSF10A-10D、TNFRSFF11A、TNFRSF11B、TNFRSF12A、TNFRSF13B、TNFRSF13C、TNFRSF14、TNFRSF17、TNFRSF18、TNFRSF19、TNFRSF21和TNFRSF25。

[0388] 在一个优选的实施方式中,TNFRSF受体是TNFRSF4(OX40)。

[0389] 在另一个优选的实施方式中,TNFRSF受体是TNFRSF9(CD137)。

[0390] CD27(TNFRSF7:基因ID 939)具有参考氨基酸序列NP_001233.1,并且可以由NM_001242.4的参考核苷酸序列编码。CD40(TNFRSF5:基因ID 958)具有NP_001241.1的参考氨基酸序列,并且可以由NM_001250.5的参考核苷酸序列编码。EDA2R(TNFRSF27:基因ID 60401)具有NP_001186616.1的参考氨基酸序列,并且可以由NM_001199687.2的参考核苷酸序列编码。EDAR(基因ID 10913)具有NP_071731.1的参考氨基酸序列,并且可以由NM_022336,3的参考核苷酸序列编码。FAS(TNFRSF6:基因ID 355)具有NP_000034.1的参考氨基酸序列,并且可以由NM_000043.5的参考核苷酸序列编码。LTBR(TNFRSF3:基因ID 4055)具有NP_001257916.1的参考氨基酸序列,并且可以由NM_001270987.1的参考核苷酸序列编码。RELT(TNFRSF19L:基因ID 84957)具有参考氨基酸序列NP_116260.2,并且可以由NM_032871.3的参考核苷酸序列编码。TNFRSF1A(基因ID 7132)具有NP_001056.1的参考氨基酸序列,并可以由NM_001065.3的参考核苷酸序列编码。TNFRSF1B(基因ID 7133)具有NP_001057.1的参考氨基酸序列,并可以由NM_001066.2的参考核苷酸序列编码。TNFRSF4(基因ID 7293)具有NP_003318的参考氨基酸序列,并且可以由NM_003327的参考核苷酸序列编码。TNFRSF6B(基因ID 8771)具有参考氨基酸序列NP_003814.1,并且可以由NM_003823.3的参考核苷酸序列编码。TNFRSF8(基因ID 943)具有NP_001234.3的参考氨基酸序列,并且可以由NM_001243.4的参考核苷酸序列编码。TNFRSF9(基因ID 3604)具有NP_001552的参考氨基酸序列,并且可以由NM001561的参考核苷酸序列编码。TNFRSF10A(基因ID 8797)的参考氨基酸序列为NP_003835.3,并可以由NM_003844.3的参考核苷酸序列编码。TNFRSF10B(基因ID 8795)具有NP_003833.4的参考氨基酸序列,并且可以由NM_003842.4的参考核苷酸序列编码。TNFRSF10C(基因ID 8794)具有参考氨基酸序列NP_003832.2,并且可以由NM_003841.4的参考核苷酸序列编码。TNFRSF10D(基因ID 8793)具有参考氨基酸序列NP_003831.2,并且可以由NM_003840.4的参考核苷酸序列编码。TNFRSF11A(基因ID 8792)具有XP_011524547.1的参考氨基酸序列,并且可以由XM_11526245.2的参考核苷酸序列编码。

TNFRSF11B(基因ID 4982)的参考氨基酸序列为NP_002537.3,并可以由NM_002546.3的参考核苷酸序列编码。TNFRSF12A(基因ID 51330)具有参考氨基酸序列NP_057723.1,并且可以由NM_016639.2的参考核苷酸序列编码。TNFRSF13B(基因ID 23495)具有参考氨基酸序列NP_0036584.1,并且可以由NM_012452.2的参考核苷酸序列编码。TNFRSF13C(基因ID 115650)具有NP_443177.1的参考氨基酸序列,并可以由NM_052945.3的参考核苷酸序列编码。TNFRSF14(基因ID 8764)具有NP_001284534.1的参考氨基酸序列,并且可以由NM_001297605.1的参考核苷酸序列编码。TNFRSF17(基因ID 608)具有NP_001183.2的参考氨基酸序列,并且可以由NM_001192.2的参考核苷酸序列编码。TNFRSF18(基因ID 8784)具有NP_004195.2的参考氨基酸序列,并且可以由NM_004186.1的参考核苷酸序列编码。TNFRSF19(基因ID 55504)具有NP_001191387.1的参考氨基酸序列,并且可以由NM_001204458.1的参考核苷酸序列编码。NFRSF21(基因ID 27242)具有参考氨基酸序列NP_055267.1,并且可以由NM_014452.4的参考核苷酸序列编码。TNFRSF25(DR3:基因ID 8718)与配体TNFSF15(TL1A)结合,具有NP_001034753.1的参考氨基酸序列,并且可以由NM_001039664.1的参考核苷酸序列编码。

[0391] 在一些实施方式中,抗体分子可以在恒定结构域(例如,抗体分子的CH3结构域)中不包含抗原结合位点。例如,抗体分子可以在抗体分子的恒定结构域(例如CH3结构域)不包含与CD137结合的抗原结合位点。具体地,抗体分子在抗体分子的恒定结构域中可以不包含CD137抗原结合位点,其中抗原结合位点在恒定结构域的一个或多个结构环中包括修饰,例如在恒定结构域的AB,CD和/或EF结构环中的一个或多个修饰。在一个具体的实施方式中,抗体分子可以不包含位于抗体分子的CH3结构域中的CD137抗原结合位点,其包括分别位于CH3结构域的AB和EF结构环中的第一序列和第二序列,其中第一和第二序列分别具有SEQ ID NO:198和199[FS22-172-003]所示的序列。例如,抗体分子可以不包含SEQ ID NO:200和201[FS22-172-003-AA/FS28-256-271]所示的轻链和重链序列。

[0392] 抗体分子可以与生物活性分子或可检测标记物偶联。在这种情况下,抗体分子可以称为偶联物。此类偶联物可用于治疗和/或诊断本文所述的疾病。

[0393] 例如,生物活性分子可以是免疫系统调节剂,例如细胞因子,优选人细胞因子。例如,细胞因子可以是刺激T细胞活化和/或增殖的细胞因子。与抗体分子偶联的细胞因子的实例包括IL-2,IL-10,IL-12,IL-15,IL-21,GM-CSF和IFN-γ。

[0394] 或者,生物活性分子可以是配体陷阱,例如细胞因子(例如TGF-β或IL-6)的配体陷阱。

[0395] 作为另一替代方案,生物活性分子可以是配体,例如CD137L,OX40L,TRAIL,CD40L,CD27L或GITRL。

[0396] 作为另一替代方案,生物活性分子可以是药物,例如微管蛋白聚合抑制剂(例如澳瑞他汀(auristatin)),微管蛋白解聚剂(例如美登素(maytansine)),DNA链断裂诱导剂(例如卡利奇霉素(calicheamicin)),DNA烷基化剂(例如倍癌霉素(duocarmycin))或RNA聚合酶抑制剂(例如α-毒蕈环肽)。

[0397] 作为另一替代方案,生物活性分子可以是治疗性放射性同位素。

[0398] 放射免疫疗法用于,例如癌症治疗。适用于放射免疫疗法的治疗性放射性同位素是本领域已知的,包括钇90,碘131,铋213,砹211,镥177,铼188,铜67,锕225,碘125。

[0399] 可以与抗体分子偶联的合适的可检测标记在本领域中是已知的,包括放射性同位素,例如碘125,碘131,钇90,铟111和锝99;荧光染料,例如荧光素,若丹明,藻红蛋白,德克萨斯红和花青染料衍生物,例如Cy7和Alexa750;生色染料,例如二氨基联苯胺;乳胶微球;酶标记,例如辣根过氧化物酶;具有光谱隔离的吸收或发射特性的荧光粉或激光染料;化学部分,例如生物素,可以通过与特定的同源可检测部分,例如标记的亲和素结合来检测。

[0400] 抗体分子可通过任何合适的共价或非共价键,例如二硫键或肽键,与生物活性分子或可检测标记偶联。当生物活性分子是细胞因子时,细胞因子可通过肽接头与抗体分子连接。合适的肽接头是本领域已知的,并且长度可以是5至25、5至20、5至15、10至25、10至20或10至15个氨基酸。

[0401] 在一些实施方式中,生物活性分子可以通过可裂解的接头与抗体分子偶联。接头可使得在治疗部位从抗体分子释放生物活性分子。接头可包括酰胺键(例如肽接头),二硫键或腙。例如,肽接头可以被位点特异性蛋白酶切割,二硫键可能会被细胞质的还原环境裂解,腙可以被酸介导的水解裂解。

[0402] 偶联物可以是包含抗体分子和生物活性分子的融合蛋白。在这种情况下,可以通过肽接头或肽键将生物活性分子与抗体分子偶联。在抗体分子是多链分子的情况下,例如在抗体分子是Fcab或包含Fcab或是mAb^2的情况下,生物活性分子可以与抗体分子的一条或多条链偶联。例如,生物活性分子可以与mAb^2分子的一条或两条重链偶联。融合蛋白的优点是易于生产和纯化,有利于临床级材料的生产。

[0403] 本发明还提供了分离的核酸分子或编码本发明的抗体分子的分子。技术人员使用本领域众所周知的方法来制备这种核酸分子将没有困难。

[0404] 所述一个或多个核酸分子可以编码VH结构域和/或VL结构域,优选以下抗体的VH结构域和VL结构域:抗体FS28-256-271,FS28-024-052,FS28-256-021,FS28-256-012,FS28-256-023,FS28-256-024,FS28-256-026,FS28-256-027,FS28-256-001,FS28-256-005,FS28-256-014,FS28-256-018,FS28-256,FS28-024-051,FS28-024-053或FS28-024,优选抗体FS28-256-271或FS28-024-052,最优选抗体FS28-256-271。

[0405] 例如,编码分别如SEQ ID NO:181、40、110、110、122、110、122、110、64、64、116、122、70、31、50和9所示的抗体FS28-256-271,FS28-024-052,FS28-256-021,FS28-256-012,FS28-256-023,FS28-256-024,FS28-256-026,FS28-256-027,FS28-256-001,FS28-256-005,FS28-256-014,FS28-256-018,FS28-256,FS28-024-051,FS28-024-053和FS28-024的VH结构域的核酸分子。

[0406] 编码分别如SEQ ID NO:57、19、94、80、94、54、54、57、94、54、80、80、80、19、19和19所示的抗体FS28-256-271,FS28-024-052,FS28-256-021,FS28-256-012,FS28-256-023,FS28-256-024,FS28-256-026,FS28-256-027,FS28-256-001,FS28-256-005,FS28-256-014,FS28-256-018,FS28-256,FS28-024-051,FS28-024-053和FS28-024的VL结构域的核酸分子。

[0407] 在一个优选的实施方式中,核酸分子编码重链和/或轻链,优选以下抗体的重链和轻链:FS28-256-271,FS28-024-052,FS28-256-021,FS28-256-012,FS28-256-023,FS28-256-024,FS28-256-026,FS28-256-027,FS28-256-001,FS28-256-005,FS28-256-014,FS28-256-018,FS28-256,FS28-024-051,FS28-024-053或FS28-024,优选抗体FS28-256-

271或FS28-024-052,最优选抗体FS28-256-271。

[0408] 例如,编码分别如SEQ ID NO:179、38、108、108、126、108、126、108、84、84、120、126、68、29、48和7所示的抗体FS28-256-271,FS28-024-052,FS28-256-021,FS28-256-012,FS28-256-023,FS28-256-024,FS28-256-026,FS28-256-027,FS28-256-001,FS28-256-005,FS28-256-014,FS28-256-018,FS28-256,FS28-024-051,FS28-024-053和FS28-024的重链(具有LALA突变)的核酸分子。

[0409] 例如,编码分别如SEQ ID NO:177、36、106、106、124、106、124、106、82、88、118、124、66、27、46和6所示的抗体FS28-256-271,FS28-024-052,FS28-256-021,FS28-256-012,FS28-256-023,FS28-256-024,FS28-256-026,FS28-256-027,FS28-256-001,FS28-256-005,FS28-256-014,FS28-256-018,FS28-256,FS28-024-051,FS28-024-053和FS28-024的重链(无LALA突变)的核酸分子。

[0410] 编码分别如SEQ ID NO:96、17、92、78、92、91、91、96、92、91、78、78、78、17、17和17所示的抗体FS28-256-271,FS28-024-052,FS28-256-021,FS28-256-012,FS28-256-023,FS28-256-024,FS28-256-026,FS28-256-027,FS28-256-001,FS28-256-005,FS28-256-014,FS28-256-018,FS28-256,FS28-024-051,FS28-024-053和FS28-024的轻链的核酸分子。

[0411] 当核酸编码本发明的抗体分子的VH和VL结构域,或重链和轻链时,两个结构域或链可以被编码在两个分开的核酸分子上。

[0412] 分离的核酸分子可以用于表达本发明的抗体分子。通常将以重组载体的形式提供核酸用于表达。因此,本发明的另一方面提供了包含如上所述的核酸的载体。可以选择或构建合适的载体,其包含合适的调控序列,包括启动子序列,终止子片段,聚腺苷酸化序列,增强子序列,标记基因和其他合适的序列。优选地,载体包含合适的调控序列以驱动核酸在宿主细胞中的表达。载体可以是质粒,病毒,例如噬菌体或噬菌粒,视情况而定。

[0413] 如本文所述的核酸分子或载体可以被引入宿主细胞。用于将核酸或载体引入宿主细胞的技术在本领域中是已经建立的,并且可以采用任何合适的技术。适用于产生重组抗体分子的一系列宿主细胞是本领域已知的,包括细菌,酵母,昆虫或哺乳动物宿主细胞。优选的宿主细胞是哺乳动物细胞,例如CHO,NSO或HEK细胞,例如HEK293细胞。

[0414] 本发明的另一方面提供了一种产生本发明的抗体分子的方法,该方法包括在宿主细胞中表达编码该抗体分子的核酸,并任选地分离和/或纯化由此产生的抗体分子。培养宿主细胞的方法是本领域众所周知的。该方法可以进一步包括分离和/或纯化抗体分子。纯化重组抗体分子的技术是本领域众所周知的,包括例如HPLC,FPLC或亲和色谱,例如使用蛋白质A或蛋白质L。在一些实施方式中,可以使用抗体分子上的亲和标签进行纯化。该方法还可以包括将抗体分子配制成药物组合物,任选地与如下所述的药学上可接受的赋形剂或其他物质一起。

[0415] 如上所述,MSLN在肿瘤细胞的表面表达,可溶性MSLN的高表达水平与几种癌症的不良预后相关。已经研究了抗MSLN抗体作为抗癌治疗剂。这些抗MSLN抗体通过其ADCC活性诱导直接的细胞杀伤,或以ADC的形式使用。

[0416] 因此,预期本文所述的抗体分子可用于治疗癌症。因此,本发明的相关方面提供:

[0417] (i)本文所述的抗体分子在治疗个体的癌症的方法中的用途,

[0418] (ii)本文所述的抗体分子在制备用于治疗个体癌症的药物中的用途;和,

[0419] (iv)一种治疗个体癌症的方法,其中所述方法包括向所述个体施用治疗有效量的本文所述的抗体分子。

[0420] 该个体可以是患者,优选是人类患者。

[0421] 与可溶性MSLN相比,已显示本发明的抗体分子优先结合存在于癌细胞表面的MSLN。因此,使用本发明的抗体分子治疗的癌症优选表达或已经确定表达MSLN。更优选地,待治疗的癌症细胞在其细胞表面包含或已经确定包含MSLN,即包含细胞表面结合的MSLN。

[0422] 其中所述抗体分子包含免疫细胞抗原(例如TNFRSF成员)的第二抗原结合位点。例如,在抗体分子的恒定结构域中,癌症优选包含或已经确定包含表达TNFRSF成员的肿瘤浸润淋巴细胞(TIL)。具体地,TIL优选在其细胞表面上包含或已经确定包含TNFRSF成员。

[0423] 确定抗原在细胞表面上的存在的方法是本领域已知的,并且包括例如流式细胞术。

[0424] 癌症可以是原发性或继发性癌症。因此,本文所述的抗体分子可用在治疗个体癌症的方法中,其中所述癌症是原发性肿瘤和/或肿瘤转移。

[0425] 使用本发明的抗体分子治疗的癌症可以是实体癌。

[0426] 癌症可以选自下组:间皮瘤,胰腺癌,卵巢癌,肺癌(例如小细胞肺癌和非小细胞肺癌),食道癌,乳腺癌,胃癌,胆管癌,结肠癌,胸腺癌,子宫内膜癌,头颈癌,肉瘤(例如双相性滑膜癌肉瘤,卡波西肉瘤,成骨肉瘤,横纹肌肉瘤或软组织肉瘤),增生性小圆形细胞瘤,白血病(例如急性淋巴细胞性白血病,慢性淋巴细胞白血病,急性粒细胞白血病,慢性粒细胞白血病,毛细胞白血病或骨髓性白血病),肾上腺皮质癌,膀胱癌,脑癌,宫颈癌,宫颈增生,睾丸绒毛膜癌,原发性血小板增多症,泌尿生殖道癌,神经胶质瘤,胶质母细胞瘤,淋巴瘤(如霍奇金病或非霍奇金淋巴瘤),恶性类癌,恶性高钙血症,黑色素瘤(也称为恶性黑色素瘤),恶性胰腺胰岛素瘤,甲状腺髓样癌,多发性骨髓瘤,蕈样肉芽肿,神经母细胞瘤,真性红细胞增多症,原发性脑癌,原发性巨球蛋白血症,前列腺癌,肾细胞癌,皮肤癌,鳞状细胞癌,胃癌,睾丸癌,甲状腺癌和威尔姆斯瘤。

[0427] 优选地,癌症选自下组:间皮瘤,胰腺癌,卵巢癌,肺癌,食道癌,乳腺癌,胃癌,胆管癌,结肠癌,胸腺癌,子宫内膜癌,头颈癌,双相性滑膜癌肉瘤和增生性小圆形细胞瘤。

[0428] 更优选地,癌症选自下组:间皮瘤,胰腺癌,卵巢癌和肺癌。

[0429] 癌症的特征是恶性癌细胞的异常增殖。当提到特定类型的癌症,例如乳腺癌时,这是指相关组织例如乳房组织的恶性细胞的异常增殖。位于乳房中但是为另一组织例如卵巢组织的恶性细胞异常增殖的结果的继发性癌症不是本文所指的乳腺癌,而是卵巢癌。

[0430] 在癌症的情况下,治疗可以包括抑制癌症的生长,包括完全的癌症缓解,和/或抑制癌症的转移,以及抑制癌症的复发。癌症的生长通常指许多指标中的任何一个,这些指标表明癌症内的形态已发展为更发达的形态。因此,用于测量对癌症生长的抑制的指标包括癌细胞存活率的降低,肿瘤体积或形态的降低(例如,如使用计算机断层扫描(CT),超声检查或其他成像方法所确定的),肿瘤生长延迟,破坏肿瘤血管,改善迟发型超敏性皮肤试验的性能,增加抗癌免疫细胞或其他抗癌免疫反应的活性以及降低肿瘤特异性抗原的水平。激活或增强个体中对癌性肿瘤的免疫应答可以提高个体抵抗癌症生长的能力,特别是已经存在于受试者中的癌症的生长和/或降低个体中癌症生长的倾向。

[0431] 尽管可以单独施用抗体分子,但是抗体分子通常会以药物组合物的形式施用,该药物组合物除了抗体分子之外还可以包含至少一种组分。因此,本发明的另一方面提供了包含如本文所述的抗体分子的药物组合物。还提供了一种方法,其包括将抗体分子配制成药物组合物。

[0432] 除抗体分子外,药物组合物还可包含药学上可接受的赋形剂,载体,缓冲液,稳定剂或本领域技术人员众所周知的其他材料。如本文所用,术语“药学上可接受的”是指化合物,材料,组合物和/或剂型,其在合理的医学判断范围内,适用于与受试者(例如人)的组织接触而没有过度的毒性,刺激,过敏反应或其他问题或并发症,并具有合理的获益/风险比。在与制剂的其他成分相容的意义上,每种载体,赋形剂等也必须是“可接受的”。载体或其他材料的精确性质将取决于给药途径,这可以通过输注,注射或任何其他合适的途径进行,如下所述。

[0433] 对于肠胃外,例如皮下或静脉内给药,例如通过注射,包含抗体分子的药物组合物可以是肠胃外可接受的水溶液形式,其不含热原并且具有合适的pH,等渗性和稳定性。本领域相关技术人员能够使用例如等渗媒介物,例如氯化钠注射液,林格注射液,乳酸钠林格注射液来制备合适的溶液。可以根据需要使用防腐剂,稳定剂,缓冲剂,抗氧化剂和/或其他添加剂,包括诸如磷酸盐,柠檬酸盐和其他有机酸的缓冲剂;抗氧化剂,例如抗坏血酸和蛋氨酸;防腐剂(例如十八烷基二甲基苄基氯化铵;氯化六甲双铵;苯扎氯铵;苄索氯铵;苯酚,丁醇或苄醇;对羟基苯甲酸烷基酯,例如对羟基苯甲酸甲酯或对羟基苯甲酸丙酯;邻苯二酚;间苯二酚;环己醇;3’-戊醇和间甲酚);低分子量多肽;蛋白质,例如血清白蛋白,明胶或免疫球蛋白;亲水聚合物,例如聚乙烯吡咯烷酮;氨基酸,例如甘氨酸,谷氨酰胺,天冬酰胺,组氨酸,精氨酸或赖氨酸;单糖,二糖和其他碳水化合物,包括葡萄糖,甘露糖或糊精;螯合剂,例如EDTA;糖,例如蔗糖,甘露醇,海藻糖或山梨糖醇;成盐的反离子,例如钠;金属配合物(例如锌蛋白络合物);和/或非离子表面活性剂,例如TWEEN™,PLURONICS™或聚乙二醇(PEG)。

[0434] 在一些实施方式中,可以以冻干形式提供抗体分子以在施用前重构。例如,冻干的抗体分子可在施用给个体之前在无菌水中重构并与盐水混合。

[0435] 可以以“治疗有效量”给药,这足以显示出对个体的益处。实际给药的量以及给药的速率和时间过程将取决于所治疗的性质和严重程度,所治疗的特定个体,个体的临床状况,疾病原因,组合物的递送部位,抗体分子的类型,给药方法,给药时间表以及医学从业人员已知的其他因素。治疗处方,例如关于剂量等的决定,是由全科医生和其他医生负责的,并且可能取决于症状的严重程度和/或所治疗疾病的进展。适当剂量的抗体分子是本领域众所周知的(Ledermann等,1991;Bagshawe等,1991)。可以使用本文所述的具体剂量,或适用于所施用抗体分子的在医师手册(2003)中指出的剂量。抗体分子的治疗有效量或合适剂量可以通过在动物模型中比较体外活性和体内活性来确定。在小鼠和其他试验动物中将有效剂量外推至人的方法是已知的。精确剂量将取决于许多因素,包括所治疗的区域的大小和位置以及抗体分子的精确性质。

[0436] 对于全身性施用,典型的抗体剂量范围为100μg至1g,对于局部施用,典型的抗体剂量范围为1μg至1mg。可以给予初始较高的负荷剂量,然后给予一个或多个较低的剂量。这是对成年个体进行单次治疗的剂量,可以针对儿童和婴儿按比例调整剂量,也可以针对其

他抗体形式按分子量调整剂量。

[0437] 根据医生的判断,可以每天,每周两次,每周或每月一次的间隔重复治疗。个体的治疗方案可能取决于抗体组合物的药代动力学和药效学性质,给药途径和所治疗病症的性质。

[0438] 治疗可以是周期性的,并且两次给药之间的时间可以是大约两周或更长时间,例如,大约三周或更长时间,大约四周或更长时间,大约每月一次或更长时间,大约五周或更长时间,或者大约六周或更长时间。例如,治疗可以是每两到四周或每四到八周。合适的制剂和给药途径如上所述。

[0439] 在癌症治疗的背景下,本文所述的抗体分子可以与另一种抗癌疗法或治疗剂(例如已证明适用于或预期适用于有关癌症的治疗的抗癌疗法或治疗剂)联合施用给个体。例如,抗体分子可以与化学治疗剂,放疗,免疫治疗剂,抗肿瘤疫苗,溶瘤病毒,过继细胞转移(ACT)治疗(例如过继NK细胞治疗或嵌合抗原受体(CAR)T细胞,自体肿瘤浸润淋巴细胞(TIL)或γ/δT细胞,或激素治疗剂治疗组合施用。

[0440] 不希望被理论所束缚,人们认为本文所述的抗体分子可在抗癌治疗中充当佐剂,其中所述抗体分子包含免疫细胞抗原例如TNFRSF受体的第二抗原结合位点。具体而言,人们认为例如与化学疗法和/或放射疗法联合或与抗肿瘤疫苗联合对个体施用抗体分子比单独使用化学疗法和/或放射疗法或抗肿瘤疫苗将引发更大的针对癌症的免疫反应。

[0441] 与本文所述的抗体分子组合施用的一种或多种化学治疗剂可以选自下组:紫杉烷类,细胞毒性抗生素,酪氨酸激酶抑制剂,PARP抑制剂,B-Raf酶抑制剂,MEK抑制剂,c-MET抑制剂,VEGFR抑制剂,PDGFR抑制剂,烷基化剂,铂类似物,核苷类似物,抗叶酸剂,沙利度胺(thalidomide)衍生物,抗肿瘤化学治疗剂等。紫杉烷类包括多烯紫杉醇,紫杉醇和白蛋白结合型紫杉醇;细胞毒性抗生素包括放线菌素,博来霉素和蒽环类药物,如阿霉素,米托蒽醌和戊柔比星(valrubicin);酪氨酸激酶抑制剂包括埃罗替尼(erlotinib),吉非替尼(gefitinib),阿昔替尼(axitinib),PLX3397,伊马替尼(imatinib),拷贝替尼(cobemitinib)和曲美替尼(trametinib);PARP抑制剂包括吡拉帕尼(piraparib);B-Raf酶抑制剂包括维罗非尼(vemurafenib)和达拉菲尼(dabrafenib);烷基化剂包括达卡巴嗪(dacarbazine),环磷酰胺和替莫唑胺(temozolomide);铂类似物包括卡铂,顺铂和奥沙利铂;核苷类似物包括阿扎胞苷(azacitidine),卡培他滨(capecitabine),氟达拉滨(fludarabine),氟尿嘧啶(fluorouraci l)和吉西他滨(gemcitabine);抗叶酸药包括甲氨蝶呤和培美曲塞(pemetrexed)。适用于本发明的其他化学治疗剂包括非昔替尼(Defactinib),恩替司他(entinostat),艾瑞布林(eribulin),伊立替康(irinotecan)和长春碱(vinblastine)。与本文所述的抗体分子一起给药的优选治疗剂是喷司他丁(pentostatin),环磷酰胺,顺铂,培美曲塞,紫杉醇,卡铂,吉西他滨,阿霉素,长春瑞滨(vinorelbine),多烯紫杉醇或依托泊苷(etoposide)。

[0442] 与本文所述的抗体分子联合给药的放射疗法可以是体外放射治疗(例如调强适形放射治疗(IMRT),立体定向放射治疗(SBRT),图像引导放疗(IGRT),术中放射治疗(IORT),电子疗法或电子束疗法(EBT),表层放射治疗(SRT))或内介入放射治疗(例如近距放射治疗,放射性同位素或放射性核素疗法,SIRT。放射疗法优选常规的体外放射治疗,外照射放疗(EBRT),立体定向放射疗法或近距放射治疗。

[0443] 与本文所述的抗体分子组合施用的免疫治疗剂可以是治疗性抗体分子,核酸,细胞因子或基于细胞因子的疗法。例如,治疗性抗体分子可以结合免疫调节分子,例如抑制性检查点分子或免疫共刺激分子,先天免疫系统的受体或肿瘤抗原,例如细胞表面肿瘤抗原或可溶性肿瘤抗原。治疗性抗体分子可以结合的免疫调节分子的例子包括抑制性检查点分子,例如CTLA-4,LAG-3,TIGIT,TIM-3,VISTA,PD-L1,PD-1或KIR,免疫共刺激分子例如OX40,CD40,CD137,GITR,CD27或ICOS,其他免疫调节分子,例如CD47,CD73,CSF-1R,HVEM,TGFB或CSF-1。治疗性抗体分子可以结合的先天免疫系统的受体的实例包括TLR1,TLR2,TLR4,TLR5,TLR7,TLR9,RIG-1样受体(例如RIG-1和MDA-5)和STING。

[0444] 与本文所述的抗体分子组合施用的核酸可以是siRNA。

[0445] 细胞因子或基于细胞因子的疗法可以选自下组:IL-2,偶联的IL-2的前药,GM-CSF,IL-7,IL-12,IL-9,IL-15,IL-18,IL-21和I型干扰素。

[0446] 用于治疗癌症的抗肿瘤疫苗既已在临床中实施,又在科学文献中进行了详细讨论(例如Rosenberg,S.2000)。这主要涉及通过使用这些细胞作为疫苗接种方法来提示免疫系统对自体或同种异体癌细胞表达的各种细胞标记物作出反应的策略,无论是否使用粒细胞-巨噬细胞集落刺激因子(GM-CSF)。GM-CSF在抗原呈递方面引起强烈反应,与上述策略一起使用时效果特别好。

[0447] 化学治疗剂,放射疗法,免疫治疗剂,抗肿瘤疫苗,溶瘤病毒,ACT疗法或激素疗法的药剂优选为针对所涉及癌症的化学治疗剂,放射疗法,免疫治疗剂,抗肿瘤疫苗,溶瘤病毒,ACT疗法或激素治疗药物,即化疗剂,放射疗法,免疫治疗剂,抗肿瘤疫苗,溶瘤病毒,ACT疗法或用于激素疗法的药剂,已证明在治疗所涉及的癌症方面是有效的。选择合适的化学治疗剂,放疗,免疫治疗剂,抗肿瘤疫苗,溶瘤病毒,ACT治疗或激素治疗剂已被证明对所涉及的癌症有效,这完全在熟练技术人员的能力范围内。

[0448] 本发明的抗体分子可用于检测MSLN,特别是用于检测固定化的MSLN,例如细胞表面结合的MSLN。抗体分子可以偶联至可检测标记,如本文其他地方所述。

[0449] 因此,本发明涉及抗体分子在检测样品中固定化MSLN是否存在,优选在其细胞表面上包含MSLN的细胞是否存在中的用途。

[0450] 还提供了一种检测MSLN的体外方法,其中该方法包括将抗体分子与目标样品一起孵育,以及检测抗体分子与样品的结合,其中抗体与样品的结合表明存在固定化的MSLN。例如,可以使用ELISA检测抗体分子与样品的结合。

[0451] 在一个优选的实施方式中,本发明涉及检测在其细胞表面包含MSLN的细胞的体外方法,其中该方法包括将抗体分子与目标细胞样品一起孵育,并确定抗体分子与存在于样品中的细胞的结合,其中抗体与样品中存在的细胞的结合表明在其细胞表面存在包含MSLN的细胞。检测抗体分子与细胞结合的方法是本领域已知的,包括ELISA和流式细胞术。

[0452] 本发明的抗体分子可以应用于癌症的检测,诊断和/或预后中。癌症可以是能用本文所述的本发明的抗体分子治疗的癌症。

[0453] 因此,提供了本发明的相关方面;

[0454] (i)本文所述的抗体分子在检测个体的癌症,诊断癌症,确定癌症预后或监测癌症预后的方法中的用途;

[0455] (ii)本文所述的抗体分子在制备用于检测癌症,诊断癌症,确定癌症预后或监测

癌症预后的诊断产品中的用途;

[0456] (iii)使用本文所述的抗体分子在个体中检测癌症,诊断癌症,确定癌症预后或监测癌症预后的方法;和

[0457] (iv)用于检测,诊断,预后或监测个体癌症预后的方法的试剂盒,该试剂盒包含本文所述的抗体分子。

[0458] 该方法可以包括向个体施用本发明的抗体分子,并确定该抗体分子在该个体体内某个部位是否存在,其中该抗体分子在该体内某个部位的存在表明肿瘤的存在,特别是包含在其细胞表面表达MSLN的细胞的肿瘤的存在。

[0459] 在一个优选的实施方式中,该方法包括在从个体获得的样品中确定在其细胞表面上表达MSLN的细胞是否存在,其中在其细胞表面上表达MSLN的细胞的存在表明该个体患有癌症。

[0460] 在一个替代的优选实施方式中,该方法包括在从个体获得的肿瘤样品中确定在其细胞表面表达MSLN的肿瘤细胞是否存在,其中在其细胞表面表达MSLN的肿瘤细胞的存在表明该个体的预后较差,例如,与患有相同癌症但不包含在其细胞表面表达MSLN的细胞的个体相比,癌症转移的风险更高。

[0461] 癌症可以是本文所指的癌症。优选地,癌症选自下组:间皮瘤,胰腺癌,卵巢癌,肺癌,食道癌,乳腺癌,胃癌,胆管癌,结肠癌,胸腺癌,子宫内膜癌,头颈癌,双相性滑膜癌肉瘤和增生性小圆形细胞瘤。更优选地,癌症选自下组:间皮瘤,胰腺癌,卵巢癌和肺癌。

[0462] 鉴于包括以下实验示例的本公开,本发明的其他方面和实施方式对于本领域技术人员而言将是显而易见的。

[0463] 本说明书中提及的所有文件均通过引用整体并入本文。

[0464] 在本文中使用的“和/或”应被理解为两个指定的特征或部件中的每个具有或不具有另一个的具体公开。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,就像每个在本文中分别列出一样。

[0465] 除非上下文另外指示,否则以上阐述的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,并且等同地适用于所描述的所有方面和实施方式。

[0466] 除非上下文另外指出,否则本发明的其他方面和实施方式向上述方面和实施方式提供了用术语“包含”替换为术语“包含”或“基本上包含”的术语。

[0467] 现在将通过示例的方式并参考上述附图来说明本发明的某些方面和实施方式。

实施例

[0468] 实施例1:抗人MSLN抗体的分离:抗原,选择和筛选

[0469] 间皮素是糖基磷脂酰肌醇(GPI)连接的糖蛋白,被合成为69kDa的前体,并被蛋白水解加工成30kDa的NH2末端分泌形式(称为巨核细胞增强因子或MPF)和40kDa的膜结合间皮素(MSLN)。在患者血清中发现了可溶形式的MSLN,它从肿瘤细胞表面脱落,并由膜结合MSLN的可变剪接或肿瘤坏死因子-α转化酶(TACE)生成。已知这种脱落肿瘤的抗原会形成漏槽(sink),其可充当治疗性抗体的诱饵(Lee等人,2018),因此必须克服这一点才能使抗体与肿瘤上的MSLN结合。为了避免这种漏槽效应,发明人着手分离与可溶性MSLN相比优先结合固定化MSLN的新型抗间皮素抗体,以期与可溶性MSLN相比,这将转化为与膜结合的MSLN

的优先结合。为此,在噬菌体选择和随后的筛选活动中采用了不同形式的MSLN抗原。

[0470] 1.1人,猕猴和小鼠间皮素抗原的产生

[0471] 从百普赛斯(Acrobiosystems)(目录号MSN-H8223)获得了缺乏C端18个氨基酸的重组生物素化人MSLN-His抗原,命名为“hMSLN-His Acro”。为了使在整个抗原上选择的结合物的多样性最大化,在内部生成了全长单体人MSLN抗原,并进行了生物素化以用于噬菌体选择。产生猕猴和小鼠MSLN的目的是为了分离能够与人和猕猴MSLN结合的结合剂,并分别分离鼠类MSLN结合剂。

[0472] 简而言之,MSLN抗原是通过克隆编码人(SEQ ID NO:169)(hMSLN-His-Avi),猕猴(SEQ ID NO:170)(cMSLN-His-Avi)或小鼠(SEDID NO:171)(mMSLN-His-Avi)MSLN的DNA,连同六个C端组氨酸残基和一个Avi序列一起进入使用EcoRI-HF和BamHI-HF限制酶修饰的pFUSE载体(Invivogen货号pfuse-mg2afc2)而产生的。将载体转染到HEK293-6E细胞(加拿大国家研究委员会)中,并使用HisTrap™excel镍柱(GE生命科学,29048586)纯化表达的MSLN。使用BirA生物素-生物素蛋白连接酶反应试剂盒(Avidity LLC,BirA500)对每种抗原进行生物素化,以产生用单个生物素分子标记的单体MSLN抗原。具体而言,将五至十毫克的抗原与BirA酶混合物混合,使酶与底物的摩尔比为1:50。然后按照制造商的建议添加添加剂,在室温下孵育过夜,然后使用HisTrap™excel镍柱(GE生命科学,29048586)纯化重组人、猕猴或小鼠MSLN,以去除过量的游离生物素。

[0473] 通过SEC-HPLC分析表征每种抗原的生物物理特性,以确定是否存在聚集体,并通过PAGE来验证分子的大小。这些抗原的SEC-HPLC显示小于10%的聚集,并且PAGE证实该抗原为单体。ELISA和表面等离振子共振(SPR)用于确认生物素化的MSLN抗原可以被MSLN特异性阳性对照抗体结合(SS1,参见第1.3节;Hassan等人2002和MOR6626参见第7.1节,专利公开号WO 2009/068204 A1)。基于此数据,所有抗原均被认为适合初次选择。

[0474] 1.2噬菌体文库选择

[0475] 合成的天然噬菌粒文库显示了CDR1,CDR2和CDR3中具有随机氨基酸的种系的人Fab结构域(MSM科技),用于选择第1.1节所述的MSLN抗原。

[0476] 最初使用链霉亲和素Dynabeads(赛默飞世尔,11205D),偶联于Dynabeads的Neutravidin结合蛋白(赛默飞世尔,31000)或抗His Dynabeads(赛默飞世尔,10103D)在三轮或四轮的多个活动中选择Fab文库进行分离与生物素化的人,猕猴或小鼠MSLN-His-Avi或hMSLN-His Acro结合的噬菌体。还使用内部产生的全长MSLN抗原进行选择活动,其中人MSLN选择轮次与猕猴MSLN抗原交替进行,目的是分离人和猕猴的交叉反应性克隆。还进行了小鼠MSLN(R&DmMSLN-His 8604-MS)结合剂的选择。使用标准噬菌体选择和噬菌体回收步骤。

[0477] 为了获得与MSLN抗原不同区域结合的克隆,使用了来自上述初始选择活动的抗MSLN抗体采用表位掩盖策略。简而言之,使用生物素化的人MSLN-His-Avi以500nM的浓度进行初次Fab库的第一轮选择。在第2轮和第3轮中,在存在从初始选择活动中分离的初始抗间皮素mAb蛋白混合物(FS28-004,FS28-024,FS28-026,FS28-091和FS28-97,每个mAb 500nM)的存在下,测试了500nM(第2轮)或100nM(第3轮)生物素化的猕猴MSLN-His-Avi的噬菌体结合力。这些表位掩蔽选择导致输出效价降低,表明选择策略正在起作用,因为已鉴定出更少的结合剂。与早期选择活动中的克隆相比,这导致了针对MSLN其他区域的克隆(FS28-243,

FS28-255和FS28-256,请参阅第2.1.3节)的识别。

[0478] 1.3筛选以鉴定抗MSLN抗体

[0479] 通过噬菌体ELISA筛选来自所有选择的第3轮和第4轮输出的约2000个克隆,以结合至25nM固定的生物素化的hMSLN-His Acro、全长生物素化的人或猕猴MSLN-His-Avi,与该轮选择中使用的抗原一致。包括链霉亲和素板或固定有无关生物素化His标记抗原的板作为阴性对照。选择具有比阴性对照的信号高至少4倍的MSLN结合信号的克隆,并对它们的可变区进行测序,从而鉴定出156种独特的VH/VL序列组合,随后被选择进行可溶性表达。从包括表位掩蔽选择在内的所有选择活动中选择克隆。对于每个克隆,将VH和VL分别克隆到含有CH1,CH2(在CH2结构域中有LALA突变)(Bruhns等,2009;Hezareh等,2001)和CH3结构域或CL结构域的pTT5表达载体(加拿大国家研究委员会)。将产生的具有LALA突变(AA)的pTT5-FS28VH和pTT5-FS28VL载体瞬时共转染到HEK293-6E细胞中,并以完整的IgG1分子形式产生这些克隆。抗体保留在上清液中或通过mAb Select SuRe蛋白A柱纯化,并按照以下说明进行进一步测试。使用相同的方法,克隆SS1的VH和VL区以及抗鸡卵清溶菌酶抗体HelD1.3并以IgG1LALA形式表达,分别产生G1-AA/SS1(SEQ ID No 167和168)和G1-AA/HelD1.3(SEQ ID No 165和166),分别用作阳性和阴性对照。

[0480] 实施例2:初始抗MSLN单克隆抗体的鉴定

[0481] 抗间皮素单克隆抗体具有广泛的潜在应用,包括其用作能够诱导ADCC的治疗剂,用作免疫毒素递送、ADC和双特异性抗体生成的肿瘤靶向臂等。抗间皮素mAb的所需特性取决于应用,因此,本发明人着手确定一组与膜结合的人和猕猴MSLN结合的,具有多种亲和力且能够靶向不同MSLN的区域的mAb。为此,进行了包括ELISA,Biacore阻断测定和细胞结合在内的一组筛选测定,以及其中比较了与MSLN的结合区域的测定。

[0482] 2.1筛选与重组MSLN的结合

[0483] 2.1.1结合ELISA

[0484] 通过ELISA筛选了包含可溶性抗MSLN结合克隆或纯化的克隆的HEK293-6E上清液与人MSLN-His Acro,hMSLN-His-Avi的结合以及对于某些活动,与cMSLN-His-Avi的结合。简而言之,将25nM的hMSLN-His Acro,hMSLN-His-Avi,cMSLN-His-Avi或无关的His标记抗原于4℃在maxisorp平板上包被过夜。第二天,将板用300μl含0.05%Tween20和2%Marvel牛奶(Marvel奶粉)的PBS封闭。将含有抗MSLN mAb的上清液或纯化的蛋白质在室温下孵育1小时,并用与辣根过氧化物酶(HRP)偶联的小鼠抗人Fc-IgG抗体检测其结合。显示与无关抗原结合或与人和猕猴抗原都不交叉反应的克隆被丢弃。此外,与截短的MSLN抗原hMSLN-His Acro结合但不与全长MSLN抗原MSLN-His-Avi结合的克隆后续也没有被使用,因为预期全长抗原将更代表表达MSLN的细胞的细胞表面上的抗原构象。

[0485] 间皮素是一种糖蛋白,其糖基化模式可能会因物种和组织而异。为了确保抗体具有与MSLN结合的特异性,还测试了抗MSLN结合克隆与糖基化和去糖基化MSLN的差异结合。使用PNGase F酶(NEB,P0704L)在37℃下将生物素化的hMSLN-His-Avi糖基化24小时,使用Amicon超离心过滤器(密理博,UFC901024)纯化,并以25nM包被在maxisorp板上。使用小鼠抗人Fc-IgG-HRP(西格玛,A0170)检测独特的抗间皮素mAb与MSLN的ELISA结合。与糖基化的MSLN抗原相比,与去糖基化的MSLN抗原的结合信号降低超过2倍的克隆被排除在初始抗MSLN结合的mAb组中。

[0486] 2.1.2BIAcore筛选

[0487] 使用胺偶联试剂盒(GE保健公司,BR10050),将人MSLN-His-Avi固定在CM5系列SBIAcore传感器芯片(GE保健公司,BR100530)的流通池2上,使其具有大约200个响应单位(RU)。流通池1留空以进行减法。用HBS-EP+(GE保健公司)将HEK293-6E上清液或纯化的蛋白质调节至每个样品约50nM抗MSLNmAb。将样品以30μl/min的速度在流通池1和2上注入2.5分钟,然后在HBS-EP缓冲液中解离2.5分钟。通过以30μl/min的速率注入pH 1.5的10mM甘氨酸(GE保健公司,BR100354)持续30秒来实现再生。使用BIAevaluation 3.2软件(GE保健公司)分析减去的数据(流通池2-流通池1)。在该实验中从结合ELISA中测试的86个克隆中,有39个克隆在50nM时显示出大于10RU的结合反应,因此被选择用于重新表达,纯化和进一步筛选。

[0488] 2.1.3基于MSLN结合的区域的抗体合并

[0489] 基于ELISA和Biacore筛选数据,然后在合并测定中测试克隆,其中在另一个单克隆抗体存在下,通过Octet(ForteBio)上的生物膜层干涉技术(BLI)测试单克隆抗体与人MSLN的结合。

[0490] 简而言之,将生物素化的hMSLN-His-Avi(5μg/ml)与链霉亲和素尖端(tips)(ForteBIO,18-5020)结合5分钟。在1×动力学缓冲液(FortéBIO,18-1092)中将G1-AA/SS1稀释至200nM,并与hMSLN-His-Avi结合5分钟。接下来,评估包含200nM的测试mAb和200nM G1-AA/SS1的混合物的结合,持续5分钟。将其与在没有结合的G1-AA/SS1的情况下测试mAb与hMSLN-His-Avi的结合进行比较,以确定在没有SS1的情况下(即,在没有竞争结合的情况下)可能结合的最大程度。如果两种抗体竞争与MSLN相同区域的结合,则测试抗体将无法结合。

[0491] 这些使用G1-AA/SS1进行的合并实验表明,测试的大多数FS28谱系抗体(23个中的19个)在G1-AA/SS1存在时无法结合MSLN,因此可以归因于结合与G1-AA/SS1相似的区域。已经报道了Fab形式的SS1抗体的MSLN结合位点(Ma等人,2012),并且被定义为包含也与MUC16结合有关的氨基酸7至64的N末端区域。大多数分离的抗MSLN结合物结合到该区域或类似区域的事实表明,这些氨基酸在重组抗原中暴露良好。鉴定出另外四个克隆FS28-185、FS28-243、FS28-255和FS28-256,它们显示与G1-AA/SS1结合MSLN的部分竞争或没有竞争,这些克隆彼此之间的合并揭示了这些克隆代表了另外两个独立的表位组,即能够与MSLN的另外两个不同区域结合。FS28-185、FS28-243和FS28-255都分配给一个表位组(“表位组2”),而FS28-256分配给一个单独的表位组(“表位组3”)。这些结果表明,在1.2节中的表位掩蔽选择是成功的,因为鉴定了与MSLN的多个区域结合的抗体。

[0492] 2.1.4亲和力

[0493] 对于2.1.3中描述的每个表位组,使用与2.1.2部分中描述的相同的方法测定结合动力学,除了将人或猕猴MSLN-His-Avi固定在50或100RU。在3倍稀释度下,在81nM至0.33nM的浓度范围内测试克隆。对结合物进行排名,并从每个表位组中选择最佳结合物:FS28-024、FS28-026和FS28-091均来自表位组1,FS28-185均来自表位组2,FS28-256均来自表位组3。所有这些克隆均显示为猕猴交叉反应,但在这些测试条件下未计算亲和力。所选抗体的亲和力示于表1,其显示在50RU的固定化MSLN获得的亲和力低于在100RU的固定化MSLN抗原获得的亲和力,表明在更高水平的MSLN上结合增加。

[0494] 表1:初始抗间皮素mAb对固定化人间皮素的亲和力

[0495]

mAb (G1-AA 形式)	对固定化人MSLN-His-Avi的亲和力K_D（nM）	
	50 RU	100 RU
FS28-024	0.77	0.23
FS28-026	0.21	0.12
FS28-091	1.24	0.76
FS28-185	37.00	29.57
FS28-256	26.20	23.16

[0496] 2.2MUC16-MSLN阻断测定

[0497] 据报道,MSLN的N末端区域(氨基酸296-359)与糖蛋白MUC16相互作用,这种相互作用可能在癌细胞粘附中起作用(Kaneko等,2009)。在阻断试验中,测试了FS28-024、FS28-026、FS28-091、FS28-185和FS28-256阻断MUC16与间皮素结合的能力。从文献中知道SS1可以阻断MUC16与MSLN的结合(Ma等,2012)。如前所述,我们将其转换为G1-AA/SS1形式,并预期这不会影响其阻断MUC16结合的能力。G1-AA/SS1和对照IgG1抗体(G1-AA/HelD1.3)分别被包括作为阳性和阴性对照。

[0498] 简而言之,将在1×PBS中的重组人MUC16(R&D系统,5809-MU-050)以0.65μg/ml的浓度包被在maxisorp板上于4℃过夜。将板用1×PBS洗涤3次,并用300μl含2%Tween20和2%Marvel牛奶的PBS封闭。将一定浓度的抗MSLN mAb(0.23nM至500nM,3倍稀释)与生物素化的hMSLN-His-Avi抗原(终浓度2μg/ml)以100μl的体积预混合,在室温下放置1小时。除去封闭溶液后,将mAb/MSLN混合物添加到平板中,并在室温下孵育1小时。将板用PBST(1×PBS和0.05%Tween20)洗涤3次,并用链霉亲和素-HRP(赛默飞科技,21126,在1xPBS中以1:1000稀释)在室温下孵育1小时。最后,将板用PBST洗涤3次并用PBS洗涤3次。通过加入100μl TMB 15分钟,然后加入100μl 1M硫酸溶液,使与MUC16结合的MSLN可视化。在450-630nm处读取吸光度(Gen5软件,BioTek)。

[0499] 表2:初始抗间皮素mAb在MUC16-MSLN阻断测定中的活性

[0500]

mAb (G1-AA形式)	MUC16-MSLN阻断活性 IC_{50} (nM)
FS28-024	2.9
FS28-026	5.2
FS28-091	4.4
FS28-185	增强结合
FS28-256	无活性
SS1	4.8
HelD1.3	无活性

[0501] 表位组1克隆FS28-024、FS28-026和FS28-091显示MUC16-MSLN相互作用的剂量依赖性阻断,IC_{50}分别为2.9nM、5.2nM和4.4nM(表2)。观察到的阻断活性类似于G1-AA/SS1。FS28-256没有显示出与阴性对照G1-AA/HelD1.3类似的任何阻断活性。而FS28-185促进了MUC16与MSLN的结合。已经报道了这种现象(专利号为US 8,911,732B2的专利)。这些结果与第2.1.3节中的合并数据一致,因为与MSLN的三个不同区域结合的克隆在配体封闭试验中显示出三种不同的行为。

[0502] 总之,结果表明,选择了一组与MSLN的3个不同区域(表位组)结合的克隆;与MSLN的一个区域结合的抗体会阻断MUC16与MSLN的结合,而与其他两个区域结合的抗体则不会。

[0503] 2.3特异性

[0504] 根据抗体组所结合的MSLN的不同区域,测试了其与MSLN结合的特异性。通过ELISA检测FS28-024、FS28-026、FS28-091、FS28-185和FS28-256的特异性,方法是比较与MSLN的结合以及与其他与细胞粘附有关的分子(例如CEACAM-5、E-钙粘蛋白、血栓调节蛋白和EpCAM)的结合。

[0505] 如第1.2.1节所述,使用类似的方案,其中maxisorp板用1μg/ml的重组人MSLN-His-Avi,人CEACAM-5-His-Fc(Sino Biological,1077-H03H),人E-钙粘蛋白(R&D系统,8505-EC),人血栓调节蛋白(Peprotech,100-58)或人EpCAM-hFc(内部生产)包被。使用抗人Fab-HRP(西格玛,A0293)检测在0.02至1000nM(3倍稀释)的浓度范围内测试抗MSLN mAb的结合。各个分子的阳性对照包括人EpCAM抗体(专利号为US8236308B2的克隆2G8),CEACAM-5抗体(专利号为US8771690B2的克隆hMN15),人E-钙粘蛋白抗体,小鼠IgG2b克隆180215(R&D系统,MAB1838)),人血栓调节蛋白抗体,小鼠IgG1,克隆501733(R&D系统,MAB3947)。使用山羊抗小鼠Fc-HRP(西格玛,A9309)作为二级mAb检测到后两个。

[0506] FS28-024、FS28-026、FS28-091和FS28-185与人MSLN-His-Avi结合(EC_{50}约为0.5nM,最大结合信号为3),但未观察到与测试的任何细胞粘附分子的结合达到1000nM。如预期的那样,阳性对照抗体与它们各自的靶标结合。因此,抗MSLN抗体显示出高水平的特异性。

[0507] 2.4细胞结合

[0508] 分析了五个选择的抗间皮素mAb与人肺癌细胞系NCI-H226上的内源性细胞表面MSLN的结合。

[0509] 简而言之,使用StemPro Accutase(Gibco,A11105-01)从T175细胞培养瓶中收获NCI-H226细胞(ATCC CRL-5826)。将细胞以1200rpm离心3分钟,然后以2×10^6细胞/ml的浓度重悬在冰冷的FACS缓冲液中,该缓冲液由DPBS(生命技术公司,14190169)和1%BSA(西格玛奥德里奇,A7906)组成,将每孔50μl接种到96孔V型平板中(Costar,3894)。将所有测试的mAb在FACS缓冲液中以0.01-200nM的浓度范围(4倍稀释)稀释至120μl。然后离心NCI-H226细胞,除去上清液,并将细胞重悬于100μl的各mAb稀释液中,并在4℃孵育45分钟。用150μl FACS缓冲液通过离心将细胞洗涤两次,重悬于100μl含山羊抗人IgG(γ链特异性)F(ab')2片段-R-藻红蛋白抗体(西格玛,P8047),以1:1000稀释于FACS缓冲液中,并在4℃下孵育45分钟。将细胞用150μl FACS缓冲液洗涤一次,然后用150μl DPBS洗涤,重悬于含1:10.000的DAPI(Biotium,40043)的150μl DPBS中,并在BDCantoII或iQue(Intellicyt)上读数。使用FlowJo v10分析数据,以确定每个孔中活细胞的PE信号几何平均值。

[0510] 细胞结合数据(表3)显示FS28-024、FS28-026和FS28-091全部与NCI-H226上的细胞表面细胞表面MSLN结合,EC_{50}在0.62至1.22nM范围内,阳性对照G1-AA/SS1也是如此。相比之下,FS28-185和FS28-256表现出弱结合,EC_{50}大于30nM,并且最大结合信号(E_{max})低。代表性的结合测定法如图1所示。

[0511] 表3:初始抗间皮素mAb与NCI-H226癌细胞的细胞结合

[0512]

mAb (G1-AA形式)	细胞与NCI-H226结合 (n=3)	
	EC_{50} (nM)	E_{max} (MFI 信号)
FS28-024	0.62	14647
FS28-026	1.08	13650
FS28-091	1.22	11926
FS28-185	37.47	2435
FS28-256	33.13	4246
SS1	0.90	19385

[0513] 2.5初始筛查程序概述

[0514] 从天然噬菌体文库的初步筛选中鉴定出的156种单克隆抗体中,基于一组筛选试验,该筛选试验首先证实了与全长、去糖基化的重组MSLN的结合以及与猕猴MSLN的结合能力,选择了五个抗人MSLN单克隆抗体克隆(FS28-024、FS28-026、FS28-091、FS28-185和FS28-256)。其次,基于它们结合的MSLN区域的多样性(表位组)和MUC16阻断活性对克隆进行分组,并从这些组中选择最高亲和力的结合剂。所得的mAb克隆FS28-024、FS28-026、FS28-091、FS28-185和FS28-256的组结合了MSLN的三个不同区域,其中一个区域(表位组1,包括FS28-024、FS28-026和FS28-091)在体外阻断MUC16与MSLN的结合。五个抗MSLNmAb的组显示出与MSLN的特异性结合,针对重组MSLN和细胞表面MSLN的不同亲和力,并选择用于进一步表征和/或优化,如以下实施例3和4中所述。

[0515] 实施例3:初始抗MSLN单克隆抗体的亲和力成熟和序列优化

[0516] 3.1FS28-185和FS28-256的亲和力成熟度

[0517] 与FS28-024、FS28-026和FS28-091相比,FS28-185和FS28-256对重组MSLN和细胞表面MSLN均具有较弱的亲和力,因此需要进行亲和力成熟。

[0518] 3.1.1FS28-185和FS28-256的亲和力成熟和筛选

[0519] 通过使用NNK引物将5到6个氨基酸的重叠盒随机化,以scFv形式将VH和VLCDR3区域进行亲和力成熟。FS28-185的随机区域为VH G95-M100F和VL S91-A95,FS28-256的随机区域为VH Y95-L100B和VL S91-I96(Kabat编号)。在文库生成之前,对CDR1和CDR3区中的潜在蛋氨酸氧化和脱酰胺位点(FS28-256VL CDR3文库除外)进行了简约诱变。噬菌粒文库是独立生成的,合并后为每个克隆产生一个VH CDR3和一个VL CDR3文库。如初始活动所述进行两轮选择,在第一轮中使用20nM生物素化的人MSLN-His-Avi,在第二轮中使用20或2nM猕猴MSLN-His-Avi。然后测试可溶性scFv(单点浓度)与卵巢癌细胞系OVCAR-3(ATCC®HTB-161™)的结合。使用StemPro Accutase(Gibco,A11105-01)收获OVCAR-3细胞,以1200rpm离心3分钟,然后以2×10^6细胞/ml的浓度重悬在FACS缓冲液(含2%BSA的DPBS)中。将100μl OVCAR-3细胞添加到96孔V型底平板中。将板以1200rpm离心3分钟,并弃去缓冲液。将150μl的scFv加入到细胞中,并在4℃下孵育1小时。包括亲本克隆FS28-185和256的ScFv作为对照。洗涤后,将细胞重悬于100μl的Penta His Alexa-Fluor 647(凯杰,109-546-098)中,并洗涤后再重悬于100μl含Sytox绿色核酸染色剂的DPBS中(英杰S7020,1:10000稀释)。在iQue(Intellicyt公司,IQue Plus)上运行样品,并记录APC的几何平均值。

[0520] 对于FS28-185和FS28-256,均已鉴定出对OVCAR-3细胞具有增强结合力的亲和力成熟克隆。根据细胞结合(MFI大于850)和序列多样性,从FS28-256VHCDR3中选择了10个克隆,从VL CDR3中选择了9个克隆。在该试验中测试的38个FS28-185亲和力成熟的克隆中,从VH CDR3选择中选择了14个,从VL CDR3选择中选择了一个。所选的克隆以mAb^2双特异性抗

体形式进一步表征。

[0521] 3.1.2基于FS28-185和FS28-256的mAb^2的生成

[0522] 为了进一步表征抗MSLN结合物,以mAb^2形式生产了FS28-185或FS28-256亲和力成熟的VH或VL区以及亲本克隆。所得的mAb^2是IgG1抗体,包含FS28-185或FS28-256克隆或衍生自它们的亲和力成熟变体的CDR,在CH2结构域中的LALA突变以及在CH3结构域中的人CD137受体结合位点。这些mAb^2分子分别命名为FS22-053-008-AA/FS28-185(SEQ ID NO:154和195)和FS22-053-008-AA/FS28-256(SEQ ID NO:156和77)和FS22-053-008-AA/FS28-256-x,表示亲和力成熟的子代。mAb^2通过在HEK293-6E细胞中瞬时表达而产生,并在需要时使用mAb Select SuRe蛋白A柱进行纯化。

[0523] 3.1.3FS28-185和FS28-256亲和力成熟克隆对固定化MSLN的亲和力筛选

[0524] 接下来通过Biacore筛选含有mAb^2的亲和力成熟CDR区的结合用于与固定的人和猕猴MSLN-His-Avi的结合。如2.1.2节所述,分析含有FS22-053-008-AA/FS28-185和FS22-053-008-AA/FS28-256亲和力成熟的克隆的HEK293-6E上清液与200RU固定化MSLN的结合。测试了两种浓度的mAb^2,即50和100nM,并将结合与也以mAb^2形式的亲本抗体的结合进行了比较。对结合剂进行排名,并且每个谱系中最好的六种猕猴交叉反应性结合物被重新表达,纯化并在如下文第3.1.4节中所述的细胞结合测定中进行测试。对于FS28-256谱系,然后将具有改进的VH CDR3的克隆与具有改进的VL CDR3的克隆混洗,创建另外九个VH/VL配对,将其作为mAb^2进行生产并进行测试。

[0525] 3.1.4在可溶性MSLN存在下的细胞结合

[0526] 如先前在第1节中讨论的,可溶性MSLN可以充当结合任何抗MSLN抗体的诱饵。因此,在存在和不存在可溶性人MSLN的情况下,筛选亲和力成熟的克隆用于与重组体和细胞表面MSLN的结合。由于可溶性脱落的MSLN缺少7或13个C末端残基(Zhang等人,2011),因此将缺乏18个C末端氨基酸的可商购的人MSLN抗原,MSLN-His Acro用作模拟物。该抗原的使用浓度为20nM,约为可溶性MSLN水平的10-20倍,被发现对于将恶性间皮瘤和肺癌患者定义为MSLN阳性具有诊断价值(Cui等人,2014)。

[0527] 使用OVCAR-3细胞的细胞结合测定与2.4节中所述的测定相似。通过在与细胞混合之前在存在或不存在可溶性MSLN的条件下预孵育抗体并确定预孵育是否影响与细胞表面MSLN的结合,来测试可溶性MSLN的存在的影响。将亲和力成熟的克隆和亲本分子(如前所述,均以mAb^2形式)在FACS缓冲液中稀释,以在96孔V底平板中获得2倍的终浓度。然后将来自每个孔的60μl加入单独的FACS缓冲液或包含60μl的40nM重组hMSLN的FACS缓冲液中(R&D系统,3265-MS-050)(以获得终浓度为20nM hMSLN)并进行预孵育在室温下放置1小时,然后将100μl加入细胞中。使用山羊抗人抗Fcγ Alexa-Fluor 488(Jackson免疫研究,109-546-098)检测结合的抗体。

[0528] 对于FS28-185谱系,与亲本克隆的结合相比,所有亲和力成熟的克隆均显示出与OVCAR-3的细胞结合有所改善(EC_{50}约为7倍)。但是,在存在20nM可溶性MSLN的情况下,这种结合降低,导致EC_{50}升高3至7倍(从1.6-1.8nM至大约5-7.8nM)。对于FS28-256谱系,选择了五个克隆作为该谱系的代表,所有这些克隆的EC_{50}范围从0.9到8.6nM不等。最重要的是,与不存在时相比,在存在20nM可溶性MSLN的情况下保留了结合亲和力,并且结合变化不到2倍。从该数据中,选择用于进一步测试的克隆包括FS28-256-012、FS28-256-021、FS28-256-

023和FS28-256-024。

[0529] 3.2使用NNK的walk策略(walk strategy)的克隆FS28-024的亲和力成熟

[0530] FS28-024以次纳摩尔亲和力与人MSLN结合,但其对猕猴MSLN的亲和力低约5倍(请参阅实施例4,表4)。为了改善与猕猴MSLN的结合,使用了对VH CDR3区域中五个残基的NNK walk策略。

[0531] FS28-024VH和VL的序列已按照3.1.2节中所述的相同mAb^2形式进行了优化。通过在VH CDR3中的RATLF残基(kabat编号95-99)的某个时间使一个氨基酸残基多样化来生成简约诱变文库,从而形成了总共五个独立的文库。用低冗余NNK密码子制成文库,以代表感兴趣位置上的所有可能的氨基酸。正向和反向引物是根据Quickchange Lightning定点诱变试剂盒(安捷伦,200518)的指南设计的,该试剂盒用于创建文库。每个突变体均在HEK293-6E细胞中少量表达,并通过BIAcore筛选上清液,以保留或改善与人和猕猴MSLN-His-Avi的结合。在筛选的84个克隆中,几乎没有保留的结合,其中大多数是T98残基的替代物。重新表达,纯化四个克隆,即FS28-024-51、FS28-024-52、FS28-024-53和FS28-024-060,并确定它们对人和猕猴MSLN的亲和力。仅一个克隆FS28-024-53显示出猕猴交叉反应性的改善,这是通过单个T98V突变实现的(Kabat编号,参见表4,实施例4)。所有四个克隆都被进一步使用,因为它们可能会根据应用提供其他序列和特征。

[0532] 3.3亲和力成熟总结

[0533] 总体而言,通过进一步扩大抗MSLN mAb的种类和多样性,FS28-024、FS28-185和FS28-256谱系的亲和力成熟和序列优化策略是成功的。

[0534] 实施例4:抗MSLN克隆的表征

[0535] 4.1亲和力

[0536] 使用Biacore T200处理单元(GE保健公司)通过SPR测量了mAb^2形式的所选抗MSLN克隆与重组人和猕猴MSLN-His-Avi抗原的结合。如前所述,希望与固定抗原的结合比与可溶性抗原的结合更牢固。为了评估克隆的结合特性,按照第2.1.2节所述确定与固定化MSLN抗原的结合动力学,并将其与溶液中MSLN抗原与捕获的克隆结合时获得的动力学进行比较。

[0537] 对于捕获实验,使用BIAcore传感器系列S芯片蛋白G(GE保健公司,29179315)捕获mAb^2形式的克隆。将mAb^2以1μg/ml的浓度在含900mM $NaCl_2$的HBS-EP缓冲液(GE保健公司,BR100188)中稀释,以30μl/min的速度分别注入流通池2、3和4中,以实现约100RU的响应。G1-AA/HelD1.3被捕获在流通池1中。将重组人和猕猴MSLN-His-Avi(第1.1节)稀释在含有900mM $NaCl_2$的HBS-EP缓冲液中,以70μl/min的速度分别将以3倍稀释的1000nM至0.051nM的浓度范围注入流通池1、2、3或4中5分钟,然后在缓冲液中解离5分钟。通过以30μl/min的速率注入10mM甘氨酸pH1.5(GE保健公司,BR100354)和表面活性剂P20(GE保健公司,BR-1000-54)20秒来实现再生。使用BIAevaluation 3.2软件(GE保健公司)分析减去的数据(流通池2-流通池1,流通池3-流通池1或流通池4-流通池1)以使用模型1:1结合,局部Rmax且折射率(RI)恒定为0来确定结合。

[0538] 表4:固定化和溶液中人间皮素的亲和力以及猕猴的交叉反应性

[0539]

克隆(FS22-053-008-AA mAb[2] 形式)	对固定化人MSLN-His-Avi的亲和力 K_D (nM)	对溶液中的人MSLN-His-Avi的亲和力 K_D (nM)	人MSLN-His-Avi的溶液/固定化中K_D的比率	对溶液中的猕猴MSLN-His-Avi 的亲和力 K_D (nM)
FS28-024	0.39	46.5	119.2	240.0
FS28-024-51	0.31	47.5	154.2	148.1
FS28-024-52	0.36	33.1	92.3	185.4
FS28-024-53	0.89	49.2	55.3	78.3
FS28-024-060	0.07	5.2	78.6	265.9
FS28-026	0.14	700.2	5001.4	886.0
FS28-091	1.1	614.9	580.1	>1000
FS28-185	30.1	452.4	15	361.5
FS28-256	23.7	888.8	37.5	737.9
FS28-256-012	4.1	861.1	209	716.7
FS28-256-021	3.3	23.2	7.0	16.2
FS28-256-023	3.3	68.6	20.8	32.6
FS28-256-024	6.7	95.4	14.3	56.7
FS28-256-026	3.2	62.3	19.5	33.2
FS28-256-027	1.1	6.0	5.3	0.7

[0540] *FS28-026对100RU固定化MSLN的亲和力可能被高估了,因为实时测量(on-rate measurements)超出了Biacore T200的限制。

[0541] 动力学数据表明,除FS28-024-060外,所有测试克隆均与猕猴MSLN-His-Avi有交叉反应,对猕猴抗原的亲和力是对人MSLN-His-Avi的5倍之内。

[0542] 另外,对于与不同MSLN结合区结合的每一组克隆,鉴定出以低纳摩尔亲和力与固定化的人MSLN-His-Avi结合的克隆。FS28-256的后代克隆具有比其各自的亲本抗体更高的亲和力,从而证实这些克隆的亲和力成熟是成功的。有趣的是,所有克隆对固定化MSLN的亲和力均高于对溶液中人MSLN-His-Avi的亲和力,该特征通过计算溶液中K_D与固定化K_D的倍数差异来量化(参见表4)。因此,可以假设抗MSLN抗体与靶标的结合亲和力不高,如对可溶性MSLN的结合亲和力低,但由于与固定化抗原的亲和力相互作用增强,因此被认为与固定化MSLN的结合更牢固。亲和力似乎是抗体特异性的。

[0543] 4.2在可溶性MSLN存在下细胞与NCI-H226的结合

[0544] 然后在不存在和存在20nM MSLN的情况下,测试所有选定的克隆,并补充其他未改组的FS28-256亲和力成熟的克隆(参见表5),以与NCI-H226细胞上的细胞表面MSLN结合。所使用的方法与第3.1.4节中所述完全相同。确定了EC_{50}和E_{max}值(表5)。

[0545] 表5:在不存在和存在可溶性间皮素的情况下的细胞结合

[0546]

克隆(CD137 mAb² 形式)	NCI-H226		NCI-H226 + 20 nM 可溶性	
	EC_{50} (nM)	E_{max} (MFI)	EC_{50} (nM)	E_{max} (MFI)
FS28-024	1.47	980955	5.04	1023695
FS28-024-051	0.78	800589	7.47	1100503
FS28-024-052	1.32	957685	4.28	985916
FS28-024-053	1.19	914344	7.52	964941
FS28-024-060	1.46	1011600	25.69	1225277
FS28-026	1.91	729876	2.65	701999
FS28-091	2.72	739899	3.97	744939
FS28-185*	16.3	5155	14.3	5031
FS28-256	15.78	275841	39.41	351430
FS28-256-001	4.98	703342	5.36	608248
FS28-256-005	5.30	759574	3.91	653731
FS28-256-012	8.48	968727	4.83	790055
FS28-256-014	3.11	771117	2.72	616427
FS28-256-018	6.98	637266	4.60	493728
FS28-256-021	3.29	919116	7.65	838717
FS28-256-023	3.29	856041	3.90	716321
FS28-256-024	3.88	812760	3.91	668584
FS28-256-026	2.43	741080	4.59	714886
FS28-256-027	3.93	986870	21.82	964426

[0547] *FS28-185数据是从BD CantoII而不是iQue(Intellicyt)获得的,从而导致更低。E_{max}值是由于机器之间的PMT电压不同。

[0548] 数据显示,测试的mAb²的抗MSLN结合Fab臂与NCI-H226细胞的亲和力从0.78到大于16nM不等,并且大多数克隆显示出低纳摩尔细胞结合亲和力,与报道的重组固定化MSLN亲和力一致。初始的FS28-024、FS28-026、FS28-091、FS28-185和FS28-256的细胞结合亲和力的排名也与以mAb形式获得的排名数据一致(表3,第2.4节)。有趣的是,在大多数克隆中观察到的20nM重组MSLN对细胞结合亲和力的影响很小,EC_{50}的增加极小(不到2.5倍)。具体地,FS28-256衍生克隆,例如FS28-256-001、FS28-256-005、FS28-256-012、FS28-256-014、FS28-256-018、FS28-256-023、FS28-256-024和FS28-256-026不受可溶性MSLN存在的影响。这表明即使存在过量的可溶性MSLN,大多数克隆仍优先与膜结合形式的MSLN结合。

[0549] 对于衍生自FS28-024的克隆,观察到可溶性MSLN的变化更大,EC_{50}的增加范围为3.4至17.6倍。

[0550] 与重组可溶性MSLN亲和力最高的两个克隆(请参见表4),即FS28-024-060和FS28-256-027(两者均与溶液中MSLN-His-Avi具有个位数nM K_D),当在可溶性MSLN存在下与细胞结合时受的影响最大,表明较高亲和力的结合剂更可能受到脱落的MSLN的影响。结果,在可溶性MSLN存在下增加EC_{50}较不优选,因为它是存在可溶性MSLN时的最终EC_{50},被认为最能反映mAb对患者体内这些肿瘤细胞的亲和力。抗MSLN抗体的实际所需亲和力取决于应用。

[0551] 实施例5:FS28-256亲和力成熟克隆的序列优化

[0552] 5.1FS28-256亲和力成熟克隆的序列优化

[0553] 所有FS28-256谱系克隆在VH CDR2(IMGT编号N55-X-S57,其中X是任何残基)中均含有潜在的N-连接糖基化位点。此外,FS28-256-001、FS28-256-021和FS28-256-023在VL CDR3区域的N116-T117(IMGT编号)处具有潜在的脱酰胺位点。与第3.2节中描述的过程类似,采用NNK的walk策略来鉴定克隆FS28-256-021中的氨基酸取代,这将消除这些潜在的糖基化和脱酰胺位点。最初,在各自的克隆中突变了VH CDR2残基N55和VL CDR3N116残基,然后筛选突变体,以保留与人和猕猴MSLN的最佳结合。对于FS28-256-021,VL CDR3N116残基

的改变导致抗原结合的丧失。在VH CDR2的N55的改变中,只有四个突变体(N55A,N55H,N55S和N55T)保留了与人MSLN的结合,尽管与亲代克隆相比,它们的结合较弱。

[0554] 由于不可能通过突变序列除去VL CDR3中潜在的脱酰胺位点,因此采用了替代策略。由于衍生自FS28-256的某些其他亲和力成熟的克隆与FS28-256-021共享相同的重链序列,但具有不同的轻链序列,因此需要进一步探索这些其他克隆。具体来说,选择FS28-256-027进行测试。如前所述,FS28-256-027对可溶性MSLN的亲和力高于FS28-256-021(6.0nM,表4),导致在存在可溶性MSLN的情况下与细胞表面表达的MSLN的结合减少(表5),并且因此,当时没有被选为首选克隆。为了探索是否可以优化此克隆以使其与细胞表面表达的MSLN结合,将针对FS28-256-021克隆鉴定的N55A,N55H,N55S或N55T突变引入FS28-256-027的重链中,并通过与实施例4.1中使用的方案相似的方式,通过SPR测量4个所得克隆的结合,其RU为约40而不是100,以结合固定化的和溶液中的MSLN。结果显示在表6中。将突变N55T引入FS28-256-027产生了克隆FS28-256-274,其与固定化的MSLN的亲和力比其他克隆弱得多,因此没有进一步进行。将突变N55H和N55S引入FS28-256-027,分别产生克隆FS28-256-272和FS28-256-273,其以与固定化的MSLN更高或相当的亲和力结合至可溶性MSLN。因此,认为这两个克隆与细胞表面表达的MSLN的结合会受到可溶性MSLN的存在的不利影响。相反,将突变N55A引入FS28-256-027产生了一个克隆FS28-256-271,该克隆显示了在测试的四个克隆中对固定化MSLN的最高亲和力,并且与可溶性MSLN的结合较弱。这些结果令人惊讶地表明,亲本克隆FS28-256-027的VH CDR2中的N55A突变降低了与固定化的和可溶性MSLN的结合亲和力,使得FS28-258-271优先靶向固定化MSLN,而不是可溶性MSLN。与其他克隆(例如FS28-256-021,其以10nM或更低的K_D与固定化的MSLN结合以及以10nM或更高的K_D与可溶性MSLN结合)一致,预期FS28-258-271与MSLN在细胞表面的结合将受到可溶性MSLN的影响较小。

[0555] 表6:对固定化的和溶液中的人间皮素的亲和力。

[0556]

克隆(CD137 mAb[2] 形式)	重链CDR2中的突变	对固定化人MSLN-His-Avi的亲和力 K_D (nM)	对溶液中的人MSLN-His-Avi的亲和力 K_D (nM)	人MSLN-His-Avi的溶液/固定化中K_D的比例
FS28-256-027	-	4.7	3.2	0.68
FS28-256-271	N55A	5.9	18.2	3
FS28-256-272	N55H	10.7	7.6	0.7
FS28-256-273	N55S	6.0	7.4	1.2
FS28-256-274	N55T	19.8	55.9	2.8

[0557] 对于mAb[2]FS22-172-003-AA/FS28-256-271,使用稳态动力学分析,通过SPR测定猕猴交叉反应性。根据制造商的说明,用hCMLN-His-Avi或cMSLN-His-Avi以大约50RU包被CM5芯片(GE保健公司BR-1005-30)。以10μl/分钟的流速注入从243nM开始以三倍稀释系列的浓度范围的mAb [2]。缔合时间为稳定状态下的1000秒,解离时间为30秒。电泳缓冲液为HBS-EP(GE保健公司BR100188)。通过以30μl/min的流速注入甘氨酸-HCl pH1.5,持续30秒,从而使流通池再生。通过相对被故意留为空白(无抗原包被)的流通池的双重参考来分析数据。使用BiaEvaluation软件3.2版,使用稳态亲和力模型分析动力学数据。与猕猴MSLN的结合在与人MSLN结合的3倍之内。

[0558] 5.2抗体依赖性细胞毒性(ADCC)活性

[0559] 为了评估MLSN mAb的效应子功能,在ADCC体外测定法中测试了这些分子。为了这个目的,FS28-256-271和FS28-024-052抗体以人IgG1形式产生,带有或不带有LALA突变(分别为LALA或G1)。

[0560] 使用Lenti-X HTX包装系统(Takara,目录号631253)通过慢病毒转导产生表达人MSLN的Raji细胞(Raji.hMSLN细胞)。将含有编码人MLSN的cDNA的Lenti-X表达载体(pLVX)(Takara,货号631253)与Lenti-X HTX包装混合物一起共转染到Lenti-X 293T细胞系(Takara,货号632180)产生病毒。然后用这些慢病毒载体转导Raji细胞系(ATCC®CCL-86™)。通过与G1/SS1阳性对照抗体结合1小时,然后与荧光标记的抗人Fc检测抗体结合(Stratech科学有限公司,目录号109-546-098-JIR),确认人MLSN在这些细胞上的表达,用于检测细胞结合。

[0561] 按照制造商的规程使用ADCC报告基因生物测定试剂盒(Promega,目录号G7010)。将ADCC试剂盒中的效应细胞与Raji.hMSLN细胞以20:1的比例混合。在96孔板上滴定mAb[2]或对照抗体SS1,并在37℃5%CO_2中孵育6小时。根据制造商的说明,通过从Bio-Glo分析系统试剂盒(Promega,目录号G7941)中添加萤光素酶底物来测量ADCC活性。将发光信号对抗体的对数浓度作图,并使用GraphPad Prism中的对数(激动剂)相对响应方程式拟合所得曲线。结果显示在图2中,证明FS28-256-271和FS28-024-052在以人IgG1形式存在时均能够引发ADCC活性。如所预期的,当将LALA突变引入这些抗体的hIgG1骨架中时,ADCC活性丧失。该数据证明本文所述的MSLN抗体可用于引发效应子功能以调节免疫应答。

[0562] 5.3FS28-256-271在原代T细胞测定中的效力

[0563] 5.3.10X40mAb2形式的FS28-256-271在体外原代T细胞测定中的效力

[0564] 从血小板捐献的副产物白细胞耗竭锥(leucocyte depletion cones)获得的外周血单核细胞(PBMC)中分离出Pan T细胞。简而言之,用PBS冲洗白细胞锥内容物并覆盖在Ficoll梯度(GE生命科学目录号17144002)上。通过离心和回收未穿过Ficoll梯度的细胞来分离PBMC。用PBS进一步洗涤PBMC,并根据制造商的说明通过添加10ml红细胞裂解缓冲液(eBioscience)裂解剩余的红细胞。计数PBMC,并在T细胞培养基(RPMI培养基(生命技术公司),含10%FBS(生命技术公司),1x青霉素链霉素(生命技术公司),丙酮酸钠(Gibco),10mM Hepes(Gibco),2mM L-谷氨酰胺(Gibco)和50μM 2-巯基乙醇(Gibco))中重悬至$2.0x10^6$细胞/ml。

[0565] 然后根据制造商的说明,使用Pan T细胞分离试剂盒II(美天旎生物技术有限公司)从PBMC中分离T细胞。通过涡旋使人T-活化剂CD3/CD28Dynabeads(英杰111.32D)重悬。用T细胞培养基(RPMI培养基(生命技术公司),含10%FBS(生命技术公司),1x青霉素链霉素(生命技术公司),丙酮酸钠(Gibco),10mM Hepes(Gibco),2mM L-谷氨酰胺(Gibco)和50μM 2-巯基乙醇(Gibco))将珠子洗涤两次。用洗涤过的人T-活化剂CD3/CD28Dynabeads以2:1的细胞与珠子的比例在T-25烧瓶(西格玛)中刺激T细胞培养基中的浓度为$1.0x10^6$个细胞/ml的T细胞,在37℃,5%CO2下孵育过夜以激活T细胞。从Dynabeads洗涤活化的T细胞,并以$2.0x10^6$细胞/ml的浓度重悬在T细胞培养基中。通过与在PBS中稀释的2.5μg/ml抗人CD3抗体(R&D系统克隆UHCT1)在37℃,5%CO2下孵育2小时,使96孔平底平板包被抗人CD3抗体,然后用PBS洗涤两次。将T细胞以$6x10^5$个细胞/孔的量添加到平板中,以20,000细胞/孔加入表达间皮素的细胞NCI-H226。在该试验中测试了包含抗OX40Fcab以及抗MSLN FabFS28-256-

271的单克隆抗体以及对照抗体。将测定板在37℃,5%CO2下孵育72小时。收集上清液,并通过人IL-2ELISA(生命技术公司,88-7025-88)测量IL-2的释放。将人IL-2(hIL-2)的浓度与抗体的对数浓度作图,并使用GraphPad Prism中的对数(激动剂)相对响应方程式拟合所得曲线。结果显示在表7中,证明mAb^2形式的FS28-256-271能够结合在细胞表面表达的MSLN并使抗体交联,使得OX40结合位点可以结合并激活OX40。

[0566] 5.3.2CD137mAb^2形式的FS28-256-271在体外原代T细胞测定中的效力

[0567] 如5.2中所述获得外周血单核细胞(PBMC)。根据制造商的说明,使用CD8+T细胞分离试剂盒II(美天旎生物技术有限公司,130-096-495)分离CD8+T细胞。将96孔平底组织培养板用在PBS中的8μg/ml抗CD3抗体(克隆UCHT1,R&D系统,MAB100-SP)于4℃包被过夜。然后将板用200μlPBS洗涤3次。将NCI-H226细胞以每孔2×10^4个细胞的量铺板在抗CD3抗体包被的(8μg/ml)96孔平底板的100μl T细胞培养基(RPMI培养基(生命技术公司,61870-044),含有10%FBS(生命技术公司),1X青霉素链霉素(生命技术公司,15140122),1mM丙酮酸钠(Gibco,11360-070),10mM Hepes(西格玛奥德里奇,H0887),2mM L-谷氨酰胺(西格玛奥德里奇,G7513)和50μM 2-巯基乙醇(Gibco,M6250))中。孵育4小时后,一旦细胞粘附,将所有T细胞培养基移出,并用含有浓度为4.0×10^5细胞/ml的T细胞的50μl T细胞培养基替换,从而得到$2.0x10^4$细胞/孔。对照抗体或包含CD137Fcab的mAb^2和MSLN Fab FS28-256-271在T细胞培养基中以4x终浓度从60nM开始稀释,并进行1:3或1:7连续稀释。将50μl抗体滴定液添加到细胞中,测定总体积为200μl,抗体浓度为1X。该测定在37℃,5%CO 2下温育72小时。收集上清液,并按照制造商的说明使用Meso ScaleDiscovery(K151QQD-4)的V-PLEX IL-2试剂盒进行测定。将人IL-2(hIL-2)的浓度与抗体的对数浓度作图,并使用GraphPad Prism中的对数(激动剂)相对响应方程式拟合所得曲线。结果显示在表7中,证明mAb^2形式的FS28-256-271能够结合细胞表面上的MSLN并使抗体交联,使得CD137结合位点可以结合并激活CD137。

[0568] 5.3.3序列优化的MSLN克隆FS28-256-271的总结及其在驱动TNFRSF成员激动中的用途。

[0569] 表7显示了5.3.1和5.3.2中描述的T细胞分析的结果,这些结果证明了mAb^2形式的抗MSLN Fab(例如FS28-256-271)交联和激活不同的TNFSFR(例如OX40-或CD137)在T细胞中诱导激动的能力。

[0570] 表7:使用FS28-256-271作为mAb^2形式的间皮素结合Fab,并使用NCI-H226细胞进行交联的T细胞活化测定

[0571]

克隆	EC_{50}(nM)	Emax(pg/ml IL-2)
OX40/FS28-256-271mAb^2	0.11	6509
CD137/FS28-256-271mAb^2	0.096	4871

[0572] 分离的抗人间皮素mAb的总结(实施例1-5)

[0573] 旨在分离与细胞表面MSLN结合的抗人MSLN抗体的噬菌体选择和抗体筛选策略,导致鉴定出一系列具有一定亲和力,MUC16-MSLN阻断活性,MSLN区域结合表位组和细胞结合特征的特异性抗间皮素结合抗体。由于进行了筛选级联,因此大多数抗MSLN结合Fab(无论是以mAb还是mAb^2形式进行测试)都优先结合到细胞表面MSLN。

[0574] 实施例6:抗小鼠MSLN抗体的选择和表征

[0575] 6.1抗小鼠MSLN单克隆抗体的初始选择

[0576] 小鼠和人MSLN之间的氨基酸同一性较低(60%)。为了在小鼠中进行体内概念验证(PoC)研究,发明人着手分离具有与实施例1-5中所述的抗人MSLN mAb相似特性的抗小鼠MSLN mAb。

[0577] 使用合成的天然噬菌体文库进行噬菌体选择,该文库显示人IgG1种系的Fab结构域,并在CDR1,CDR2和CDR3中随机化(MSM技术),用于通过生物素化的小鼠MSLN-His-Avi(SEQ ID NO 171,请参见第1.1节)进行选择,如第1.2节所述。在降低生物素化的mMSLN-His-Avi浓度的情况下进行了四轮选择,与抗人MSLN选择类似,在随后的活动中进行了表位掩蔽策略。此外,在第一轮使用重组抗原后,产生了HEK293-mMSLN细胞,并用于第2、3和4轮。

[0578] 简而言之,将小鼠MSLN序列亚克隆到pcDNA5/FRT/TO载体(生命技术公司,V652020)中,然后与Flp重组酶表达质粒pOG44(生命技术公司,V600520)共转染到Flp-In TREx 293细胞系中(生命技术公司,R78007)。使细胞在含有10%FBS,100μg/ml潮霉素B(Melford实验室有限公司,Z2475)和15μg/ml杀稻瘟素(Melford实验室有限公司,B1105)的DMEM中生长3-4周,直到形成稳定转化的细胞集落为止。这些集落在1μg/ml强力霉素(西格玛奥德里奇,D9891)存在下扩增,并使用抗小鼠MSLN(LS Bio,LS-C179484)测试MSLN的表达。

[0579] 总共筛选了来自富集群体的47个单个mAb的抗原结合,并亚克隆了45种独特的阳性结合物,并如先前实施例1.3中所述,以IgG1LALA形式表达为可溶性mAb。通过ELISA表征mAb与固定化的mMSLN-His-Avi的特异性结合,并在使用Biacore分析的动力学实验中基于对约50或200RU的固定化的mMSLN-His-Avi的亲和力进行排序。这确定了一组mAb,包括FS28m-194、FS28m-201、FS28m-209、FS28m-216、FS28m-228、FS28m-261和FS28m-265,亲和力范围为1至25nM。另外,如2.1.3节所述测试与MSLN不同区域的结合。通过克隆MOR6626克隆的VH和VL(专利公开号WO 2009/068204 A1)产生的小鼠交叉反应性mAb G1-AA/MOR6626被用作阳性对照。大多数克隆,其中FS28m-228未能结合已与MOR6626结合的MSLN,而其他克隆如FS28-194或FS28-026则分别显示了部分或全部结合。因此,分离了结合至不同区域(表位组)的克隆。MOR6626的抗MSLN结合区已经用于体内PoC研究(专利公开号US 2017/0342169 A1)。根据获得的数据,FS28m-228可能与MSLN上与MOR6626相似的区域结合。

[0580] 6.2抗小鼠MSLN单克隆抗体的亲和力成熟

[0581] FS28m-228的VH和VL CDR3区以scFv形式并行优化,方法是如实施例3.1.1所述使用NNK引物随机化5个氨基酸的重叠盒。在第1轮中使用50nM生物素化的mMSLN-His-Avi和在第2轮中使用0.2nM mMSLN-His-Avi进行两轮选择。对于第二轮,通过添加1000倍过量(200nM)的mMSLN-His-Avi(未生物素化)并在室温下孵育抗原/噬菌体混合物2.5小时,也施加了失速选择压力。然后使用Octet测试可溶性scFv(单点浓度)与mMSLN-His-Avi的结合。简而言之,将链霉亲和素传感器(ForteBio,18-5019)与mMSLN-His-Avi(10μg/ml)孵育5分钟。分析了用10x动力学缓冲液稀释至1x缓冲液终浓度(ForteBio,18-1092)的可溶性scFv与mMSLN的缔合5分钟,然后进行5分钟的解离步骤。与亲本FS28m-228scFv相比,测试的85个克隆中约有66个显示出改善的结合。利用与上述相同的克隆和表达方法(第3.1.2节),将9个克隆表达为mAb^2形式,将Fab臂与结合至小鼠CD137的Fcab(称为FS22-063-AA)结合在一起。测试指定的所得mAb^2的MSLN结合亲和力。

[0582] 6.3抗小鼠MSLN mAb^{2}与固定化和可溶性小鼠MSLN的结合亲和力

[0583] 与抗人MSLN结合剂一样,使用Biacore测试了衍生自FS28m-228的亲和力成熟变体与固定化和可溶性MSLN的结合。与固定化MSLN结合的程序与第2.1.4节中所述的方法类似,其中mMSLN-His-Avi以50RU固定。为了确定对可溶性MSLN的亲和力,通过抗人Fc捕获mAb^2。简而言之,将25μg/ml抗人IgG(Fc)抗体(GE保健公司,人类抗体捕获试剂盒,BR100839)包被在Biacore传感器芯片CM5(GE保健公司,BR100530)的流通池1、2、3和4上,以达到大约750RU的最终响应。在HBS-EP缓冲液(GE Healthcare,BR100188)中稀释的50nM的mAb^{2}克隆以30μl/min的速度分别注入流通池2、3和4,以实现约100RU的响应。在HBS-EP缓冲液中稀释的重组mMSLN-His-Avi抗原视情况3倍稀释以243nM至0.11nM的浓度范围以70μl/分钟注入到流通池1、2、3或4中5分钟,然后在缓冲液中解离5分钟。通过以30μl/min的速率注入3M氯化镁(GE保健公司,人类抗体捕获试剂盒,BR100839)30秒来实现再生。

[0584] 固定化亲和力和溶液亲和力的动力学数据(表8)显示,与亲本FS28m-228Fab臂相比,亲和力成熟的克隆显示出与小鼠MSLN-His-Avi抗原的结合改善。此外,所有克隆均显示出不同的比率,其对固定化的亲和力高于对可溶性MSLN的结合动力学。像第4.1节和第5.1节中所述的人克隆一样,认为由于增强的亲和结合相互作用,这些克隆对膜结合的MSLN的结合比可溶脱落的MSLN更强。因此,FS28m-228的亲和力成熟导致了一组亲和力成熟的克隆,这些克隆对小鼠MSLN的亲和力增强,并且所有克隆与固定化MSLN的结合比可溶性MSLN更牢固。选择克隆FS28m-228-010作为优选克隆,因为它对固定化小鼠MSLN的亲和力最高,而对溶液中小鼠MSLN的亲和力低。

[0585] 表8对固定化和溶液中人间皮素的亲和力

[0586]

克隆 (FS22-063AA mAb^{2}形式)	对固定化mMSLN-His-Avi的亲和力 K_D (nM)	对溶液中mMSLN-His-Avi的亲和力 K_D (nM)	小鼠MSLN-His-Avi的溶液/固定化中K_D的比例
FS28m-228	7.90	252	31.9
FS28m-228-010	2.6	60.24	23.2

[0587] 6.4分离抗小鼠间皮素单克隆抗体的总结

[0588] 噬菌体的选择和抗体筛选策略导致鉴定出一组具有一定亲和力并且结合到mMSLN的不同区域的抗小鼠间皮素结合克隆。与抗人MSLN结合剂一样,相比可溶mMSLN,这些克隆显示出更有利于与固定化mMSLN结合的结合特性,从而使其成为适合在小鼠体内PoC研究中研究的分子。

[0589] 6.5包含抗小鼠MSLN mAb FS28m-228-010的mAb^{2}的体内功效

[0590] 已经表明,在hIgG1同种型中的抗MLSN mAb能够引起ADCC活性,因此希望证明该抗MLSN mAb能够以CD137mAb^{2}形式体内驱动MLSN依赖性交联。

[0591] 构建表达小鼠MSLN的同系小鼠肿瘤模型。使用pcDNA3.1载体(+)通过脂转染(Lipofectamine 3000,赛默飞世尔科技,目录号L3000008)生产表达全长小鼠间皮素(SEQ ID NO:171)的CT26结肠癌细胞(ATCC,CRL-2638)(赛默飞世尔科技,目录号V79020)。按照制造商的规程,将CT26细胞用含有小鼠MSLN cDNA的pcDNA3.1载体转染。在完全培养基(RPMI,10%FBS)中,使用遗传霉素作为选择抗生素(600μg/ml)实现了稳定的转染。通过使用阳性对照抗体MOR6626(WO 2009/068204 A1),通过流式细胞术确认了小鼠MSLN在CT26细胞上的表达。具体地,将细胞与阳性对照抗体一起温育1小时,然后使用荧光标记的抗人IgG检测抗

体(Stratech科技有限公司,目录号109-546-098-JIR)检测细胞结合。扩增克隆群体,然后使用相同的流式细胞仪分析以确定相对表达水平,然后选择一个克隆并命名为CT26.G10。

[0592] 在体内证实了CT26.G10肿瘤的生长。将8-10周龄的Balb/c雌性小鼠(查尔斯河)植入微芯片,并赋予其唯一标识符。每组有17只小鼠,每只动物接受皮下注射到左背侧的100μl无血清培养基中的$1x10^5$个细胞。每周用卡尺进行三次肿瘤体积测量,以确定最长轴和最短轴为肿瘤的最长轴和最短轴。以下公式用于计算肿瘤体积:

[0593] 体积＝LxS22

[0594] 其中L＝最长轴;S＝最短轴

[0595] 根据英国动物(科学程序)法和欧盟指令EU86/609,当肿瘤体积达到人道终点时,该试验被中止。在研究结束时收集肿瘤组织,并通过免疫组织化学染色在福尔马林固定石蜡包埋的(FFPE)肿瘤组织中确认膜结合间皮素的表达,方法如下:将4μm FFPE组织切片去石蜡,并在97℃(Dako PT Link)下用低pH 6.1进行抗原回收,然后用过氧化物酶封闭和蛋白质封闭,然后与浓度为1μg/ml的抗间皮素一抗(生命周期生物科学,目录号LS-C407883)一起孵育。使用标记的聚合物HRP抗兔第二试剂和DAB(3,3'-二氨基联苯胺)终点显色(Dako EnVision+系统)检测抗间皮素抗体。

[0596] 为了评估抗体FS28m-228-010,在体内测试了以下分子或组合:具有LALA突变的人IgG1同种型的FS28m-228-010抗体(G1-AA/FS28m-228-010),两个"模拟"$CD137mAb^2$(FS22m-063-AA/HelD1.3和FS22m-063-AA/4420),FS28m-228-010抗体与带有LALA突变的模拟$CD137mAb^2$(G1-AA/FS28m-228-010+FS22m-063-AA/HelD1.3)的组合,人同种型对照抗体(G1-AA/HelD1.3),最后是具有LALA突变的CD137/MSLNmAb2(FS22m-063-AA/FS28m-228-010)(SEQ IDNO:196和197)。

[0597] 在研究开始之前,将8-10周龄且每只体重20-25g的Balb/c雌性小鼠(查尔斯河)驯化1周。将所有动物植入微芯片,并赋予唯一的标识符。除FS22m-063-AA/4420(n＝10只小鼠)外,每组包括20只小鼠。扩增CT26.G10结肠癌细胞系并产生细胞库。每只动物接受左侧腹皮下注射的在100μl无血清培养基中的$1x10^5$个细胞。肿瘤细胞接种后12天没有肿瘤的任何小鼠均从研究中移出。

[0598] 制备了200μg剂量的每种抗体(∽10mg/kg),并将其腹膜内(IP)注射到小鼠中。另外,对于组合的组,G1-AA/FS28m-228-010+FS22m-063-AA/HelD1.3各均以每剂量200μg(∽10mg/kg)的剂量制备。接种肿瘤后第12、14和16天(q2dx3),向小鼠施用200μl剂量。每周使用卡尺进行三次肿瘤体积测量,并密切监测小鼠。研究终点是根据小鼠的肿瘤体积和状况通过人道终点确定的。

[0599] 如图3所示,与G1-AA/HelD1.3同种型对照相比,FS22m-063-AA/FS28m-228-010mAb^2显著抑制了肿瘤的生长。表9显示了在整个研究过程中使用混合模型分析对所有治疗组的肿瘤生长率的成对比较,将所有组与G1-AA/HelD1.3同种型对照进行了比较。

[0600] 在研究结束时,所有携带等于或小于$62.5mm^3$的肿瘤的动物均被视为完全反应的动物(见表10)。在研究结束时,与G1-AA/HelD1.3同种型对照、FS22m-063-AA/HelD1.3、FS22m-063-AA/4420、以及FS22m-063-AA/HelD1.3和G1-AA/FS28m-228-010组合组中的0%相比,抗CD137/MSLN mAb^2治疗的动物中有35%对治疗完全反应。

[0601] 生存分析(图4和表11)显示,与G1-AA/HelD1.3抗体相比,FS22m-063-AA/FS28m-

228-010mAb[2]诱导了显著的生存获益,而G1-AA/FS28m-228-010、FS22m-063-AA/HelD1.3和FS22m-063-AA/4420)没有显示生存优势。此外,与G1-AA/HelD1.3(29天)、FS22m-063-AA/HelD1.3(30天)、FS22m-063-AA/4420(29天)、G1-AA/FS28m-228-010(30天)以及FS22m-063-AA/HelD1.3与G1-AA/FS28m-228-010的组合(29天)相比,FS22m-063-AA/FS28m-228-010mAb[2]的中位生存时间延长了42.5天。

[0602] 这些数据表明mAb[2]通过MSLN交联能够驱动肿瘤中的CD137激动。这种双特异性抗体的作用优于单独靶向CD137和/或MSLN(甚至组合)的作用,从而显著提高了荷瘤小鼠的存活率。在本研究中,具有LALA突变的mAb自身(G1-AA/FS28m-228-010)没有表现出内在活性。不希望受理论的束缚,预期抗体FS28m-228-010的具有效应子功能的版本(不包括LALA突变)将显示与5.2节中观察到的体外结果一致的ADCC活性和抗肿瘤功效。

[0603] 表9:使用混合模型分析对肿瘤生长进行成对比较的结果,将所有组与G1-AA/HelD1.3同型对照进行比较。

[0604]

组	混合模型分析	
G1-AA/HelD1.3 10mg/kg (阴性对照)	P值	显著性
G1-AA/FS28m-228-010 10mg/kg	0.4367	NS
FS22m-063-AA/HelD1.3 10mg/kg	0.0017	***
FS22m-063-AA/4420 10mg/kg	0.7067	NS
G1-AA/FS28m-228-010 10mg/kg + FS22m-063-AA/HelD1.3 10mg/kg	0.2093	NS
FS22m-063-AA/FS28m-228-010 10mg/kg	0.0000	****

[0605] NS-不显著p≥0.05;****-p值<0.0001;***-p值0.0001-0.001

[0606] 表10:到研究结束时,在CT26.G10同系肿瘤模型中无肿瘤小鼠(肿瘤≤62.mm[3])的数量和百分比。

[0607]

组	研究结束时无瘤小鼠
G1-AA/HelD1.3 10mg/kg (阴性对照)	0/20 (0%)
G1-AA/FS28m-228-010 10mg/kg	1/20 (5%)
FS22m-063-AA/HelD1.3 10mg/kg	0/20 (0%)
FS22m-063-AA/4420 10mg/kg	0/10 (0%)
G1-AA/FS28m-228-010 10mg/kg + FS22m-063-AA/HelD1.3 10mg/kg	0/20 (0%)
FS22m-063-AA/FS28m-228-010 10mg/kg	7/20 (35%)

[0608] 表11:用每种化合物治疗的动物的中位存活时间,以及CT26.G10同系肿瘤模型中的成对统计分析(对数秩)的结果

[0609]

组	中位生存期（天）	对数秩	
G1-AA/HelD1.3 10mg/kg	29	P值	显著性
G1-AA/FS28m-228-010 10mg/kg	30	0.993	NS
FS22m-063-AA/HelD1.3 10mg/kg	30	0.3952	NS
FS22m-063-AA/4420 10mg/kg	29	0.9645	NS
G1-AA/FS28m-228-010 10mg/kg + FS22m-063-AA/HelD1.3 10mg/kg	29	0.4706	NS
FS22m-063-AA/FS28m-228-010 10mg/kg	42.5	<0.0001	****

[0610] NS-不显著p≥0.05;****-p值<0.0001

[0611] 6.6包含抗小鼠MLSN mAb FS28m-228-010的抗小鼠CD137/MSLN mAb^{2}的作用机理

[0612] 为了进一步了解含有抗小鼠MSLN mAb FS28m-228-010的FS22m-063-AA/FS28m-228-010所观察到的抗肿瘤反应的药理作用,研究了CD137/MSLN mAb^{2}在MSLN阳性同系肿瘤模型中的作用机理。

[0613] 如实施例6.5所述制备小鼠,并用CT26.G10结肠癌细胞系接种。每个组由20只小鼠组成。FS22m-063-AA/FS28-228-010(CD137/MSLN)mAb^2、人IgG1同种型对照(G1-AA/4420)和抗CD137激动剂抗体(克隆3H3;G1/3H3;Rickert等,2016)也包括在内以进行比较。所有这三种抗体均以每剂量134μg(在20g小鼠中约为6.7mg/kg)在DPBS+1mM精氨酸+0.05%Tween 80中制备,并腹膜内(IP)注射到小鼠中。接种肿瘤后第20天,每只小鼠接受以200μl腹膜内注射的134μg固定剂量的抗体。如实施例6.5中所述,使用卡尺每周进行三次肿瘤体积测量,并密切监测小鼠。

[0614] 在接种肿瘤后第20天,在给药后24、72、144和192小时对每组六只小鼠进行尸检(neropsied)。从经FS22m-063-AA/FS28-228-010、G1-AA/4420或G1/3H3治疗的CT26.G10荷瘤小鼠中取出脾脏,血液和肿瘤组织进行分析。通过流式细胞术研究了所有样品的T细胞丰度和增殖,因为已知T细胞活化和增殖标记是CD137激动作用的下游效应(Fisher等人,2012)。另外,还从血液中收集血清用于检测和定量可溶性MSLN的表达。通过标准的机械和酶法将脾脏和肿瘤组织分解为单细胞悬液,然后在红细胞裂解缓冲液(美天旎生物技术有限公司,130-094-183)中将红细胞裂解一次。通过终末心脏出血收集血液,一半收集到含EDTA的试管中,通过流式细胞术进行单细胞分析,另一半血液收集到凝血激活剂/血清试管中,以分析可溶性MSLN。根据制造商的说明,将含有EDTA的试管中收集的全血在红细胞裂解缓冲液(美天旎生物技术有限公司,130-094-183)中裂解3次。通过离心分离收集在血清试管中的血液,并去除血清以分析可溶性MSLN。

[0615] 然后对来自脾脏,肿瘤和血液的单细胞进行相同的处理,并将细胞用PBS洗涤一次,并用可固定活性染料(eBioscience,65-0865-14)将样品染色。随后在Fc阻断剂(eBioscience,16-0161-85,1:25)存在下用表12中所示的抗体染色板(除细胞内标志物Ki67和FoxP3以外的所有标志物)在4℃下对细胞进行细胞表面标志物染色45分钟。然后按照制造商的说明将细胞固定并用eBioscience FoxP3染色试剂盒(eBioscience,00-5523-00)进行透化。将细胞重悬于含有细胞内标志物Ki67和FoxP3抗体的100μl透化缓冲液中,并在黑暗中于4℃孵育过夜。在BD Fortessa流式细胞仪上获得之前,将细胞用透化缓冲液洗

涤一次,然后重悬于120μl含0.5%BSA的PBS中。使用BD FACS Diva软件获取数据,并使用FlowJo(V10)和Microsoft Excel进行分析。数据显示给药后144小时CD8+T细胞的丰度和增殖,以亲代群体的百分比表示。

[0616] 表12:流式细胞仪面板

[0617]

靶标	克隆	荧光团	制造商	货号
CD45	30-F11	Alexa700	eBioscience	56-0451
CD3e	145-2C11	PE-Cy7	eBioscience	25-0031-82
CD8	53-6.7	BUV737	BD生物科学	564297
CD4	RM4-5	BUV395	BD生物科学	740208
FoxP3	FJK-16s	PerCP-Cy5.5	eBioscience	45-5773
CD49b	DX5	BV421	生物传奇	563063
CD103	M290	BV786	BD生物科学	564322
CD137	17B5	APC	eBioscience	106110
CD69	H1.2F3	BV510	生物传奇	104505
PD1	29F.1A12	FITC	生物传奇	135220
Ki67	SolA15	PE	eBioscience	12-5698-82
生存力	N/A	eFluor780	eBioscience	65-0865-14

[0618] 如表13所示,与对照处理组(G1-AA/4420)相比,在用G1/3H3和FS22m-063-AA/FS28-228-010mAb^{2}给药后144小时,观察到肿瘤中CD8+T细胞的百分比增加。给药后144小时,肿瘤中CD8+T细胞的平均百分比从32.1%(G1-AA/4420)增加到56.1%(G1/3H3)和58.4%(FS22m-063-AA/FS28m-228-010)。

[0619] 此外,在血液和脾脏中也观察到CD8+T细胞丰度的增加,但与IgG1对照相比,只有G1/3H3出现了增加。在给药后144小时的血液中,CD8+T细胞的平均百分比从22.6%(G1-AA/4420)增加到57.0%(G1/3H3),但是对于FS22m-063-AA/FS28m-228-010(25.8%)却没有观察到这种增加。同样,在脾脏中,CD8+T细胞的平均百分比从28.8%(G1-AA/4420)增加到使用G1/3H3的38.0%,但是对于FS22m-063-AA/FS28m-228-010(29%)却没有观察到这种增加。

[0620] 这表明FS22m-063-AA/FS28m-228-010mAb^{2}特别在表达MSLN的肿瘤中增加CD8+T细胞,而靶向CD137的抗体G1/3H3也证明了CD8+T细胞的外周(血液和脾脏)增加。

[0621] 为了确定给药后CD8+T细胞的增殖是否存在任何差异,在肿瘤、血液和脾脏中的CD8+T细胞上分析了增殖标志物Ki67。如表14所示,在对照组中高比例的CD8+T细胞表达Ki67+(平均表达为75.1%),表明在CT26.G10模型中肿瘤中高水平的增殖性CD8+T细胞。这可能导致剂量组之间肿瘤中CD8+T细胞上Ki67表达不清楚的差异。

[0622] 相比之下,与IgG1对照相比,在用G1/3H3给药后144小时,血液和脾脏中CD8+T细胞上的Ki67+表达明显增加。在血液中,同种型对照治疗的小鼠在CD8+T细胞上显示的平均Ki67+表达为10.4%,而在用G1/3H3给药后,在CD8+T细胞上Ki67的平均表达在给药后144小时显示为86.3%。相比之下,FS22m-063-AA/FS28m-228-010未观察到这种增加,在血液中施用mAb^{2}后,在CD8+T细胞上观察到的平均Ki67+表达为13.1%。类似地,在脾脏中,与同型对照给药后观察到的8.1%和FS22m-063-AA/FS28m-228-010观察到的11.4%相比,在用G1/

3H3给药后,在36.1%的CD8+T细胞上观察到平均Ki67+表达,。

[0623] 表13:在用G1-AA/4420,G1/3H3或FS22m-063-AA/FS28m-228-010给药后144小时,肿瘤、血液和脾脏中CD8+T细胞在总CD3+细胞中的平均百分比。数据显示了总CD3+T细胞中CD8+T细胞的平均百分比±平均值的标准误差。

[0624]

	G1-AA/4420	G1/3H3	FS22m-063-AA/FS28m-228-010
	%±SEM	%±SEM	%±SEM
肿瘤	32.1±5.8	56.1±2.8	58.4±5.0
血液	22.6±0.6	57.0±1.6	25.8±0.6
脾脏	28.8±0.4	38.0±0.8	29.0±0.9

[0625] 表14:在用G1-AA/4420,G1/3H3或FS22m-063-AA/FS28m-228-010给药后144小时,在肿瘤、血液和脾脏的CD8+T细胞上表达的Ki67的平均百分比。数据显示总CD8+T细胞中Ki67+的平均百分比±平均值的标准误差。

[0626]

	G1-AA/4420	G1/3H3	FS22m-063-AA/FS28m-228-010
	%±SEM	%±SEM	%±SEM
肿瘤	75.1%±2.9	85.1%±2.8	77.6%±5.0
血液	10.4%±1.0	86.3%±0.7	13.1±3.4
脾脏	8.1%±0.3	36.1±1.7	11.4%±1.4

[0627] 总而言之,这些数据表明,包含抗小鼠MLSN mAb FS28m-228-010,FS22m-063-AA/FS28m-228-010的mAb[2]介导肿瘤中细胞毒性CD8+T细胞的肿瘤特异性增加。尽管在G1/3H3中也观察到了这种情况,但这种靶向CD137的激动剂也促进血液和脾脏中CD8+T细胞的外周增加。此外,在用G1/3H3给药后,这些CD8+T细胞也显示出增殖增加。

[0628] 序列表

[0629] 亲本克隆FS28-256的重链氨基酸序列,显示适用于亲本克隆和亲和力成熟的克隆FS28-256-001,FS28-256-005,FS28-256-012,FS28-256-014,FS28-256-018,FS28-256-021,FS28-256-023,FS28-256-024,FS28-256-026和FS28-256-027的“主要的”CDR2序列。带双下划线的“X”代表所有可能的取代,以去除可能的N-连接的糖基化。产生的克隆可以包含一个或另一个取代,或两者都包含。

[0630] SEQ ID NO:1 重链AA(无LALA)

[0631] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTETYMS**WVRQAPGKGLEWVS**XIXPTYSTT**NYADSVK*
*GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCA**RYNSYQGGLDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN
VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK
TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG
SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0632] SEQ ID NO:2 重链AA(具有LALA)

[0633] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTETYMS**WVRQAPGKGLEWVS**XIXPTYSTT**NYADSVK*
*GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCA**RYNSYQGGLDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN
VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0634] 适用于克隆FS28-256-001,FS28-256-021和FS28-256-023的主要的轻链氨基酸序列。带双下划线的“X”代表所有潜在的取代基,用于去除可能的脱酰胺位点。产生的克隆可以包含一个或另一个取代,或同时包含两个。

[0635] SEQ ID NO:3 轻链

[0636] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSYLA**WYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQHNQYPXX**FGQGTKVEIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLN

[0637] NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGEC

[0638] FS28-024mAb重链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0639] SEQ ID NO:4 重链AA(无LALA)

[0640] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTLSYSS**MSWVRQAPGKGLEWVSF**ITPSTGYT**HYADSVKG RFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARRALTFDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0641] SEQ ID NO:6 重链DNA(无LALA)

[0642] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG GCCAGTGGCTTTACCCTCAGTTATTCTTCTATGTCATGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG CTTTATTACTCCGTCTACTGGCTATACCCACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGACGGGCG CTGACGTTCGACTACTGGGGCCAGGGAACCTTGGTCACCGTCTCGAGTGCTAGCACTAAGGGCCCGTCGGTGTTCCC GCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACTTTCCCGAGC CCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAGTCCTCTGGC CTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAATGTCAACCA TAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCCCGCCTTGCC CAGCCCCGGAACTGCTGGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATGATCTCACGG ACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTACGTGGATGG AGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGTCCGTGCTCA CTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCTGCCCCAATT GAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCGGGACGAGCT GACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAATGGGAAAGCA ACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTGTACTCCAAG CTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCTGCACAACCA CTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[0643] SEQ ID NO:5 重链AA(具有LALA)

[0644] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTLSYSS**MSWVRQAPGKGLEWVSF**ITPSTGYT**HYADSVKG RFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARRALTFDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0645] SEQ ID NO:7 重链DNA(具有LALA)

[0646] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG GCCAGTGGCTTTACCCTCAGTTATTCTTCTATGTCATGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG CTTTATTACTCCGTCTACTGGCTATACCCACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGACGGGCG CTGACGTTCGACTACTGGGGCCAGGGAACCTTGGTCACCGTCTCGAGTGCTAGCACTAAGGGCCCGTCGGTGTTCCC GCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACTTTCCCGAGC CCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAGTCCTCTGGC CTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAATGTCAACCA TAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCCCGCCTTGCC CAGCCCCGGAAGCTGCCGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATGATCTCACGG ACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTACGTGGATGG AGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGTCCGTGCTCA CTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCTGCCCCAATT GAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCGGGACGAGCT GACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAATGGGAAAGCA ACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTGTACTCCAAG CTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCTGCACAACCA CTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[0647] SEQ ID NO:8 可变结构域AA

[0648] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTLSYSSMS**WVRQAPGKGLEWVSF**ITPSTGYT**HYADSVKG RFTISRDNSKNTLYLQMNSLRAEDTAVYYCA**RRALTFDY**WGQGTLVTVSS*

[0649] SEQ ID NO:9 可变结构域DNA

[0650] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG GCCAGTGGCTTTACCCTCAGTTATTCTTCTATGTCATGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG CTTTATTACTCCGTCTACTGGCTATACCCACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGACGGGCG CTGACGTTCGACTACTGGGGCCAGGGAACCTTGGTCACCGTCTCGAGT

[0651]

SEQ ID NO: 10	CDR1 (AA) (IMGT)	***GFTLSYSS***
SEQ ID NO: 13	CDR1 (AA) (Kabat)	*YSSMS*
SEQ ID NO: 11	CDR2 (AA) (IMGT)	***ITPSTGYT***
SEQ ID NO: 14	CDR2 (AA) Kabat)	*FITPSTGYTHYADSVKG*
SEQ ID NO: 12	CDR3 (AA) (IMGT)	***ARRALTFDY***
SEQ ID NO: 15	CDR3 (AA) (Kabat)	*RALTFDY*

[0652] FS28-024mAb轻链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0653] SEQ ID NO:16 轻链AA

[0654] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQASSYPLT**FGQGTKVEIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC

[0655] SEQ ID NO:17 轻链DNA

[0656] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT

TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA
CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAAGCTTCTTCTTATCCTCTCACGTTCGGC
CAAGGGACCAAGGTGGAAATCAAACGTACTGTGGCCGCTCCTAGCGTGTTCATTTTTCCGCCATCCGACGAGCAGCT
CAAGTCCGGCACCGCCTCCGTGGTCTGCCTGCTCAACAACTTCTACCCTCGCGAAGCTAAGGTCCAGTGGAAGGTCG
ACAATGCCCTGCAGTCCGGAAACTCGCAGGAAAGCGTGACTGAACAGGACTCCAAGGACTCCACCTATTCACTGTCC
TCGACTCTGACCCTGAGCAAGGCGGATTACGAAAAGCACAAAGTGTACGCATGCGAAGTGACCCACCAGGGTCTTTC
GTCCCCCGTGACCAAGAGCTTCAACAGAGGAGAGTGT

[0657] SEQ ID NO:18 可变结构域AA

[0658] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQASSYPLT**FGQGTKVEIK*

[0659] SEQ ID NO:19 可变结构域DNA

[0660] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC
CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT
TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA
CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAAGCTTCTTCTTATCCTCTCACGTTCGGC
CAAGGGACCAAGGTGGAAATCAAA

[0661]

SEQ ID NO: 20	CDR1 (AA) (IMGT)	***QSVSSSY***
SEQ ID NO: 23	CDR1 (AA) (Kabat)	*RASQSVSSSYLA*
SEQ ID NO: 21	CDR2 (AA) (IMGT)	***GAS***
SEQ ID NO: 24	CDR2 (AA) (Kabat)	*GASSRAT*
SEQ ID NO: 22	CDR3 (AA) (IMGT)	***QQASSYPLT***
SEQ ID NO: 22	CDR3 (AA) (Kabat)	*QQASSYPLT*

[0662] FS28-024-051mAb重链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0663] SEQ ID NO:26 重链AA(无LALA)

[0664] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTLSYSS**MSWVRQAPGKGLEWVSF**ITPSTGYT**HYADSVKG RFTISRDNSKNTLYLQMNSLRAEDTAVYYCA**RRALIFDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGG
TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP
SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY
SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0665] SEQ ID NO:27 重链DNA(无LALA)

[0666] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG
GCCAGTGGCTTTACCCTCAGTTATTCTTCTATGTCATGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CTTTATTACTCCGTCTACTGGCTATACCCACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGACGGGCG
CTGATTTTCGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGTGCTAGCACTAAGGGCCCGTCGGTGTTCCC
GCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACTTTCCCGAGC
CCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAGTCCTCTGGC
CTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAATGTCAACCA
TAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCCCGCCTTGCC
CAGCCCCGGAACTGCTGGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATGATCTCACGG
ACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTACGTGGATGG
AGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGTCCGTGCTCA

CTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCTGCCCCAATT
GAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCGGGACGAGCT
GACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAATGGGAAAGCA
ACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTGTACTCCAAG
CTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCTGCACAACCA
CTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[0667] SEQ ID NO:28 重链AA(具有LALA)

[0668] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTLSYSS**MSWVRQAPGKGLEWVSF**ITPSTGYT**HYADSVKG RFTISRDNSKNTLYLQMNSLRAEDTAVYYCA**RRALIFDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0669] SEQ ID NO:29 重链DNA(具有LALA)

[0670] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG
GCCAGTGGCTTTACCCTCAGTTATTCTTCTATGTCATGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CTTTATTACTCCGTCTACTGGCTATACCCACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGACGGGCG
CTGATTTTCGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGTGCTAGCACTAAGGGCCCGTCGGTGTTCCC
GCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACTTTCCCGAGC
CCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAGTCCTCTGGC
CTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAATGTCAACCA
TAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCCCGCCTTGCC
CAGCCCCGGAAGCTGCCGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATGATCTCACGG
ACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTACGTGGATGG
AGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGTCCGTGCTCA
CTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCTGCCCCAATT
GAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCGGGACGAGCT
GACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAATGGGAAAGCA
ACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTGTACTCCAAG
CTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCTGCACAACCA
CTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[0671] SEQ ID NO:30 可变结构域AA

[0672] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTLSYSS**MSWVRQAPGKGLEWVSF**ITPSTGYT**HYADSVKG RFTISRDNSKNTLYLQMNSLRAEDTAVYYCA**RRALIFDY**WGQGTLVTVSS*

[0673] SEQ ID NO:31 可变结构域DNA

[0674] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG
GCCAGTGGCTTTACCCTCAGTTATTCTTCTATGTCATGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CTTTATTACTCCGTCTACTGGCTATACCCACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGACGGGCG
CTGATTTTCGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGT

[0675]

SEQ ID NO: 10	CDR1 (AA) (IMGT)	***GFTLSYSS***
SEQ ID NO: 13	CDR1 (AA) (Kabat)	*YSSMS*
SEQ ID NO: 11	CDR2 (AA) (IMGT)	***ITPSTGYT***
SEQ ID NO: 14	CDR2 (AA) Kabat)	*FITPSTGYTHYADSVKG*
SEQ ID NO: 32	CDR3 (AA) (IMGT)	***ARRALIFDY***
SEQ ID NO: 33	CDR3 (AA) (Kabat)	*RALIFDY*

[0676] FS28-024-051mAb轻链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0677] SEQ ID NO:16 轻链AA

[0678] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQASSYPLT**FGQGTKVEIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC

[0679] SEQ ID NO:17 轻链DNA

[0680] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAAGCTTCTTCTTATCCTCTCACGTTCGGC CAAGGGACCAAGGTGGAAATCAAACGTACTGTGGCCGCTCCTAGCGTGTTCATTTTTCCGCCATCCGACGAGCAGCT CAAGTCCGGCACCGCCTCCGTGGTCTGCCTGCTCAACAACTTCTACCCTCGCGAAGCTAAGGTCCAGTGGAAGGTCG ACAATGCCCTGCAGTCCGGAAACTCGCAGGAAAGCGTGACTGAACAGGACTCCAAGGACTCCACCTATTCACTGTCC TCGACTCTGACCCTGAGCAAGGCGGATTACGAAAAGCACAAAGTGTACGCATGCGAAGTGACCCACCAGGGTCTTTC GTCCCCCGTGACCAAGAGCTTCAACAGAGGAGAGTGT

[0681] SEQ ID NO:18 可变结构域AA

[0682] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQASSYPLT**FGQGTKVEIK*

[0683] SEQ ID NO:19 可变结构域DNA

[0684] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAAGCTTCTTCTTATCCTCTCACGTTCGGC CAAGGGACCAAGGTGGAAATCAAA

[0685]

SEQ ID NO: 20	CDR1 (AA) (IMGT)	***QSVSSSY***
SEQ ID NO: 23	CDR1 (AA) (Kabat)	*RASQSVSSSYLA*
SEQ ID NO: 21	CDR2 (AA) (IMGT)	***GAS***
SEQ ID NO: 24	CDR2 (AA) (Kabat)	*GASSRAT*
SEQ ID NO: 22	CDR3 (AA) (IMGT)	***QQASSYPLT***
SEQ ID NO: 22	CDR3 (AA) (Kabat)	*QQASSYPLT*

[0686] FS28-024-052mAb重链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0687] SEQ ID NO:35 重链AA(无LALA)

[0688] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTLSYSS**MSWVRQAPGKGLEWVSF**ITPSTGYT**HYADSVKG RFTISRDNSKNTLYLQMNSLRAEDTAVYYCA**RRALLFDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0689] SEQ ID NO:36 重链DNA(无LALA)

[0690] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG
GCCAGTGGCTTTACCCTCAGTTATTCTTCTATGTCATGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CTTTATTACTCCGTCTACTGGCTATACCCACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGACGGGCG
CTGCTTTTCGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGTCGGCTAGCACTAAGGGCCCGTCGGTGTTCCC
GCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACTTTCCCGAGC
CCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAGTCCTCTGGC
CTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAATGTCAACCA
TAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCCCGCCTTGCC
CAGCCCCGGAACTGCTGGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATGATCTCACGG
ACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTACGTGGATGG
AGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGTCCGTGCTCA
CTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCTGCCCCAATT
GAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCGGGACGAGCT
GACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAATGGGAAAGCA
ACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTGTACTCCAAG
CTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCTGCACAACCA
CTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[0691] SEQ ID NO:37 重链AA(具有LALA)

[0692] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTLSYSSMS**WVRQAPGKGLEWVS**FITPSTGYT**HYADSVKG
RFTISRDNSKNTLYLQMNSLRAEDTAVYYCA**RRALLFDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGG
TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP
SNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY
SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG*

[0693] SEQ ID NO:38 重链DNA(具有LALA)

[0694] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG
GCCAGTGGCTTTACCCTCAGTTATTCTTCTATGTCATGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CTTTATTACTCCGTCTACTGGCTATACCCACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGACGGGCG
CTGCTTTTCGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGTCGGCTAGCACTAAGGGCCCGTCGGTGTTCCC
GCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACTTTCCCGAGC
CCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAGTCCTCTGGC
CTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAATGTCAACCA
TAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCCCGCCTTGCC
CAGCCCCGGAAGCTGCCGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATGATCTCACGG
ACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTACGTGGATGG
AGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGTCCGTGCTCA
CTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCTGCCCCAATT
GAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCGGGACGAGCT
GACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAATGGGAAAGCA

ACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTGTACTCCAAG CTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCTGCACAACCA CTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[0695] SEQ ID NO:39 可变结构域AA

[0696] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTLSYSS**MSWVRQAPGKGLEWVSF**ITPSTGYT**HYADSVKG RFTISRDNSKNTLYLQMNSLRAEDTAVYYCA**RRALLFDY**WGQGTLVTVSS*

[0697] SEQ ID NO:40 可变结构域DNA

[0698] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG GCCAGTGGCTTTACCCTCAGTTATTCTTCTATGTCATGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG CTTTATTACTCCGTCTACTGGCTATACCCACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGACGGGCG CTGCTTTTCGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGTCG

[0699]

SEQ ID NO: 10	CDR1 (AA) (IMGT)	***GFTLSYSS***
SEQ ID NO: 13	CDR1 (AA) (Kabat)	*YSSMS*
SEQ ID NO: 11	CDR2 (AA) (IMGT)	***ITPSTGYT***
SEQ ID NO: 14	CDR2 (AA) Kabat)	*FITPSTGYTHYADSVKG*
SEQ ID NO: 41	CDR3 (AA) (IMGT)	***ARRALLFDY***
SEQ ID NO: 42	CDR3 (AA) (Kabat)	*RALLFDY*

[0700] FS28-024-052mAb轻链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0701] SEQ ID NO:16 轻链AA

[0702] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSYL**AWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQASSYPLT**FGQGTKVEIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC

[0703] SEQ ID NO:17 轻链DNA

[0704] AAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGCC GGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGATT TACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGAC AATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAAGCTTCTTCTTATCCTCTCACGTTCGGCC AAGGGACCAAGGTGGAAATCAAACGTACTGTGGCCGCTCCTAGCGTGTTCATTTTTCCGCCATCCGACGAGCAGCTC AAGTCCGGCACCGCCTCCGTGGTCTGCCTGCTCAACAACTTCTACCCTCGCGAAGCTAAGGTCCAGTGGAAGGTCGA CAATGCCCTGCAGTCCGGAAACTCGCAGGAAAGCGTGACTGAACAGGACTCCAAGGACTCCACCTATTCACTGTCCT CGACTCTGACCCTGAGCAAGGCGGATTACGAAAAGCACAAAGTGTACGCATGCGAAGTGACCCACCAGGGTCTTTCG TCCCCCGTGACCAAGAGCTTCAACAGAGGAGAGTGT

[0705] SEQ ID NO:18 可变结构域AA

[0706] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSYL**AWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS*

[0707] *GTDFTLTISRLEPEDFAVYYC**QQASSYPLT**FGQGTKVEIK*

[0708] SEQ ID NO:19 可变结构域DNA

[0709] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAAGCTTCTTCTTATCCTCTCACGTTCGGC

CAAGGGACCAAGGTGGAAATCAAA

[0710]

SEQ ID NO: 20	CDR1 (AA) (IMGT)	***QSVSSSY***
SEQ ID NO: 23	CDR1 (AA) (Kabat)	*RASQSVSSSYLA*
SEQ ID NO: 21	CDR2 (AA) (IMGT)	***GAS***
SEQ ID NO: 24	CDR2 (AA) (Kabat)	*GASSRAT*
SEQ ID NO: 22	CDR3 (AA) (IMGT)	***QQASSYPLT***
SEQ ID NO: 22	CDR3 (AA) (Kabat)	*QQASSYPLT*

[0711] FS28-024-053mAb重链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0712] SEQ ID NO:45 重链AA(无LALA)

[0713] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTLSYSS**MSWVRQAPGKGLEWVSF**ITPSTGYT**HYADSVKG RFTISRDNSKNTLYLQMNSLRAEDTAVYYCA**RRALVFDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0714] SEQ ID NO:46 重链DNA(无LALA)

[0715] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG GCCAGTGGCTTTACCCTCAGTTATTCTTCTATGTCATGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG CTTTATTACTCCGTCTACTGGCTATACCCACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGACGGGCG CTGGTGTTCGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGTCGGCTAGCACTAAGGGCCCGTCGGTGTTCCC GCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACTTTCCCGAGC CCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAGTCCTCTGGC CTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAATGTCAACCA TAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCCCGCCTTGCC CAGCCCCGGAACTGCTGGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATGATCTCACGG ACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTACGTGGATGG AGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGTCCGTGCTCA CTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCTGCCCCAATT GAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCGGGACGAGCT GACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAATGGGAAAGCA ACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTGTACTCCAAG CTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCTGCACAACCA CTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[0716] SEQ ID NO:47 重链AA(具有LALA)

[0717] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTLSYSS**MSWVRQAPGKGLEWVSF**ITPSTGYT**HYADSVKG RFTISRDNSKNTLYLQMNSLRAEDTAVYYCA**RRALVFDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0718] SEQ ID NO:48 重链DNA(具有LALA)

[0719] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG GCCAGTGGCTTTACCCTCAGTTATTCTTCTATGTCATGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG

CTTTATTACTCCGTCTACTGGCTATACCCACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGACGGGCG
CTGGTGTTCGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGTCGGCTAGCACTAAGGGCCCGTCGGTGTTCCC
GCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACTTTCCCGAGC
CCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAGTCCTCTGGC
CTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAATGTCAACCA
TAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCCCGCCTTGCC
CAGCCCCGGAAGCTGCCGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATGATCTCACGG
ACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTACGTGGATGG
AGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGTCCGTGCTCA
CTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCTGCCCCAATT
GAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCGGGACGAGCT
GACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAATGGGAAAGCA
ACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTGTACTCCAAG
CTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCTGCACAACCA
CTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[0720] SEQ ID NO:49 可变结构域AA

[0721] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTLSYSS**MSWVRQAPGKGLEWVSF**ITPSTGYT**HYADSVKG RFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARRALVFDY**WGQGTLVTVSS*

[0722] SEQ ID NO:50 可变结构域DNA

[0723] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG
GCCAGTGGCTTTACCCTCAGTTATTCTTCTATGTCATGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CTTTATTACTCCGTCTACTGGCTATACCCACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGACGGGCG
CTGGTGTTCGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGTCG

[0724]

SEQ ID NO: 10	CDR1 (AA) (IMGT)	***GFTLSYSS***
SEQ ID NO: 13	CDR1 (AA) (Kabat)	*YSSMS*
SEQ ID NO: 11	CDR2 (AA) (IMGT)	***ITPSTGYT***
SEQ ID NO: 14	CDR2 (AA) Kabat)	*FITPSTGYTHYADSVKG*
SEQ ID NO: 51	CDR3 (AA) (IMGT)	***ARRALVFDY***
SEQ ID NO: 52	CDR3 (AA) (Kabat)	*RALVFDY*

[0725] FS28-024-053mAb轻链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0726] SEQ ID NO:16 轻链AA

[0727] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSYL**AWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQASSYPLT**FGQGTKVEIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC

[0728] SEQ ID NO:17 轻链DNA

[0729] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC
CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT
TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA
CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAAGCTTCTTCTTATCCTCTCACGTTCGGC

CAAGGGACCAAGGTGGAAATCAAACGTACTGTGGCCGCTCCTAGCGTGTTCATTTTTCCGCCATCCGACGAGCAGCT
CAAGTCCGGCACCGCCTCCGTGGTCTGCCTGCTCAACAACTTCTACCCTCGCGAAGCTAAGGTCCAGTGGAAGGTCG
ACAATGCCCTGCAGTCCGGAAACTCGCAGGAAAGCGTGACTGAACAGGACTCCAAGGACTCCACCTATTCACTGTCC
TCGACTCTGACCCTGAGCAAGGCGGATTACGAAAAGCACAAAGTGTACGCATGCGAAGTGACCCACCAGGGTCTTTC
GTCCCCCGTGACCAAGAGCTTCAACAGAGGAGAGTGT

[0730] SEQ ID NO:18 可变结构域AA

[0731] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQASSYPLT**FGQGTKVEIK*

[0732] SEQ ID NO:19 可变结构域DNA

[0733] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC
CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT
TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA
CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAAGCTTCTTCTTATCCTCTCACGTTCGGC
CAAGGGACCAAGGTGGAAATCAAA

[0734]

SEQ ID NO: 20	CDR1 (AA) (IMGT)	***QSVSSSY***
SEQ ID NO: 23	CDR1 (AA) (Kabat)	*RASQSVSSSYLA*
SEQ ID NO: 21	CDR2 (AA) (IMGT)	***GAS***
SEQ ID NO: 24	CDR2 (AA) (Kabat)	*GASSRAT*
SEQ ID NO: 22	CDR3 (AA) (IMGT)	***QQASSYPLT***
SEQ ID NO: 22	CDR3 (AA) (Kabat)	*QQASSYPLT*

[0735] FS28-024-060mAb(具有LALA)的重链和轻链的氨基酸序列

[0736] SEQ ID NO:55 重链AA(具有LALA)

[0737] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTLSYSS**MSWVRQAPGKGLEWVSF**ITPSTGYT**HYADSVKG RFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARRALWFDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSG
GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH
KPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE
VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF
FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0738] SEQ ID NO:16 轻链AA

[0739] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQASSYPLT**FGQGTKVEIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN
FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP
VTKSFNRGEC

[0740] FS28-026mAb(具有LALA)的重链和轻链的氨基酸序列

[0741] SEQ ID NO:58 重链AA(具有LALA)

[0742] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFSNYA**MTWVRQAPGKGLEWVSS**ITPYYSKT**DYADSVK GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARNWYRFDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSKSTS
GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN
HKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS
FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0743] SEQ ID NO:59 轻链AA

[0744] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQYSSYPIT**FGQGTKVEIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN
FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP
VTKSFNRGEC

[0745] FS28-091mAb(具有LALA)的重链和轻链的氨基酸序列

[0746] SEQ ID NO:60 重链AA(具有LALA)

[0747] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTNYAMS**WVRQAPGKGLEWVS**SIKPYDGNTYYADSVK**GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARNRWVFDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSKSTS
GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN
HKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS
FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0748] SEQ ID NO 61 轻链AA

[0749] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRAT*GIPDRFSGSGS
*GTDFTLTISRLEPEDFAVYYC**QQYSSSPFT**FGQGTKVEIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN
FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP
VTKSFNRGEC

[0750] FS28-185mAb(具有LALA)的重链和轻链的氨基酸序列

[0751] SEQ ID NO:62 重链AA(具有LALA)

[0752] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTTSAMS**WVRQAPGKGLEWVS**RINPYEGET**NYADSVK**GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARGWSIATYYKSAMDY**WGQGTLVTVSS*ASTKGPSVFPLA
PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT
YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVD
VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV
LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0753] SEQ ID NO:195 轻链AA

[0754] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRAT*GIPDRFSGSGS
*GTDFTLTISRLEPEDFAVYYC**QQSSYSAPVT**FGQGTKVEIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLN
NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS
PVTKSFNRGEC

[0755] FS28-256mAb重链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0756] SEQ ID NO:65 重链AA(无LALA)

[0757] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTNTYMS**WVRQAPGKGLEWVSN**ISPTYSTT**NYADSVK**GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARYNSYQGGLDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN
VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK
TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG
SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0758] SEQ ID NO:66 重链DNA(无LALA)

[0759] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG
GCCAGTGGCTTTACCTTCACTAACACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC
TCTTACCAGGGTGGCTTGGACTACTGGGGCCAGGGAACCTTGGTCACCGTCTCGAGTGCTAGCACTAAGGGCCCGTC
GGTGTTCCCGCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACT
TTCCCGAGCCCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAG
TCCTCTGGCCTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAA
TGTCAACCATAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCC
CGCCTTGCCCAGCCCCGGAACTGCTGGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATG
ATCTCACGGACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTA
CGTGGATGGAGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGT

CCGTGCTCACTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCT
GCCCCAATTGAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCG
GGACGAGCTGACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAAT
GGGAAAGCAACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTG
TACTCCAAGCTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCT
GCACAACCACTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[0760] SEQ ID NO:67 重链AA(具有LALA)

[0761] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTNTY**MSWVRQAPGKGLEWVSN**ISPTYSTT**NYADSVK*
*GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCA**RYNSYQGGLDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN
VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0762] SEQ ID NO:68 重链DNA(具有LALA)

[0763] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG
GCCAGTGGCTTTACCTTCACTAACACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC
TCTTACCAGGGTGGCTTGGACTACTGGGGCCAGGGAACCTTGGTCACCGTCTCGAGTGCTAGCACTAAGGGCCCGTC
GGTGTTCCCGCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACT
TTCCCGAGCCCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAG
TCCTCTGGCCTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAA
TGTCAACCATAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCC
CGCCTTGCCCAGCCCCGGAAGCTGCCGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATG
ATCTCACGGACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTA
CGTGGATGGAGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGT
CCGTGCTCACTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCT
GCCCCAATTGAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCG
GGACGAGCTGACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAAT
GGGAAAGCAACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTG
TACTCCAAGCTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCT
GCACAACCACTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[0764] SEQ ID NO:69 可变结构域AA

[0765] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTNTY**MSWVRQAPGKGLEWVSN**ISPTYSTT**NYADSVK*
*GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCA**RYNSYQGGLDY**WGQGTLVTVSS*

[0766] SEQ ID NO:70 可变结构域DNA

[0767] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG
GCCAGTGGCTTTACCTTCACTAACACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC
TCTTACCAGGGTGGCTTGGACTACTGGGGCCAGGGAACCTTGGTCACCGTCTCGAGT

[0768]

SEQ ID NO: 71	CDR1 (AA) (IMGT)	***GFTFTNTY***
SEQ ID NO: 72	CDR1 (AA) (Kabat)	*NTYMS*
SEQ ID NO: 73	CDR2 (AA) (IMGT)	***ISPTYSTT***
SEQ ID NO: 74	CDR2 (AA) Kabat)	*NISPTYSTTNYADSVKG*
SEQ ID NO: 75	CDR3 (AA) (IMGT)	***ARYNSYQGGLDY***
SEQ ID NO: 76	CDR3 (AA) (Kabat)	*YNSYQGGLDY*

[0769] FS28-256mAb轻链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0770] SEQ ID NO:77 轻链AA

[0771] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQSYYYPIT**FGQGTKVEIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC

[0772] SEQ ID NO:78 轻链DNA

[0773] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAATCTTATTATTATCCTATCACGTTCGGC CAAGGGACCAAGGTGGAAATCAAACGTACTGTGGCCGCTCCTAGCGTGTTCATTTTTCCGCCATCCGACGAGCAGCT CAAGTCCGGCACCGCCTCCGTGGTCTGCCTGCTCAACAACTTCTACCCTCGCGAAGCTAAGGTCCAGTGGAAGGTCG ACAATGCCCTGCAGTCCGGAAACTCGCAGGAAAGCGTGACTGAACAGGACTCCAAGGACTCCACCTATTCACTGTCC TCGACTCTGACCCTGAGCAAGGCGGATTACGAAAAGCACAAAGTGTACGCATGCGAAGTGACCCACCAGGGTCTTTC GTCCCCCGTGACCAAGAGCTTCAACAGAGGAGAGTGT

[0774] SEQ ID NO:79 可变结构域AA

[0775] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQSYYYPIT**FGQGTKVEIK*

[0776] SEQ ID NO:80 可变结构域DNA

[0777] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAATCTTATTATTATCCTATCACGTTCGGC CAAGGGACCAAGGTGGAAATCAAA

[0778]

SEQ ID NO: 20	CDR1 (AA) (IMGT)	***QSVSSSY***
SEQ ID NO: 23	CDR1 (AA) (Kabat)	*RASQSVSSSYLA*
SEQ ID NO: 21	CDR2 (AA) (IMGT)	***GAS***
SEQ ID NO: 24	CDR2 (AA) (Kabat)	*GASSRAT*
SEQ ID NO: 25	CDR3 (AA) (IMGT)	***QQSYYYPIT***
SEQ ID NO: 25	CDR3 (AA) (Kabat)	*QQSYYYPIT*

[0779] FS28-256-001mAb重链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0780] SEQ ID NO:81 重链AA(无LALA)

[0781] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTETY**MSWVRQAPGKGLEWVSN**ISPTYSTT**NYADSVKG RFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARYNSYQGGLDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSKST SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0782] SEQ ID NO:82 重链DNA(无LALA)

[0783] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG
GCCAGTGGCTTTACCTTCACTGAGACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC
TCTTACCAGGGTGGCTTGGACTACTGGGGCCAGGGAACCTTGGTCACCGTCTCGAGTGCTAGCACTAAGGGCCCGTC
GGTGTTCCCGCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACT
TTCCCGAGCCCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAG
TCCTCTGGCCTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAA
TGTCAACCATAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCC
CGCCTTGCCCAGCCCCGGAACTGCTGGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATG
ATCTCACGGACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTA
CGTGGATGGAGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGT
CCGTGCTCACTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCT
GCCCCAATTGAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCG
GGACGAGCTGACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAAT
GGGAAAGCAACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTG
TACTCCAAGCTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCT
GCACAACCACTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[0784] SEQ ID NO:89 重链AA(具有LALA)

[0785] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTETY**MSWVRQAPGKGLEWVSN**ISPTYSTT**NYADSVKG*
*RFTISRDNSKNTLYLQMNSLRAEDTAVYYCA**RYNSYQGGLDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN
HKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS
FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0786] SEQ ID NO:84 重链DNA(具有LALA)

[0787] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG
GCCAGTGGCTTTACCTTCACTGAGACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC
TCTTACCAGGGTGGCTTGGACTACTGGGGCCAGGGAACCTTGGTCACCGTCTCGAGTGCTAGCACTAAGGGCCCGTC
GGTGTTCCCGCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACT
TTCCCGAGCCCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAG
TCCTCTGGCCTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAA
TGTCAACCATAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCC
CGCCTTGCCCAGCCCCGGAAGCTGCCGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATG
ATCTCACGGACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTA
CGTGGATGGAGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGT
CCGTGCTCACTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCT

GCCCCAATTGAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCG GGACGAGCTGACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAAT GGGAAAGCAACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTG TACTCCAAGCTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCT GCACAACCACTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[0788] SEQ ID NO:63 可变结构域AA

[0789] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTETYMS**WVRQAPGKGLEWVSN**ISPTYSTT**NYADSVKG RFTISRDNSKNTLYLQMNSLRAEDTAVYYCA**RYNSYQGGLDY**WGQGTLVTVSS*

[0790] SEQ ID NO:64 可变结构域DNA

[0791] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG GCCAGTGGCTTTACCTTCACTGAGACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC TCTTACCAGGGTGGCTTGGACTACTGGGGCCAGGGAACCTTGGTCACCGTCTCGAGT

[0792]

SEQ ID NO: 85	CDR1 (AA) (IMGT)	***GFTFTETY***
SEQ ID NO: 86	CDR1 (AA) (Kabat)	*ETYMS*
SEQ ID NO: 73	CDR2 (AA) (IMGT)	***ISPTYSTT***
SEQ ID NO: 74	CDR2 (AA) Kabat)	*NISPTYSTTNYADSVKG*
SEQ ID NO: 75	CDR3 (AA) (IMGT)	***ARYNSYQGGLDY***
SEQ ID NO: 76	CDR3 (AA) (Kabat)	*YNSYQGGLDY*

[0793] FS28-256-001mAb轻链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0794] SEQ ID NO:83 轻链AA

[0795] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQHNQYPNT**FGQGTKVEIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLN NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGEC

[0796] SEQ ID NO:92 轻链DNA

[0797] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAACATAATCAGTATCCGAATACGTTCGGC CAAGGGACCAAGGTGGAAATCAAACGTACTGTAGCAGCTCCTTCCGTGTTCATCTTTCCGCCCAGTGATGAGCAGCT GAAGTCAGGTACTGCTTCCGTGGTTTGCCTGCTCAACAACTTTTACCCCAGAGAAGCCAAAGTCCAGTGGAAAGTGG ACAATGCGTTGCAAAGCGGGAACTCTCAGGAATCCGTCACAGAGCAGGACTCTAAGGACTCCACCTATAGCCTCTCT AGTACGCTGACACTGAGCAAAGCCGATTACGAGAAGCACAAGGTGTATGCCTGTGAGGTTACCCATCAAGGCCTTAG CTCACCAGTGACCAAGAGCTTCAATAGGGGAGAATGC

[0798] SEQ ID NO:93 可变结构域AA

[0799] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQHNQYPNT**FGQGTKVEIK*

[0800] SEQ ID NO:94 可变结构域DNA

[0801] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA

CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAACATAATCAGTATCCGAATACGTTCGGC
CAAGGGACCAAGGTGGAAATCAAA

[0802]

SEQ ID NO: 20	CDR1 (AA) (IMGT)	***QSVSSSY***
SEQ ID NO: 23	CDR1 (AA) (Kabat)	*RASQSVSSSYLA*
SEQ ID NO: 21	CDR2 (AA) (IMGT)	***GAS***
SEQ ID NO: 24	CDR2 (AA) (Kabat)	*GASSRAT*
SEQ ID NO: 34	CDR3 (AA) (IMGT)	***QQHNQYPNT***
SEQ ID NO: 34	CDR3 (AA) (Kabat)	*QQHNQYPNT*

[0803] FS28-256-005mAb重链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0804] SEQ ID NO:87 重链AA(无LALA)

[0805]
*EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTETY**MSWVRQAPGKGLEWVSN**ISPTYSTT**NYADSVKG*
*RFTISRDNSKNTLYLQMNSLRAEDTAVYYCA**RYNSYQGGLDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN
HKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS
FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0806] SEQ ID NO:88 重链DNA(无LALA)

[0807] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG
GCCAGTGGCTTTACCTTCACTGAGACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC
TCTTACCAGGGTGGCTTGGACTACTGGGGCCAGGGAACCTTGGTCACCGTCTCGAGTGCTAGCACTAAGGGCCCGTC
GGTGTTCCCGCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACT
TTCCCGAGCCCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAG
TCCTCTGGCCTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAA
TGTCAACCATAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCC
CGCCTTGCCCAGCCCCGGAACTGCTGGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATG
ATCTCACGGACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTA
CGTGGATGGAGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGT
CCGTGCTCACTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCT
GCCCCAATTGAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCG
GGACGAGCTGACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAAT
GGGAAAGCAACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTG
TACTCCAAGCTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCT
GCACAACCACTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[0808] SEQ ID NO:89 重链AA(具有LALA)

[0809]
*EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTETY**MSWVRQAPGKGLEWVSN**ISPTYSTT**NYADSVKG*
*RFTISRDNSKNTLYLQMNSLRAEDTAVYYCA**RYNSYQGGLDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN
HKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS
FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0810] SEQ ID NO:84 重链DNA(具有LALA)

[0811] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG

GCCAGTGGCTTTACCTTCACTGAGACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC
TCTTACCAGGGTGGCTTGGACTACTGGGGCCAGGGAACCTTGGTCACCGTCTCGAGTGCTAGCACTAAGGGCCCGTC
GGTGTTCCCGCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACT
TTCCCGAGCCCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAG
TCCTCTGGCCTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAA
TGTCAACCATAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCC
CGCCTTGCCCAGCCCCGGAAGCTGCCGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATG
ATCTCACGGACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTA
CGTGGATGGAGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGT
CCGTGCTCACTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCT
GCCCCAATTGAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCG
GGACGAGCTGACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAAT
GGGAAAGCAACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTG
TACTCCAAGCTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCT
GCACAACCACTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[0812] SEQ ID NO:63 可变结构域AA

[0813] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTETY**MSWVRQAPGKGLEWVSN**ISPTYSTT**NYADSVKG RFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARYNSYQGGLDY**WGQGTLVTVSS*

[0814] SEQ ID NO:64 可变结构域DNA

[0815] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG
GCCAGTGGCTTTACCTTCACTGAGACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC
TCTTACCAGGGTGGCTTGGACTACTGGGGCCAGGGAACCTTGGTCACCGTCTCGAGT

[0816]

SEQ ID NO: 85	CDR1 (AA) (IMGT)	***GFTFTETY***
SEQ ID NO: 86	CDR1 (AA) (Kabat)	*ETYMS*
SEQ ID NO: 73	CDR2 (AA) (IMGT)	***ISPTYSTT***
SEQ ID NO: 74	CDR2 (AA) Kabat)	*NISPTYSTTNYADSVKG*
SEQ ID NO: 75	CDR3 (AA) (IMGT)	***ARYNSYQGGLDY***
SEQ ID NO: 76	CDR3 (AA) (Kabat)	*YNSYQGGLDY*

[0817] FS28-256-005mAb轻链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0818] SEQ ID NO:90 轻链AA

[0819] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSYLA**WYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQALGYPHT**FGQGTKVEIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLN NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGEC

[0820] SEQ ID NO:91 轻链DNA

[0821] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC
CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT
TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA

CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAAGCTTTGGGTTATCCTCATACGTTCGGC
CAAGGGACCAAGGTGGAAATCAAACGTACTGTAGCAGCTCCTTCCGTGTTCATCTTTCCGCCCAGTGATGAGCAGCT
GAAGTCAGGTACTGCTTCCGTGGTTTGCCTGCTCAACAACTTTTACCCCAGAGAAGCCAAAGTCCAGTGGAAAGTGG
ACAATGCGTTGCAAAGCGGGAACTCTCAGGAATCCGTCACAGAGCAGGACTCTAAGGACTCCACCTATAGCCTCTCT
AGTACGCTGACACTGAGCAAAGCCGATTACGAGAAGCACAAGGTGTATGCCTGTGAGGTTACCCATCAAGGCCTTAG
CTCACCAGTGACCAAGAGCTTCAATAGGGGAGAATGC

[0822] SEQ ID NO:53 可变结构域AA

[0823] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQALGYPHT**FGQGTKVEIK*

[0824] SEQ ID NO:54 可变结构域DNA

[0825] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC
CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT
TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA
CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAAGCTTTGGGTTATCCTCATACGTTCGGC
CAAGGGACCAAGGTGGAAATCAAA

[0826]

SEQ ID NO: 20	CDR1 (AA) (IMGT)	***QSVSSSY***
SEQ ID NO: 23	CDR1 (AA) (Kabat)	*RASQSVSSSYLA*
SEQ ID NO: 21	CDR2 (AA) (IMGT)	***GAS***
SEQ ID NO: 24	CDR2 (AA) (Kabat)	*GASSRAT*
SEQ ID NO: 43	CDR3 (AA) (IMGT)	***QQALGYPHT***
SEQ ID NO: 43	CDR3 (AA) (Kabat)	*QQALGYPHT*

[0827] FS28-256-012mAb重链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0828] SEQ ID NO:105 重链AA(无LALA)

[0829] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTHTYMS**WVRQAPGKGLEWVSN**ISPTYSTT**NYADSVK GRFTISRDNNKNTLYLQMNSLRAEDTAVYYCA**RYNAYHAALDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE

[0830] DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0831] SEQ ID NO:106 重链DNA(无LALA)

[0832] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG
GCCAGTGGCTTTACCTTCACTCATACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
ACAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC
GCGTATCATGCTGCTCTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGTGCTAGCACTAAGGGCCCGTC
GGTGTTCCCGCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACT
TTCCCGAGCCCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAG
TCCTCTGGCCTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAA
TGTCAACCATAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCC
CGCCTTGCCCAGCCCCGGAACTGCTGGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATG
ATCTCACGGACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTA
CGTGGATGGAGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGT

CCGTGCTCACTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCT
GCCCCAATTGAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCG
GGACGAGCTGACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAAT
GGGAAAGCAACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTG
TACTCCAAGCTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCT
GCACAACCACTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[0833] SEQ ID NO:107 重链AA(具有LALA)

[0834] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTHTY**MSWVRQAPGKGLEWVSN**ISPTYSTT**NYADSVK GRFTISRDNNKNTLYLQMNSLRAEDTAVYYCA**RYNAYHAALDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0835] SEQ ID NO:108 重链DNA(具有LALA)

[0836] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG
GCCAGTGGCTTTACCTTCACTCATACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
ACAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC
GCGTATCATGCTGCTCTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGTGCTAGCACTAAGGGCCCGTC
GGTGTTCCCGCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACT
TTCCCGAGCCCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAG
TCCTCTGGCCTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAA
TGTCAACCATAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCC
CGCCTTGCCCAGCCCCGGAAGCTGCCGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATG
ATCTCACGGACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTA
CGTGGATGGAGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGT
CCGTGCTCACTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCT
GCCCCAATTGAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCG
GGACGAGCTGACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAAT
GGGAAAGCAACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTG
TACTCCAAGCTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCT
GCACAACCACTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[0837] SEQ ID NO:109 可变结构域AA

[0838] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTHTY**MSWVRQAPGKGLEWVSN**ISPTYSTT**NYADSVK*

[0839] *GRFTISRDNNKNTLYLQMNSLRAEDTAVYYCA**RYNAYHAALDY**WGQGTLVTVSS*

[0840] SEQ ID NO:110 可变结构域DNA

[0841] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG
GCCAGTGGCTTTACCTTCACTCATACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
ACAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC

GCGTATCATGCTGCTCTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGT

[0842]

SEQ ID NO: 98	CDR1 (AA) (IMGT)	***GFTFTHTY***
SEQ ID NO: 97	CDR1 (AA) (Kabat)	*HTYMS*
SEQ ID NO: 73	CDR2 (AA) (IMGT)	***ISPTYSTT***
SEQ ID NO: 74	CDR2 (AA) Kabat)	*NISPTYSTTNYADSVKG*
SEQ ID NO: 99	CDR3 (AA) (IMGT)	***ARYNAYHAALDY***
SEQ ID NO: 100	CDR3 (AA) (Kabat)	*YNAYHAALDY*

[0843] FS28-256-012mAb轻链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0844] SEQ ID NO:77 轻链AA

[0845] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQSYYYPIT**FGQGTKVEIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC

[0846] SEQ ID NO:78 轻链DNA

[0847] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAATCTTATTATTATCCTATCACGTTCGGC CAAGGGACCAAGGTGGAAATCAAACGTACTGTGGCCGCTCCTAGCGTGTTCATTTTTCCGCCATCCGACGAGCAGCT CAAGTCCGGCACCGCCTCCGTGGTCTGCCTGCTCAACAACTTCTACCCTCGCGAAGCTAAGGTCCAGTGGAAGGTCG ACAATGCCCTGCAGTCCGGAAACTCGCAGGAAAGCGTGACTGAACAGGACTCCAAGGACTCCACCTATTCACTGTCC TCGACTCTGACCCTGAGCAAGGCGGATTACGAAAAGCACAAAGTGTACGCATGCGAAGTGACCCACCAGGGTCTTTC GTCCCCCGTGACCAAGAGCTTCAACAGAGGAGAGTGT

[0848] SEQ ID NO:79 可变结构域AA

[0849] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQSYYYPIT**FGQGTKVEIK*

[0850] SEQ ID NO:80 可变结构域DNA

[0851] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAATCTTATTATTATCCTATCACGTTCGGC CAAGGGACCAAGGTGGAAATCAAA

[0852]

SEQ ID NO: 20	CDR1 (AA) (IMGT)	***QSVSSSY***
SEQ ID NO: 23	CDR1 (AA) (Kabat)	*RASQSVSSSYLA*
SEQ ID NO: 21	CDR2 (AA) (IMGT)	***GAS***
SEQ ID NO: 24	CDR2 (AA) (Kabat)	*GASSRAT*
SEQ ID NO: 25	CDR3 (AA) (IMGT)	***QQSYYYPIT***
SEQ ID NO: 25	CDR3 (AA) (Kabat)	*QQSYYYPIT*

[0853] FS28-256-014mAb重链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0854] SEQ ID NO:117 重链AA(无LALA)

[0855] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTDTY**MSWVRQAPGKGLEWVSN**ISPTYSTT**NYADSVK GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARYNAYAAGLDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0856] SEQ ID NO:118 重链DNA(无LALA)

[0857] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG GCCAGTGGCTTTACCTTCACTGATACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC GCGTATGCGGCGGGTCTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGTGCTAGCACTAAGGGCCCGTC GGTGTTCCCGCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACT TTCCCGAGCCCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAG TCCTCTGGCCTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAA TGTCAACCATAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCC CGCCTTGCCCAGCCCCGGAACTGCTGGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATG ATCTCACGGACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTA CGTGGATGGAGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGT CCGTGCTCACTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCT GCCCCAATTGAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCG GGACGAGCTGACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAAT GGGAAAGCAACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTG TACTCCAAGCTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCT GCACAACCACTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[0858] SEQ ID NO:119 重链AA(具有LALA)

[0859] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTDTY**MSWVRQAPGKGLEWVSN**ISPTYSTT**NYADSVK GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARYNAYAAGLDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0860] SEQ ID NO:120 重链DNA(具有LALA)

[0861] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGC GGCCAGTGGCTTTACCTTCACTGATACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTT AGCAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACA ACAGCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATA CAACGCGTATGCGGCGGGTCTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGTGCTAGCACTAAGGGC CCGTCGGTGTTCCCGCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGG ATTACTTTCCCGAGCCCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGT GCTTCAGTCCTCTGGCCTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTAT ATCTGTAATGTCAACCATAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTC

ACACTTGCCCGCCTTGCCCAGCCCCGGAAGCTGCCGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGA
TACCCTGATGATCTCACGGACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAA
TTCAATTGGTACGTGGATGGAGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCT
ACCGCGTGGTGTCCGTGCTCACTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAA
CAAGGCGCTGCCTGCCCCAATTGAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACC
CTGCCTCCCTCTCGGGACGAGCTGACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGG
ATATCGCCGTGGAATGGGAAAGCAACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGA
CGGGAGCTTCTTCTTGTACTCCAAGCTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCC
GTGATGCATGAGGCGCTGCACAACCACTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGASEQ ID NO:115 可变结构域AA

[0862] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTDTY**MSWVRQAPGKGLEWVSN**ISPTYSTT**NYADSVK GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCA**RYNAYAAGLDY**WGQGTLVTVSS*

[0863] SEQ ID NO:116 可变结构域DNA

[0864] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG
GCCAGTGGCTTTACCTTCACTGATACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC
GCGTATGCGGCGGGTCTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGT

[0865]

SEQ ID NO: 111	CDR1 (AA) (IMGT)	***GFTFTDTY***
SEQ ID NO: 112	CDR1 (AA) (Kabat)	*DTYMS*
SEQ ID NO: 73	CDR2 (AA) (IMGT)	***ISPTYSTT***
SEQ ID NO: 74	CDR2 (AA) Kabat)	*NISPTYSTTNYADSVKG*
SEQ ID NO: 113	CDR3 (AA) (IMGT)	***ARYNAYAAGLDY***
SEQ ID NO: 114	CDR3 (AA) (Kabat)	*YNAYAAGLDY*

[0866] FS28-256-014mAb轻链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0867] SEQ ID NO:77 轻链AA

[0868] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQSYYYPIT**FGQGTKVEIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC

[0869] SEQ ID NO:78 轻链DNA

[0870] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC
CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT
TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA
CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAATCTTATTATTATCCTATCACGTTCGGC
CAAGGGACCAAGGTGGAAATCAAACGTACTGTGGCCGCTCCTAGCGTGTTCATTTTTCCGCCATCCGACGAGCAGCT
CAAGTCCGGCACCGCCTCCGTGGTCTGCCTGCTCAACAACTTCTACCCTCGCGAAGCTAAGGTCCAGTGGAAGGTCG
ACAATGCCCTGCAGTCCGGAAACTCGCAGGAAAGCGTGACTGAACAGGACTCCAAGGACTCCACCTATTCACTGTCC
TCGACTCTGACCCTGAGCAAGGCGGATTACGAAAAGCACAAAGTGTACGCATGCGAAGTGACCCACCAGGGTCTTTC
GTCCCCCGTGACCAAGAGCTTCAACAGAGGAGAGTGT

[0871] SEQ ID NO:79 可变结构域AA

[0872] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQSYYYPIT**FGQGTKVEIK*

[0873] SEQ ID NO:80 可变结构域DNA

[0874] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGCCGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGATTTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGACAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAATCTTATTATTATCCTATCACGTTCGGCCAAGGGACCAAGGTGGAAATCAAA

[0875]

SEQ ID NO: 20	CDR1 (AA) (IMGT)	***QSVSSSY***
SEQ ID NO: 23	CDR1 (AA) (Kabat)	*RASQSVSSSYLA*
SEQ ID NO: 21	CDR2 (AA) (IMGT)	***GAS***
SEQ ID NO: 24	CDR2 (AA) (Kabat)	*GASSRAT*
SEQ ID NO: 25	CDR3 (AA) (IMGT)	***QQSYYYPIT***
SEQ ID NO: 25	CDR3 (AA) (Kabat)	*QQSYYYPIT*

[0876] FS28-256-018mAb重链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0877] SEQ ID NO:123 重链AA(无LALA)

[0878] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTQTY**MSWVRQAPGKGLEWVSNISPTYSTTNYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARYNAYQIGLDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0879] SEQ ID NO:124 重链DNA(无LALA)

[0880] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCGGCCAGTGGCTTTACCTTCACTCAGACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAGCAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACAGCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAACGCTTATCAGATTGGGTTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGTGCTAGCACTAAGGGCCCGTCGGTGTTCCCGCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACTTTCCCGAGCCCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAGTCCTCTGGCCTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAATGTCAACCATAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCCCGCCTTGCCCAGCCCCGGAACTGCTGGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATGATCTCACGGACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTACGTGGATGGAGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGTCCGTGCTCACTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCTGCCCCAATTGAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCGGGACGAGCTGACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAATGGGAAAGCAACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTGTACTCCAAGCTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCTGCACAACCACTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[0881] SEQ ID NO:125 重链AA(具有LALA)

[0882] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTQTY**MSWVRQAPGKGLEWVSN**ISPTYSTT**NYADSVK GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARYNAYQIGLDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0883] SEQ ID NO:126 重链DNA(具有LALA)

[0884] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG GCCAGTGGCTTTACCTTCACTCAGACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC GCTTATCAGATTGGGTTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGTGCTAGCACTAAGGGCCCGTC GGTGTTCCCGCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACT TTCCCGAGCCCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAG TCCTCTGGCCTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAA TGTCAACCATAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCC CGCCTTGCCCAGCCCCGGAAGCTGCCGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATG ATCTCACGGACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTA CGTGGATGGAGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGT CCGTGCTCACTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCT GCCCCAATTGAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCG GGACGAGCTGACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAAT GGGAAAGCAACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTG TACTCCAAGCTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCT GCACAACCACTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[0885] SEQ ID NO:121 可变结构域AA

[0886] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTQTY**MSWVRQAPGKGLEWVSN**ISPTYSTT**NYADSVK GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARYNAYQIGLDY**WGQGTLVTVSS*

[0887] SEQ ID NO:122 可变结构域DNA

[0888] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG GCCAGTGGCTTTACCTTCACTCAGACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC GCTTATCAGATTGGGTTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGT

[0889]

SEQ ID NO: 101	CDR1 (AA) (IMGT)	***GFTFTQTY***
SEQ ID NO: 102	CDR1 (AA) (Kabat)	*QTYMS*
SEQ ID NO: 73	CDR2 (AA) (IMGT)	***ISPTYSTT***
SEQ ID NO: 74	CDR2 (AA) Kabat)	*NISPTYSTTNYADSVKG*
SEQ ID NO: 103	CDR3 (AA) (IMGT)	***ARYNAYQIGLDY***
SEQ ID NO: 104	CDR3 (AA) (Kabat)	*YNAYQIGLDY*

[0890] FS28-256-018mAb轻链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0891] SEQ ID NO:77 轻链AA

[0892] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQSYYYPIT**FGQGTKVEIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC

[0893] SEQ ID NO:78 轻链DNA

[0894] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAATCTTATTATTATCCTATCACGTTCGGC CAAGGGACCAAGGTGGAAATCAAACGTACTGTGGCCGCTCCTAGCGTGTTCATTTTTCCGCCATCCGACGAGCAGCT CAAGTCCGGCACCGCCTCCGTGGTCTGCCTGCTCAACAACTTCTACCCTCGCGAAGCTAAGGTCCAGTGGAAGGTCG ACAATGCCCTGCAGTCCGGAAACTCGCAGGAAAGCGTGACTGAACAGGACTCCAAGGACTCCACCTATTCACTGTCC TCGACTCTGACCCTGAGCAAGGCGGATTACGAAAAGCACAAAGTGTACGCATGCGAAGTGACCCACCAGGGTCTTTC GTCCCCCGTGACCAAGAGCTTCAACAGAGGAGAGTGT

[0895] SEQ ID NO:79 可变结构域AA

[0896] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQSYYYPIT**FGQGTKVEIK*

[0897] SEQ ID NO:80 可变结构域DNA

[0898] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAATCTTATTATTATCCTATCACGTTCGGC CAAGGGACCAAGGTGGAAATCAAA

[0899]

SEQ ID NO: 20	CDR1 (AA) (IMGT)	***QSVSSSY***
SEQ ID NO: 23	CDR1 (AA) (Kabat)	*RASQSVSSSYLA*
SEQ ID NO: 21	CDR2 (AA) (IMGT)	***GAS***
SEQ ID NO: 24	CDR2 (AA) (Kabat)	*GASSRAT*

[0900]

SEQ ID NO: 25	CDR3 (AA) (IMGT)	***QQSYYYPIT***
SEQ ID NO: 25	CDR3 (AA) (Kabat)	*QQSYYYPIT*

[0901] FS28-256-021mAb重链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0902] SEQ ID NO:105 重链AA(无LALA)

[0903] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTHTYMS**WVRQAPGKGLEWVSN**ISPTYSTT**NYADSVK GRFTISRDNNKNTLYLQMNSLRAEDTAVYYCA**RYNAYHAALDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0904] SEQ ID NO:106 重链DNA(无LALA)

[0905] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG GCCAGTGGCTTTACCTTCACTCATACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA ACAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC GCGTATCATGCTGCTCTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGTGCTAGCACTAAGGGCCCGTC

GGTGTTCCCGCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACT
TTCCCGAGCCCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAG
TCCTCTGGCCTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAA
TGTCAACCATAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCC
CGCCTTGCCCAGCCCCGGAACTGCTGGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATG
ATCTCACGGACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTA
CGTGGATGGAGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGT
CCGTGCTCACTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCT
GCCCCAATTGAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCG
GGACGAGCTGACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAAT
GGGAAAGCAACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTG
TACTCCAAGCTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCT
GCACAACCACTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[0906] SEQ ID NO:107 重链AA(具有LALA)

[0907] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTHTY**MSWVRQAPGKGLEWVSN**ISPTYSTT**NYADSVK
GRFTISRDNNKNTLYLQMNSLRAEDTAVYYCA**RYNAYHAALDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN
VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0908] SEQ ID NO:108 重链DNA(具有LALA)

[0909] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG
GCCAGTGGCTTTACCTTCACTCATACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
ACAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC
GCGTATCATGCTGCTCTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGTGCTAGCACTAAGGGCCCGTC
GGTGTTCCCGCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACT
TTCCCGAGCCCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAG
TCCTCTGGCCTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAA
TGTCAACCATAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCC
CGCCTTGCCCAGCCCCGGAAGCTGCCGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATG
ATCTCACGGACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTA
CGTGGATGGAGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGT
CCGTGCTCACTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCT
GCCCCAATTGAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCG
GGACGAGCTGACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAAT
GGGAAAGCAACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTG
TACTCCAAGCTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCT
GCACAACCACTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[0910] SEQ ID NO:109 可变结构域AA

[0911] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTHTY**MSWVRQAPGKGLEWVS**NISPTYSTT**NYADSVKGRFTISRDNNKNTLYLQMNSLRAEDTAVYYCA**RYNAYHAALDY**WGQGTLVTVSS*

[0912] SEQ ID NO:110 可变结构域DNA

[0913] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCGGCCAGTGGCTTTACCTTCACTCATACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAGCAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACAACAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAACGCGTATCATGCTGCTCTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGT

[0914]

SEQ ID NO: 98	CDR1 (AA) (IMGT)	***GFTFTHTY***
SEQ ID NO: 97	CDR1 (AA) (Kabat)	*HTYMS*
SEQ ID NO: 73	CDR2 (AA) (IMGT)	***ISPTYSTT***
SEQ ID NO: 74	CDR2 (AA) Kabat)	*NISPTYSTTNYADSVKG*
SEQ ID NO: 99	CDR3 (AA) (IMGT)	***ARYNAYHAALDY***
SEQ ID NO: 100	CDR3 (AA) (Kabat)	*YNAYHAALDY*

[0915] FS28-256-021mAb轻链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0916] SEQ ID NO:83 轻链AA

[0917] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQHNQYPNT**FGQGTKVEIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[0918] SEQ ID NO:92 轻链DNA

[0919] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGCCGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGATTTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGACAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAACATAATCAGTATCCGAATACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGTACTGTAGCAGCTCCTTCCGTGTTCATCTTTCCGCCCAGTGATGAGCAGCTGAAGTCAGGTACTGCTTCCGTGGTTTGCCTGCTCAACAACTTTTACCCCAGAGAAGCCAAAGTCCAGTGGAAAGTGGACAATGCGTTGCAAAGCGGGAACTCTCAGGAATCCGTCACAGAGCAGGACTCTAAGGACTCCACCTATAGCCTCTCTAGTACGCTGACACTGAGCAAAGCCGATTACGAGAAGCACAAGGTGTATGCCTGTGAGGTTACCCATCAAGGCCTTAGCTCACCAGTGACCAAGAGCTTCAATAGGGGAGAATGC

[0920] SEQ ID NO:93 可变结构域AA

[0921] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQHNQYPNT**FGQGTKVEIK*

[0922] SEQ ID NO:94 可变结构域DNA

[0923] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGCCGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGATTTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGACAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAACATAATCAGTATCCGAATACGTTCGGCCAAGGGACCAAGGTGGAAATCAAA

[0924]

SEQ ID NO: 20	CDR1 (AA) (IMGT)	***QSVSSSY***
SEQ ID NO: 23	CDR1 (AA) (Kabat)	*RASQSVSSSYLA*
SEQ ID NO: 21	CDR2 (AA) (IMGT)	***GAS***
SEQ ID NO: 24	CDR2 (AA) (Kabat)	*GASSRAT*
SEQ ID NO: 34	CDR3 (AA) (IMGT)	***QQHNQYPNT***
SEQ ID NO: 34	CDR3 (AA) (Kabat)	*QQHNQYPNT*

[0925] FS28-256-023mAb重链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0926] SEQ ID NO:123 重链AA(无LALA)

[0927] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTQTY**MSWVRQAPGKGLEWVSN**ISPTYSTT**NYADSVK GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARYNAYQIGLDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT ISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0928] SEQ ID NO:124 重链DNA(无LALA)

[0929] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG GCCAGTGGCTTTACCTTCACTCAGACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC GCTTATCAGATTGGGTTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGTGCTAGCACTAAGGGCCCGTC GGTGTTCCCGCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACT TTCCCGAGCCCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAG TCCTCTGGCCTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAA TGTCAACCATAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCC CGCCTTGCCCAGCCCCGGAACTGCTGGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATG ATCTCACGGACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTA CGTGGATGGAGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGT CCGTGCTCACTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCT GCCCCAATTGAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCG GGACGAGCTGACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAAT GGGAAAGCAACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTG TACTCCAAGCTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCT GCACAACCACTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[0930] SEQ ID NO:125 重链AA(具有LALA)

[0931] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTQTY**MSWVRQAPGKGLEWVSN**ISPTYSTT**NYADSVK GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARYNAYQIGLDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0932] SEQ ID NO:126 重链DNA(具有LALA)

[0933] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG GCCAGTGGCTTTACCTTCACTCAGACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA

GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC
GCTTATCAGATTGGGTTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGTGCTAGCACTAAGGGCCCGTC
GGTGTTCCCGCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACT
TTCCCGAGCCCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAG
TCCTCTGGCCTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAA
TGTCAACCATAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCC
CGCCTTGCCCAGCCCCGGAAGCTGCCGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATG
ATCTCACGGACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTA
CGTGGATGGAGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGT
CCGTGCTCACTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCT
GCCCCAATTGAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCG
GGACGAGCTGACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAAT
GGGAAAGCAACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTG
TACTCCAAGCTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCT
GCACAACCACTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[0934] SEQ ID NO:121 可变结构域AA

[0935] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTQTY**MSWVRQAPGKGLEWVSN**ISPTYSTT**NYADSVK GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARYNAYQIGLDY**WGQGTLVTVSS*

[0936] SEQ ID NO:122 可变结构域DNA

[0937] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG
GCCAGTGGCTTTACCTTCACTCAGACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC
GCTTATCAGATTGGGTTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGT

[0938]

SEQ ID NO: 101	CDR1 (AA) (IMGT)	***GFTFTQTY***
SEQ ID NO: 102	CDR1 (AA) (Kabat)	*QTYMS*
SEQ ID NO: 73	CDR2 (AA) (IMGT)	***ISPTYSTT***
SEQ ID NO: 74	CDR2 (AA) Kabat)	*NISPTYSTTNYADSVKG*
SEQ ID NO: 103	CDR3 (AA) (IMGT)	***ARYNAYQIGLDY***
SEQ ID NO: 104	CDR3 (AA) (Kabat)	*YNAYQIGLDY*

[0939] FS28-256-026mAb重链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0940] SEQ ID NO:123 重链AA(无LALA)

[0941] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTQTY**MSWVRQAPGKGLEWVSN**ISPTYSTT**NYADSVK GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARYNAYQIGLDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSKS
TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED
PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKT
ISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS
FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0942] SEQ ID NO:124 重链DNA(无LALA)

[0943] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG
GCCAGTGGCTTTACCTTCACTCAGACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA

GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC
GCTTATCAGATTGGGTTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGTGCTAGCACTAAGGGCCCGTC
GGTGTTCCCGCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACT
TTCCCGAGCCCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAG
TCCTCTGGCCTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAA
TGTCAACCATAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCC
CGCCTTGCCCAGCCCCGGAACTGCTGGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATG
ATCTCACGGACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTA
CGTGGATGGAGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGT
CCGTGCTCACTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCT
GCCCCAATTGAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCG
GGACGAGCTGACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAAT
GGGAAAGCAACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTG
TACTCCAAGCTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCT
GCACAACCACTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[0944] SEQ ID NO:125 重链AA(具有LALA)

[0945] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTQTY**MSWVRQAPGKGLEWVSN**ISPTYSTT**NYADSVK*
*GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC**ARYNAYQIGLDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSKS
TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK
TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG
SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0946] SEQ ID NO:126 重链DNA(具有LALA)

[0947] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG
GCCAGTGGCTTTACCTTCACTCAGACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC
GCTTATCAGATTGGGTTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGTGCTAGCACTAAGGGCCCGTC
GGTGTTCCCGCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACT
TTCCCGAGCCCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAG
TCCTCTGGCCTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAA
TGTCAACCATAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCC
CGCCTTGCCCAGCCCCGGAAGCTGCCGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATG
ATCTCACGGACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTA
CGTGGATGGAGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGT
CCGTGCTCACTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCT
GCCCCAATTGAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCG
GGACGAGCTGACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAAT
GGGAAAGCAACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTG
TACTCCAAGCTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCT
GCACAACCACTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[0948] SEQ ID NO:121 可变结构域AA

[0949] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTQTY**MSWVRQAPGKGLEWVSN**ISPTYSTT**NYADSVK GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCA**RYNAYQIGLDY**WGQGTLVTVSS*

[0950] SEQ ID NO:122 可变结构域DNA

[0951] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG GCCAGTGGCTTTACCTTCACTCAGACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA GCAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC GCTTATCAGATTGGGTTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGT

[0952]

SEQ ID NO: 101	CDR1 (AA) (IMGT)	***GFTFTQTY***
SEQ ID NO: 102	CDR1 (AA) (Kabat)	*QTYMS*
SEQ ID NO: 73	CDR2 (AA) (IMGT)	***ISPTYSTT***
SEQ ID NO: 74	CDR2 (AA) Kabat)	*NISPTYSTTNYADSVKG*
SEQ ID NO: 103	CDR3 (AA) (IMGT)	***ARYNAYQIGLDY***
SEQ ID NO: 104	CDR3 (AA) (Kabat)	*YNAYQIGLDY*

[0953] FS28-256-023mAb轻链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0954] SEQ ID NO:83 轻链AA

[0955] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSYL**AWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQHNQYPNT**FGQGTKVEIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLN NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGEC

[0956] SEQ ID NO:92 轻链DNA

[0957] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAACATAATCAGTATCCGAATACGTTCGGC CAAGGGACCAAGGTGGAAATCAAACGTACTGTAGCAGCTCCTTCCGTGTTCATCTTTCCGCCCAGTGATGAGCAGCT GAAGTCAGGTACTGCTTCCGTGGTTTGCCTGCTCAACAACTTTTACCCCAGAGAAGCCAAAGTCCAGTGGAAAGTGG ACAATGCGTTGCAAAGCGGGAACTCTCAGGAATCCGTCACAGAGCAGGACTCTAAGGACTCCACCTATAGCCTCTCT AGTACGCTGACACTGAGCAAAGCCGATTACGAGAAGCACAAGGTGTATGCCTGTGAGGTTACCCATCAAGGCCTTAG CTCACCAGTGACCAAGAGCTTCAATAGGGGAGAATGC

[0958] SEQ ID NO:93 可变结构域AA

[0959] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSYL**AWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQHNQYPNT**FGQGTKVEIK*

[0960] SEQ ID NO:94 可变结构域DNA

[0961] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAACATAATCAGTATCCGAATACGTTCGGC CAAGGGACCAAGGTGGAAATCAAA

[0962]

SEQ ID NO: 20	CDR1 (AA) (IMGT)	***QSVSSSY***
SEQ ID NO: 23	CDR1 (AA) (Kabat)	*RASQSVSSSYLA*
SEQ ID NO: 21	CDR2 (AA) (IMGT)	***GAS***
SEQ ID NO: 24	CDR2 (AA) (Kabat)	*GASSRAT*
SEQ ID NO: 34	CDR3 (AA) (IMGT)	***QQHNQYPNT***
SEQ ID NO: 34	CDR3 (AA) (Kabat)	*QQHNQYPNT*

[0963] FS28-256-024mAb重链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0964] SEQ ID NO:105 重链AA(无LALA)

[0965] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTHTYMS**WVRQAPGKGLEWVSN**ISPTYSTT**NYADSVK GRFTISRDNNKNTLYLQMNSLRAEDTAVYYCA**RYNAYHAALDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0966] SEQ ID NO:106 重链DNA(无LALA)

[0967] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG GCCAGTGGCTTTACCTTCACTCATACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA ACAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC GCGTATCATGCTGCTCTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGTGCTAGCACTAAGGGCCCGTC GGTGTTCCCGCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACT TTCCCGAGCCCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAG TCCTCTGGCCTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAA TGTCAACCATAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCC CGCCTTGCCCAGCCCCGGAACTGCTGGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATG ATCTCACGGACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTA CGTGGATGGAGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGT CCGTGCTCACTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCT GCCCCAATTGAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCG GGACGAGCTGACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAAT GGGAAAGCAACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTG TACTCCAAGCTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCT GCACAACCACTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[0968] SEQ ID NO:107 重链AA(具有LALA)

[0969] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTHTYMS**WVRQAPGKGLEWVSN**ISPTYSTT**NYADSVK GRFTISRDNNKNTLYLQMNSLRAEDTAVYYCA**RYNAYHAALDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[0970] SEQ ID NO:108 重链DNA(具有LALA)

[0971] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG GCCAGTGGCTTTACCTTCACTCATACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA

ACAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC
GCGTATCATGCTGCTCTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGTGCTAGCACTAAGGGCCCGTC
GGTGTTCCCGCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACT
TTCCCGAGCCCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAG
TCCTCTGGCCTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAA
TGTCAACCATAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCC
CGCCTTGCCCAGCCCCGGAAGCTGCCGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATG
ATCTCACGGACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTA
CGTGGATGGAGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGT
CCGTGCTCACTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCT
GCCCCAATTGAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCG
GGACGAGCTGACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAAT
GGGAAAGCAACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTG
TACTCCAAGCTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCT
GCACAACCACTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[0972] SEQ ID NO:109 可变结构域AA

[0973] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTHTY**MSWVRQAPGKGLEWVSN**ISPTYSTT**NYADSVK GRFTISRDNNKNTLYLQMNSLRAEDTAVYYC**ARYNAYHAALDY**WGQGTLVTVSS*

[0974] SEQ ID NO:110 可变结构域DNA

[0975] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG
GCCAGTGGCTTTACCTTCACTCATACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
ACAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC
GCGTATCATGCTGCTCTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGT

[0976]

SEQ ID NO: 98	CDR1 (AA) (IMGT)	***GFTFTHTY***
SEQ ID NO: 97	CDR1 (AA) (Kabat)	*HTYMS*

[0977]

SEQ ID NO: 73	CDR2 (AA) (IMGT)	***ISPTYSTT***
SEQ ID NO: 74	CDR2 (AA) Kabat)	*NISPTYSTTNYADSVKG*
SEQ ID NO: 99	CDR3 (AA) (IMGT)	***ARYNAYHAALDY***
SEQ ID NO: 100	CDR3 (AA) (Kabat)	*YNAYHAALDY*

[0978] FS28-256-024mAb轻链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0979] SEQ ID NO:90 轻链AA

[0980] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQALGYPHT**FGQGTKVEIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLN NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGEC

[0981] SEQ ID NO:91 轻链DNA

[0982] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC
CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT
TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA
CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAAGCTTTGGGTTATCCTCATACGTTCGGC
CAAGGGACCAAGGTGGAAATCAAACGTACTGTAGCAGCTCCTTCCGTGTTCATCTTTCCGCCCAGTGATGAGCAGCT

GAAGTCAGGTACTGCTTCCGTGGTTTGCCTGCTCAACAACTTTTACCCCAGAGAAGCCAAAGTCCAGTGGAAAGTGG ACAATGCGTTGCAAAGCGGGAACTCTCAGGAATCCGTCACAGAGCAGGACTCTAAGGACTCCACCTATAGCCTCTCT AGTACGCTGACACTGAGCAAAGCCGATTACGAGAAGCACAAGGTGTATGCCTGTGAGGTTACCCATCAAGGCCTTAG CTCACCAGTGACCAAGAGCTTCAATAGGGGAGAATGC

[0983] SEQ ID NO:53 可变结构域AA

[0984] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQALGYPHT**FGQGTKVEIK*

[0985] SEQ ID NO:54 可变结构域DNA

[0986] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAAGCTTTGGGTTATCCTCATACGTTCGGC CAAGGGACCAAGGTGGAAATCAAA

[0987]

SEQ ID NO: 20	CDR1 (AA) (IMGT)	***QSVSSSY***
SEQ ID NO: 23	CDR1 (AA) (Kabat)	*RASQSVSSSYLA*
SEQ ID NO: 21	CDR2 (AA) (IMGT)	***GAS***
SEQ ID NO: 24	CDR2 (AA) (Kabat)	*GASSRAT*
SEQ ID NO: 43	CDR3 (AA) (IMGT)	***QQALGYPHT***
SEQ ID NO: 43	CDR3 (AA) (Kabat)	*QQALGYPHT*

[0988] FS28-256-026mAb轻链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0989] SEQ ID NO:90 轻链AA

[0990] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQALGYPHT**FGQGTKVEIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLN NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGEC

[0991] SEQ ID NO:91 轻链DNA

[0992] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAAGCTTTGGGTTATCCTCATACGTTCGGC CAAGGGACCAAGGTGGAAATCAAACGTACTGTAGCAGCTCCTTCCGTGTTCATCTTTCCGCCCAGTGATGAGCAGCT GAAGTCAGGTACTGCTTCCGTGGTTTGCCTGCTCAACAACTTTTACCCCAGAGAAGCCAAAGTCCAGTGGAAAGTGG ACAATGCGTTGCAAAGCGGGAACTCTCAGGAATCCGTCACAGAGCAGGACTCTAAGGACTCCACCTATAGCCTCTCT AGTACGCTGACACTGAGCAAAGCCGATTACGAGAAGCACAAGGTGTATGCCTGTGAGGTTACCCATCAAGGCCTTAG CTCACCAGTGACCAAGAGCTTCAATAGGGGAGAATGC

[0993] SEQ ID NO:53 可变结构域AA

[0994] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQALGYPHT**FGQGTKVEIK*

[0995] SEQ ID NO:54 可变结构域DNA

[0996] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAAGCTTTGGGTTATCCTCATACGTTCGGC

CAAGGGACCAAGGTGGAAATCAAA

[0997]

SEQ ID NO: 20	CDR1 (AA) (IMGT)	***QSVSSSY***
SEQ ID NO: 23	CDR1 (AA) (Kabat)	*RASQSVSSSYLA*
SEQ ID NO: 21	CDR2 (AA) (IMGT)	***GAS***
SEQ ID NO: 24	CDR2 (AA) (Kabat)	*GASSRAT*
SEQ ID NO: 43	CDR3 (AA) (IMGT)	***QQALGYPHT***
SEQ ID NO: 43	CDR3 (AA) (Kabat)	*QQALGYPHT*

[0998] FS28-256-027mAb重链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[0999] SEQ ID NO:105 重链AA(无LALA)

[1000] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTHTY**MSWVRQAPGKGLEWVSN**ISPTYSTT**NYADSVK GRFTISRDNNKNTLYLQMNSLRAEDTAVYYC**ARYNAYHAALDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[1001] SEQ ID NO:106 重链DNA(无LALA)

[1002] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG GCCAGTGGCTTTACCTTCACTCATACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA ACAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC GCGTATCATGCTGCTCTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGTGCTAGCACTAAGGGCCCGTC GGTGTTCCCGCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACT TTCCCGAGCCCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAG TCCTCTGGCCTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAA TGTCAACCATAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCC CGCCTTGCCCAGCCCCGGAACTGCTGGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATG ATCTCACGGACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTA CGTGGATGGAGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGT CCGTGCTCACTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCT GCCCCAATTGAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCG GGACGAGCTGACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAAT GGGAAAGCAACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTG TACTCCAAGCTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCT GCACAACCACTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[1003] SEQ ID NO:107 重链AA(具有LALA)

[1004] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTHTY**MSWVRQAPGKGLEWVSN**ISPTYSTT**NYADSVK*

[1005] *GRFTISRDNNKNTLYLQMNSLRAEDTAVYYC**ARYNAYHAALDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[1006] SEQ ID NO:108 重链DNA(具有LALA)

[1007] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG

GCCAGTGGCTTTACCTTCACTCATACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
ACAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC
GCGTATCATGCTGCTCTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGTGCTAGCACTAAGGGCCCGTC
GGTGTTCCCGCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACT
TTCCCGAGCCCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAG
TCCTCTGGCCTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAA
TGTCAACCATAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCC
CGCCTTGCCCAGCCCCGGAAGCTGCCGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATG
ATCTCACGGACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTA
CGTGGATGGAGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGT
CCGTGCTCACTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCT
GCCCCAATTGAGAAAACTATCTCGAAAGCCAAGGGACAGCCTCGAGAGCCTCAAGTGTACACCCTGCCTCCCTCTCG
GGACGAGCTGACCAAGAACCAAGTCTCCCTGACCTGTCTGGTCAAGGGATTCTACCCATCGGATATCGCCGTGGAAT
GGGAAAGCAACGGACAGCCCGAGAACAACTACAAGACGACTCCGCCCGTGCTGGATTCCGACGGGAGCTTCTTCTTG
TACTCCAAGCTGACCGTCGACAAGAGCAGATGGCAGCAGGGAAACGTGTTCTCCTGCTCCGTGATGCATGAGGCGCT
GCACAACCACTACACTCAGAAGAGCTTGTCCCTGTCGCCCGGA

[1008] SEQ ID NO:109 可变结构域AA

[1009] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTHTYMS**WVRQAPGKGLEWVSN**ISPTYSTT**NYADSVK GRFTISRDNNKNTLYLQMNSLRAEDTAVYYCA**RYNAYHAALDY**WGQGTLVTVSS*

[1010] SEQ ID NO:110 可变结构域DNA

[1011] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG
GCCAGTGGCTTTACCTTCACTCATACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CAATATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
ACAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC
GCGTATCATGCTGCTCTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGT

[1012]

SEQ ID NO: 98	CDR1 (AA) (IMGT)	***GFTFTHTY***
SEQ ID NO: 97	CDR1 (AA) (Kabat)	*HTYMS*
SEQ ID NO: 73	CDR2 (AA) (IMGT)	***ISPTYSTT***
SEQ ID NO: 74	CDR2 (AA) Kabat)	*NISPTYSTTNYADSVKG*
SEQ ID NO: 99	CDR3 (AA) (IMGT)	***ARYNAYHAALDY***
SEQ ID NO: 100	CDR3 (AA) (Kabat)	*YNAYHAALDY*

[1013] FS28-256-027mAb轻链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[1014] SEQ ID NO:95 轻链AA

[1015] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQTVPYPYT**FGQGTKVEIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLN NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGEC

[1016] SEQ ID NO:96 轻链DNA

[1017] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC
CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT
TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA

CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAAACTGTGCCGTATCCGTATACGTTCGGC
CAAGGGACCAAGGTGGAAATCAAACGTACTGTGGCCGCTCCTAGCGTGTTCATTTTTCCGCCATCCGACGAGCAGCT
CAAGTCCGGCACCGCCTCCGTGGTCTGCCTGCTCAACAACTTCTACCCTCGCGAAGCTAAGGTCCAGTGGAAGGTCG
ACAATGCCCTGCAGTCCGGAAACTCGCAGGAAAGCGTGACTGAACAGGACTCCAAGGACTCCACCTATTCACTGTCC
TCGACTCTGACCCTGAGCAAGGCGGATTACGAAAAGCACAAAGTGTACGCATGCGAAGTGACCCACCAGGGTCTTTC
GTCCCCCGTGACCAAGAGCTTCAACAGAGGAGAGTGT

[1018] SEQ ID NO:56 可变结构域AA

[1019] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQTVPYPYT**FGQGTKVEIK*

[1020] SEQ ID NO:57 可变结构域DNA

[1021] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC
CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT
TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA
CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAAACTGTGCCGTATCCGTATACGTTCGGC
CAAGGGACCAAGGTGGAAATCAAA

[1022]

SEQ ID NO: 20	CDR1 (AA) (IMGT)	***QSVSSSY***
SEQ ID NO: 23	CDR1 (AA) (Kabat)	*RASQSVSSSYLA*
SEQ ID NO: 21	CDR2 (AA) (IMGT)	***GAS***
SEQ ID NO: 24	CDR2 (AA) (Kabat)	*GASSRAT*
SEQ ID NO: 44	CDR3 (AA) (IMGT)	***QQTVPYPYT***
SEQ ID NO: 44	CDR3 (AA) (Kabat)	*QQTVPYPYT*

[1023] SEQ ID NO:175人MSLN前蛋白

[1024] cDNAAAGCTTGAATTCGCCGCCACCATGGCCCTGCCTACCGCTAGGCCTCTGCTCGGATCCTGCGGCA
CACCTGCCCTGGGAAGCCTCCTGTTCCTGCTGTTCTCCCTGGGCTGGGTGCAGCCCTCCAGAACACTGGCCGGCGAA
ACAGGACAAGAGGCTGCCCCTCTCGATGGCGTGCTCGCTAACCCCCCCAACATCAGCTCCCTGTCCCCTAGGCAGCT
CCTGGGCTTTCCCTGTGCCGAGGTCAGCGGCCTCTCCACCGAGAGGGTGAGGGAGCTGGCTGTGGCCCTGGCTCAGA
AGAACGTGAAACTGAGCACCGAGCAACTCAGGTGCCTGGCTCATAGGCTGTCCGAGCCCCCCGAGGATCTGGATGCC
CTGCCTCTCGACCTGCTGCTGTTCCTGAACCCCGACGCTTTTAGCGGCCCCCAGGCCTGCACAAGGTTCTTCAGCAG
AATCACCAAGGCCAACGTGGATCTGCTGCCCAGAGGCGCTCCCGAGAGGCAAAGACTGCTGCCCGCCGCTCTCGCCT
GTTGGGGCGTCAGAGGATCCCTGCTGAGCGAGGCCGACGTGAGAGCCCTGGGCGGCCTGGCTTGTGATCTGCCCGGC
AGGTTTGTCGCTGAGAGCGCCGAAGTGCTCCTGCCCAGACTGGTGAGCTGCCCTGGACCTCTGGACCAGGATCAACA
GGAGGCCGCCAGAGCTGCTCTGCAGGGAGGAGGACCCCCCTACGGACCTCCTAGCACCTGGTCCGTGAGCACAATGG
ACGCCCTGAGAGGCCTGCTGCCTGTGCTGGGACAGCCCATCATTAGGAGCATTCCCCAGGGCATTGTGGCCGCCTGG
AGACAGAGGAGCAGCAGGGACCCCTCCTGGAGGCAGCCTGAGAGAACAATCCTGAGGCCCAGATTCAGAAGAGAGGT
GGAGAAAACCGCCTGCCCTAGCGGCAAGAAGGCCAGAGAGATTGACGAGAGCCTGATCTTCTATAAAAAGTGGGAGC
TCGAAGCCTGCGTGGATGCTGCCCTGCTGGCCACACAGATGGACAGGGTGAACGCCATCCCCTTCACCTACGAGCAG
CTGGACGTCCTGAAGCACAAGCTCGATGAGCTGTACCCCCAGGGCTACCCCGAGTCCGTGATTCAGCATCTCGGCTA
CCTGTTCCTGAAAATGAGCCCCGAAGACATCAGGAAGTGGAACGTGACAAGCCTGGAGACCCTCAAGGCCCTGCTGG
AAGTGAACAAGGGACACGAGATGAGCCCCCAGGTGGCCACCCTCATCGACAGATTTGTGAAGGGAAGGGGACAGCTG
GATAAGGACACCCTCGACACCCTGACCGCCTTCTACCCTGGATACCTCTGCAGCCTGTCCCCCGAAGAGCTGTCCAG
CGTGCCTCCCTCCTCCATCTGGGCCGTCAGACCCCAGGATCTCGACACATGCGACCCCAGACAGCTGGATGTGCTGT

ACCCCAAGGCTAGGCTGGCCTTCCAGAACATGAACGGATCCGAATATTTCGTCAAAATCCAGAGCTTTCTGGGCGGA
GCCCCCACAGAGGACCTCAAAGCCCTGAGCCAGCAGAACGTCAGCATGGACCTGGCCACCTTTATGAAACTGAGAAC
CGACGCCGTCCTCCCTCTGACAGTGGCCGAAGTGCAGAAGCTCCTGGGCCCCCATGTGGAAGGCCTGAAGGCCGAGG
AGAGACACAGACCCGTGAGAGACTGGATTCTGAGGCAGAGGCAGGACGATCTGGATACCCTGGGCCTGGGACTGCAG
GGCGGCATTCCTAACGGATACCTGGTCCTCGACCTGAGCATGCAGGAAGCCCTGAGCGGCACACCTTGTCTGCTGGG
ACCTGGCCCTGTCCTCACCGTGCTCGCTCTGCTGCTGGCTTCCACCCTCGCCTGATGAGCGGCCGC

[1025] FS28-256-271mAb重链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[1026] SEQ ID NO:176 重链AA(无LALA)

[1027] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTHTY**MSWVRQAPGKGLEWVSA**ISPTYSTT**NYADSVK*
*GRFTISRDNNKNTLYLQMNSLRAEDTAVYYC**ARYNAYHAALDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN
VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK
TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG
SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[1028] SEQ ID NO:177 重链DNA(无LALA)

[1029] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG
GCCAGTGGCTTTACCTTCACTCATACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CGCGATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
ACAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC
GCGTATCATGCTGCTCTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGTGCTAGCACTAAGGGCCCGTC
GGTGTTCCCGCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACT
TTCCCGAGCCCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAG
TCCTCTGGCCTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAA
TGTCAACCATAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCC
CGCCTTGCCCAGCCCCGGAACTGCTGGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATG
ATCTCACGGACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTA
CGTGGATGGAGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGT
CCGTGCTCACTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCT
GCCCCAATTGAGAAAACTATCTCGAAAGCCAAGGGCCAGCCTCGAGAACCACAGGTGTACACCCTGCCCCCATCCCG
GGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGT
GGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGATCCTTCTTCCTC
TACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCCTGCAGCGTGATGCATGAGGCTCT
GCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCCGGGT

[1030] SEQ ID NO:178 重链AA(具有LALA)

[1031] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTHTY**MSWVRQAPGKGLEWVSA**ISPTYSTT**NYADSVK*
*GRFTISRDNNKNTLYLQMNSLRAEDTAVYYC**ARYNAYHAALDY**WGQGTLVTVSS*ASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN
VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[1032] SEQ ID NO:179 重链DNA(具有LALA)

[1033] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG

GCCAGTGGCTTTACCTTCACTCATACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CGCGATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
ACAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC
GCGTATCATGCTGCTCTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGTGCTAGCACTAAGGGCCCGTC
GGTGTTCCCGCTGGCCCCATCGTCCAAGAGCACATCAGGGGGTACCGCCGCCCTGGGCTGCCTTGTGAAGGATTACT
TTCCCGAGCCCGTCACAGTGTCCTGGAACAGCGGAGCCCTGACCTCCGGAGTGCATACTTTCCCGGCTGTGCTTCAG
TCCTCTGGCCTGTACTCATTGTCCTCCGTGGTCACCGTCCCTTCGTCCTCCCTGGGCACCCAGACCTATATCTGTAA
TGTCAACCATAAGCCCTCGAACACCAAGGTCGACAAGAAGGTCGAGCCGAAGTCGTGCGACAAGACTCACACTTGCC
CGCCTTGCCCAGCCCCGGAAGCTGCCGGTGGTCCTTCGGTGTTCCTCTTCCCGCCCAAGCCGAAGGATACCCTGATG
ATCTCACGGACCCCCGAAGTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCGGAAGTGAAATTCAATTGGTA
CGTGGATGGAGTGGAAGTGCACAACGCCAAGACCAAGCCACGGGAAGAACAGTACAACTCTACCTACCGCGTGGTGT
CCGTGCTCACTGTGCTGCACCAAGACTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTGTCCAACAAGGCGCTGCCT
GCCCCAATTGAGAAAACTATCTCGAAAGCCAAGGGCCAGCCTCGAGAACCACAGGTGTACACCCTGCCCCCATCCCG
GGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGT
GGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGATCCTTCTTCCTC
TACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCCTGCAGCGTGATGCATGAGGCTCT
GCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCCGGGT

[1034] SEQ ID NO:180 可变结构域AA

[1035] *EVQLLESGGGLVQPGGSLRLSCAAS**GFTFTHTYMS**WVRQAPGKGLEWVSA**ISPTYSTT**NYADSVK GRFTISRDNNKNTLYLQMNSLRAEDTAVYYCA**RYNAYHAALDY**WGQGTLVTVSS*

[1036] SEQ ID NO:181 可变结构域DNA

[1037] GAAGTGCAACTGCTGGAGTCCGGTGGTGGTCTGGTACAGCCGGGTGGTTCTCTGCGTCTGAGTTGCGCG
GCCAGTGGCTTTACCTTCACTCATACTTATATGAGCTGGGTGCGTCAGGCTCCGGGCAAAGGTCTGGAATGGGTTAG
CGCGATTTCTCCGACTTATAGCACTACCAACTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCTCGCGACAACA
ACAAGAACACGCTGTACCTGCAGATGAACTCACTGCGTGCCGAAGATACGGCCGTGTATTACTGTGCGAGATACAAC
GCGTATCATGCTGCTCTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGT

[1038]

SEQ ID NO: 98	CDR1 (AA) (IMGT)	***GFTFTHTY***
SEQ ID NO: 97	CDR1 (AA) (Kabat)	*HTYMS*
SEQ ID NO: 73	CDR2 (AA) (IMGT)	***ISPTYSTT***
SEQ ID NO: 182	CDR2 (AA) Kabat)	*AISPTYSTTNYADSVKG*
SEQ ID NO: 99	CDR3 (AA) (IMGT)	***ARYNAYHAALDY***
SEQ ID NO: 100	CDR3 (AA) (Kabat)	*YNAYHAALDY*

[1039] FS28-256-271mAb轻链的氨基酸和cDNA序列及其CDR的可变结构域和氨基酸序列

[1040] SEQ ID NO:95 轻链AA

[1041] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSYLA**WYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQTVPYPYT**FGQGTKVEIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLN NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGEC

[1042] SEQ ID NO:96 轻链DNA

[1043] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC
CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT
TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA

CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAAACTGTGCCGTATCCGTATACGTTCGGC
CAAGGGACCAAGGTGGAAATCAAACGTACTGTGGCCGCTCCTAGCGTGTTCATTTTTCCGCCATCCGACGAGCAGCT
CAAGTCCGGCACCGCCTCCGTGGTCTGCCTGCTCAACAACTTCTACCCTCGCGAAGCTAAGGTCCAGTGGAAGGTCG
ACAATGCCCTGCAGTCCGGAAACTCGCAGGAAAGCGTGACTGAACAGGACTCCAAGGACTCCACCTATTCACTGTCC
TCGACTCTGACCCTGAGCAAGGCGGATTACGAAAAGCACAAAGTGTACGCATGCGAAGTGACCCACCAGGGTCTTTC
GTCCCCCGTGACCAAGAGCTTCAACAGAGGAGAGTGT

[1044] SEQ ID NO:56 可变结构域AA

[1045] *EIVLTQSPGTLSLSPGERATLSCRAS**QSVSSSY**LAWYQQKPGQAPRLLIY**GAS**SRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQTVPYPYT**FGQGTKVEIK*

[1046] SEQ ID NO:57 可变结构域DNA

[1047] GAAATTGTGCTGACCCAGTCTCCGGGCACGTTATCTCTGAGCCCTGGTGAGCGCGCCACTCTGTCATGC
CGGGCTTCTCAAAGTGTTAGCAGTAGCTACCTGGCGTGGTATCAGCAAAAACCGGGCCAGGCCCCGCGTCTGCTGAT
TTACGGTGCATCCAGCCGTGCCACCGGCATTCCAGATCGTTTTTCCGGTAGTGGTTCTGGGACGGACTTCACTCTGA
CAATCTCACGCCTGGAACCGGAGGATTTTGCGGTGTATTACTGCCAGCAAACTGTGCCGTATCCGTATACGTTCGGC
CAAGGGACCAAGGTGGAAATCAAA

[1048]

SEQ ID NO: 20	CDR1 (AA) (IMGT)	***QSVSSSY***
SEQ ID NO: 23	CDR1 (AA) (Kabat)	*RASQSVSSSYLA*
SEQ ID NO: 21	CDR2 (AA) (IMGT)	***GAS***

[1049]

SEQ ID NO: 24	CDR2 (AA) (Kabat)	*GASSRAT*
SEQ ID NO: 44	CDR3 (AA) (IMGT)	***QQTVPYPYT***
SEQ ID NO: 44	CDR3 (AA) (Kabat)	*QQTVPYPYT*

[1050] FS22-053-008/FS28-024mAb^{2}重链和轻链的氨基酸序列

[1051] SEQ ID NO:143 重链AA(无LALA)

[1052] EVQLLESGGGLVQPGGSLRLSCAASGFTLSYSSMSWVRQAPGKGLEWVSFITPSTGYTHYADSVKGRFT
ISRDNSKNTLYLQMNSLRAEDTAVYYCARRALTFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK
DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH
TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1053] SEQ ID NO:144 重链AA(具有LALA)

[1054] *EVQLLESGGGLVQPGGSLRLSCAASGFTLSYSSMSWVRQAPGKGLEWVSFITPSTGYTHYADSVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYYCARRALTFDYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1055] SEQ ID NO:16 轻链AA

[1056] EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSG
TDFTLTISRLEPEDFAVYYCQQASSYPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK
VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1057] FS22-053-008/FS28-024-051mAb^{2}重链和轻链的氨基酸序列

[1058] SEQ ID NO:145 重链AA(无LALA)

[1059] EVQLLESGGGLVQPGGSLRLSCAASGFTLSYSSMSWVRQAPGKGLEWVSFITPSTGYTHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARRALIFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1060] SEQ ID NO:146 重链AA(具有LALA)

[1061] *EVQLLESGGGLVQPGGSLRLSCAASGFTLSYSSMSWVRQAPGKGLEWVSFITPSTGYTHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARRALIFDYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1062] SEQ ID NO:16 轻链AA

[1063] EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQASSYPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1064] FS22-053-008/FS28-024-052mAb^{2}重链和轻链的氨基酸序列

[1065] SEQ ID NO:147 重链AA(无LALA)

[1066] EVQLLESGGGLVQPGGSLRLSCAASGFTLSYSSMSWVRQAPGKGLEWVSFITPSTGYTHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARRALLFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1067] SEQ ID NO:148 重链AA(具有LALA)

[1068] *EVQLLESGGGLVQPGGSLRLSCAASGFTLSYSSMSWVRQAPGKGLEWVSFITPSTGYTHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARRALLFDYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1069] SEQ ID NO:16 轻链AA

[1070] EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQASSYPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1071] FS22-053-008/FS28-024-053mAb^{2}重链和轻链的氨基酸序列

[1072] SEQ ID NO:149 重链AA(无LALA)

[1073] EVQLLESGGGLVQPGGSLRLSCAASGFTLSYSSMSWVRQAPGKGLEWVSFITPSTGYTHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARRALVFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR

VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFY PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1074] SEQ ID BO:150 重链AA(具有LALA)

[1075] *EVQLLESGGGLVQPGGSLRLSCAASGFTLSYSSMSWVRQAPGKGLEWVSFITPSTGYTHYADSVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYYCARRALVFDYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1076] SEQ ID NO:16 轻链AA

[1077] EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSG TDFTLTISRLEPEDFAVYYCQQASSYPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1078] FS22-053-008-AA/FS28-024-060mAb^2(带有LALA)的重链和轻链的氨基酸序列

[1079] SEQ ID NO:151 重链AA(具有LALA)

[1080] EVQLLESGGGLVQPGGSLRLSCAASGFTLSYSSMSWVRQAPGKGLEWVSFITPSTGYTHYADSVKGR

[1081] *FTISRDNSKNTLYLQMNSLRAEDTAVYYCARRALWFDYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1082] SEQ ID NO:16 轻链AA

[1083] EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSG TDFTLTISRLEPEDFAVYYCQQASSYPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1084] FS22-053-008-AA/FS28-026mAb^2(具有LALA)的重链和轻链的氨基酸序列

[1085] SEQ ID NO:152 重链AA(具有LALA)

[1086] *EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMTWVRQAPGKGLEWVSSITPYYSKTDYADSVKG RFTISRDNSKNTLYLQMNSLRAEDTAVYYCARNWYRFDYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1087] SEQ ID NO:59 轻链AA

[1088] EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSG TDFTLTISRLEPEDFAVYYCQQYSSYPITFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1089] FS22-053-008-AA/FS28-091mAb^2(具有LALA)的重链和轻链的氨基酸序列

[1090] SEQ ID NO:153 重链AA(具有LALA)

[1091] *EVQLLESGGGLVQPGGSLRLSCAASGFTFTNYAMSWVRQAPGKGLEWVSSIKPYDGNTYYADSVKG RFTISRDNSKNTLYLQMNSLRAEDTAVYYCARNRWVFDYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1092] SEQ ID NO:61 轻链AA

[1093] EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYSSSPFTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1094] FS22-053-008-AA/FS28-185mAb^2(具有LALA)的重链和轻链的氨基酸序列

[1095] SEQ ID NO:154 重链AA(具有LALA)

[1096] *EVQLLESGGGLVQPGGSLRLSCAASGFTFTTSAMSWVRQAPGKGLEWVSRINPYEGETNYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGWSIATYYKSAMDYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP

[1097] PVLDSDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1098] SEQ ID NO:195 轻链AA

[1099] EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQSSYSAPVTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1100] FS22-053-008/FS28-256mAb^{2}重链和轻链的氨基酸序列

[1101] SEQ ID NO:155 重链AA(无LALA)

[1102] EVQLLESGGGLVQPGGSLRLSCAASGFTFTNTYMSWVRQAPGKGLEWVSNISPTYSTTNYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARYNSYQGGLDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1103] SEQ ID NO:156 重链AA(具有LALA)

[1104] *EVQLLESGGGLVQPGGSLRLSCAASGFTFTNTYMSWVRQAPGKGLEWVSNISPTYSTTNYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARYNSYQGGLDYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1105] SEQ ID NO:77 轻链AA

[1106] EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQSYYYPITFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1107] FS22-053-008/FS28-256-001mAb^{2}重链和轻链的氨基酸和cDNA序列

[1108] SEQ ID NO:157 重链AA(无LALA)

[1109] EVQLLESGGGLVQPGGSLRLSCAASGFTFTETYMSWVRQAPGKGLEWVSNISPTYSTTNYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARYNSYQGGLDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVK

GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1110] SEQ ID NO:158 重链AA(具有LALA)

[1111] *EVQLLESGGGLVQPGGSLRLSCAASGFTFTETYMSWVRQAPGKGLEWVSNISPTYSTTNYADSVKGR*
*FTISRDNSKNTLYLQMNSLRAEDTAVYYCARYNSYQGGLDYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTS
GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN
HKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1112] SEQ ID NO:83 轻链AA

[1113] EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSG
TDFTLTISRLEPEDFAVYYCQQHNQYPNTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK
VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1114] FS22-053-008/FS28-256-005mAb^{2}重链和轻链的氨基酸和cDNA序列

[1115] SEQ ID NO:159 重链AA(无LALA)

[1116] EVQLLESGGGLVQPGGSLRLSCAASGFTFTETYMSWVRQAPGKGLEWVSNISPTYSTTNYADSVKGRFT
ISRDNSKNTLYLQMNSLRAEDTAVYYCARYNSYQGGLDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC
LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD
KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVK
GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1117] SEQ ID NO:160 重链AA(具有LALA)

[1118] *EVQLLESGGGLVQPGGSLRLSCAASGFTFTETYMSWVRQAPGKGLEWVSNISPTYSTTNYADSVKGR*
*FTISRDNSKNTLYLQMNSLRAEDTAVYYCARYNSYQGGLDYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTS
GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN
HKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1119] SEQ ID NO:90 轻链AA

[1120] EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSG
TDFTLTISRLEPEDFAVYYCQQALGYPHTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK
VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1121] FS22-053-008/FS28-256-012mAb^{2}重链和轻链的氨基酸和cDNA序列

[1122] SEQ ID NO:127 重链AA(无LALA)

[1123] EVQLLESGGGLVQPGGSLRLSCAASGFTFTHTYMSWVRQAPGKGLEWVSNISPTYSTTNYADSVKGRFT
ISRDNNKNTLYLQMNSLRAEDTAVYYCARYNAYHAALDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC
LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD
KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVK
GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1124] SEQ ID NO:128 重链AA(具有LALA)

[1125] *EVQLLESGGGLVQPGGSLRLSCAASGFTFTHTYMSWVRQAPGKGLEWVSNISPTYSTTNYADSVKGR FTISRDNNKNTLYLQMNSLRAEDTAVYYCARYNAYHAALDYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1126] SEQ ID NO:77 轻链AA

[1127] EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSG TDFTLTISRLEPEDFAVYYCQQSYYYPITFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1128] FS22-053-008/FS28-256-014mAb^{2}重链和轻链的氨基酸和cDNA序列

[1129] SEQ ID NO:129 重链AA(无LALA)

[1130] EVQLLESGGGLVQPGGSLRLSCAASGFTFTDTYMSWVRQAPGKGLEWVSNISPTYSTTNYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCARYNAYAAGLDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1131] SEQ ID NO:130 重链AA(具有LALA)

[1132] *EVQLLESGGGLVQPGGSLRLSCAASGFTFTDTYMSWVRQAPGKGLEWVSNISPTYSTTNYADSVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYYCARYNAYAAGLDYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1133] SEQ ID NO:77 轻链AA

[1134] EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSG TDFTLTISRLEPEDFAVYYCQQSYYYPITFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1135] FS22-053-008/FS28-256-018mAb^{2}重链和轻链的氨基酸和cDNA序列

[1136] SEQ ID NO:131 重链AA(无LALA)

[1137] EVQLLESGGGLVQPGGSLRLSCAASGFTFTQTYMSWVRQAPGKGLEWVSNISPTYSTTNYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCARYNAYQIGLDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVK GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1138] SEQ ID NO:132 重链AA(具有LALA)

[1139] *EVQLLESGGGLVQPGGSLRLSCAASGFTFTQTYMSWVRQAPGKGLEWVSNISPTYSTTNYADSVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYYCARYNAYQIGLDYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1140] SEQ ID NO:77 轻链AA

[1141] EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQSYYYPITFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1142] FS22-053-008/FS28-256-021mAb^{2}重链和轻链的氨基酸和cDNA序列

[1143] SEQ ID NO:133 重链AA(无LALA)

[1144] EVQLLESGGGLVQPGGSLRLSCAASGFTFTHTYMSWVRQAPGKGLEWVSNISPTYSTTNYADSVKGRFTISRDNNKNTLYLQMNSLRAEDTAVYYCARYNAYHAALDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1145] SEQ ID NO:134 重链AA(具有LALA)

[1146] *EVQLLESGGGLVQPGGSLRLSCAASGFTFTHTYMSWVRQAPGKGLEWVSNISPTYSTTNYADSVKGRFTISRDNNKNTLYLQMNSLRAEDTAVYYCARYNAYHAALDYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1147] SEQ ID NO:83 轻链AA

[1148] EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQHNQYPNTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1149] FS22-053-008/FS28-256-023mAb^{2}重链和轻链的氨基酸和cDNA序列

[1150] SEQ ID NO:135 重链AA(无LALA)

[1151] EVQLLESGGGLVQPGGSLRLSCAASGFTFTQTYMSWVRQAPGKGLEWVSNISPTYSTTNYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARYNAYQIGLDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1152] SEQ ID NO:136 重链AA(具有LALA)

[1153] *EVQLLESGGGLVQPGGSLRLSCAASGFTFTQTYMSWVRQAPGKGLEWVSNISPTYSTTNYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARYNAYQIGLDYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1154] SEQ ID NO:83 轻链AA

[1155] EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQHNQYPNTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1156] FS22-053-008/FS28-256-024mAb[2]重链和轻链的氨基酸和cDNA序列

[1157] SEQ ID NO:137 重链AA(无LALA)

[1158] EVQLLESGGGLVQPGGSLRLSCAASGFTFTHTYMSWVRQAPGKGLEWVSNISPTYSTTNYADSVKGRFTISRDNNKNTLYLQMNSLRAEDTAVYYCARYNAYHAALDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1159] SEQ ID NO:138 重链AA(具有LALA)

[1160] *EVQLLESGGGLVQPGGSLRLSCAASGFTFTHTYMSWVRQAPGKGLEWVSNISPTYSTTNYADSVKGRFTISRDNNKNTLYLQMNSLRAEDTAVYYCARYNAYHAALDYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1161] SEQ ID NO:90 轻链AA

[1162] EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQALGYPHTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1163] FS22-053-008/FS28-256-026重链和轻链的氨基酸序列

[1164] SEQ ID NO:139 重链AA(无LALA)

[1165] EVQLLESGGGLVQPGGSLRLSCAASGFTFTQTYMSWVRQAPGKGLEWVSNISPTYSTTNYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARYNAYQIGLDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1166] SEQ ID NO:140 重链AA(具有LALA)

[1167] *EVQLLESGGGLVQPGGSLRLSCAASGFTFTQTYMSWVRQAPGKGLEWVSNISPTYSTTNYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARYNAYQIGLDYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1168] SEQ ID NO:90轻链AA

[1169] EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQALGYPHTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1170] FS22-053-008/FS28-256-027mAb[2]重链和轻链的氨基酸序列

[1171] SEQ ID NO:141 重链AA(无LALA)

[1172] EVQLLESGGGLVQPGGSLRLSCAASGFTFTHTYMSWVRQAPGKGLEWVSNISPTYSTTNYADSVKGRFTISRDNNKNTLYLQMNSLRAEDTAVYYCARYNAYHAALDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC

LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD
KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVK
GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1173] SEQ ID NO:142 重链AA(具有LALA)

[1174] *EVQLLESGGGLVQPGGSLRLSCAASGFTFTHTYMSWVRQAPGKGLEWVSNISPTYSTTNYADSVKGR*
*FTISRDNNKNTLYLQMNSLRAEDTAVYYCARYNAYHAALDYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTS
GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN

[1175] HKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSRDELNPPYLFSNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDYWRWLEGNVFSCSVMHEALHNHYTQKSLSLSPG

[1176] SEQ ID NO:95 轻链AA

[1177] EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSG
TDFTLTISRLEPEDFAVYYCQQTVPYPYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK
VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1178] FS22-172-003-AA/FS28-256-271mAb^{2}重链和轻链序列的氨基酸序列

[1179] SEQ ID NO:187 重链AA(具有LALA)

[1180] EVQLLESGGGLVQPGGSLRLSCAASGFTFTHTYMSWVRQAPGKGLEWVSAISPTYSTTNYADSVKGRF
TISRDNNKNTLYLQMNSLRAEDTAVYYCARYNAYHAALDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAAL
GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK
SCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE
QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELPYIIPPYNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVGADRWLEGNVFSCSVMHEALHNHYTQKSL
SLSPG SEQ ID NO:188

[1181] 轻链AA

[1182] EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSG
TDFTLTISRLEPEDFAVYYCQQTVPYPYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK
VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1183] OX40(FS20-022-049)/FS28-256-271mAb^{2}重链和轻链序列的氨基酸序列

[1184] SEQ ID NO:189 重链AA(具有LALA)

[1185] EVQLLESGGGLVQPGGSLRLSCAASGFTFTHTYMSWVRQAPGKGLEWVSAISPTYSTTNYADSVKGRFT
ISRDNNKNTLYLQMNSLRAEDTAVYYCARYNAYHAALDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC
LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD
KTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEYWDQEVSLTCLVKGFYPS
DIAVEWESNGDEQFAYKTTPPVLDSDGSFFLYSKLTVDQYRWNPADYFSCSVMHEALHNHYTQKSLSLSPG

[1186] SEQ ID NO:190 轻链AA

[1187] EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSG
TDFTLTISRLEPEDFAVYYCQQTVPYPYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK
VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1188] FS28m-228mAb(具有LALA)的重链和轻链的氨基酸序列

[1189] SEQ ID NO:161 重链AA(具有LALA)

[1190] *EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYFMVWVRQAPGKGLEWVSMISPKSSNTYYADSVKG*
*RFTISRDNSKNTLYLQMNSLRAEDTAVYYCARWFTPARFDYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTS
GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN
HKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS
FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[1191] SEQ ID NO:162 轻链AA

[1192] EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSG TDFTLTISRLEPEDFAVYYCQQPFPFSFTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1193] 具有LALA的FS22-063-AA/FS28m-228mAb[2]的重链和轻链的氨基酸序列

[1194] SEQ ID NO:163 重链AA(具有LALA)

[1195] *EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYFMVWVRQAPGKGLEWVSMISPKSSNTYYADSVKG*
*RFTISRDNSKNTLYLQMNSLRAEDTAVYYCARWFTPARFDYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTS
GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN
HKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQVYTLPPSRDEPYWSYVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS
FFLYSKLTVMNYRWELGNVFSCSVMHEALHNHYTQKSLSLSPG

[1196] SEQ ID NO:164 轻链AA

[1197] EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSG TDFTLTISRLEPEDFAVYYCQQPFPFSFTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1198] FS22m-063-AA/FS28m-228-010mAb[2]的重链和轻链的氨基酸序列

[1199] SEQ ID NO:196 重链AA(具有LALA)

[1200] EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYFMVWVRQAPGKGLEWVSMISPKSSNTYYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCARYHISPRFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDK THTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEPYWSYVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVMNYRWELGNVFSCSVMHEALHNHYTQKSLSLSPG

[1201] SEQ ID NO:197 轻链AA

[1202] EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSG TDFTLTISRLEPEDFAVYYCQQPFPFSFTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1203] FS22m-063-AA/HelD1.3mAb[2](具有LALA)的重链和轻链的氨基酸序列

[1204] SEQ ID NO:191 重链AA(具有LALA)

[1205] QVQLQESGPGLVRPSQTLSLTCTVSGSTFSGYGVNWVRQPPGRGLEWIGMIWGDGNTDYNSALKSRVTM LVDTSKNQFSLRLSSVTAADTAVYYCARERDYRLDYWGQGSLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTH TCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR

VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEPYWSYVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVMNYRWELGNVFSCSVMHEALHNHYTQKSLSLSPG

[1206] SEQ ID NO:192 轻链AA

[1207] DIQMTQSPASLSASVGETVTITCRASGNIHNYLAWYQQKQGKSPQLLVYNAKTLADGVPSRFSGSGSGT QYSLKINSLQPEDFGSYYCQHFWSTPRTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1208] FS22m-063-AA/4420mAb^2(具有LALA)的重链和轻链的氨基酸序列

[1209] SEQ ID NO:193 重链AA(具有LALA)

[1210] EVKLDETGGGLVQPGRPMKLSCVASGFTFSDYWMNWVRQSPEKGLEWVAQIRNKPYNYETYYSDSVKGR FTISRDDSKSSVYLQMNNLRVEDMGIYYCTGSYYGMDYWGQGTSVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDK THTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEPYWSYVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVMNYRWELGNVFSCSVMHEALHNHYTQKSLSLSPG

[1211] SEQ ID NO:194 轻链AA

[1212] DVVMTQTPLSLPVSLGDQASISCRSSQSLVHSNGNTYLRWYLQKPGQSPKVLIYKVSNRFSGVPDRFSG SGSGTDFTLKISRVEAEDLGVYFCSQSTHVPWTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYP REAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1213] G1-AA/HelD1.3mAb(具有LALA)的重链和轻链的氨基酸序列

[1214] SEQ ID NO:165 重链AA(具有LALA)

[1215] *QVQLQESGPGLVRPSQTLSLTCTVSGSTFSGYGVNWVRQPPGRGLEWIGMIWGDGNTDYNSALKSR VTMLVDTSKNQFSLRLSSVTAADTAVYYCARERDYRLDYWGQGSLVTVSS*ASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[1216] SEQ ID NO:166 轻链AA

[1217] DIQMTQSPASLSASVGETVTITCRASGNIHNYLAWYQQKQGKSPQLLVYNAKTLADGVPSRFSGSGSGT QYSLKINSLQPEDFGSYYCQHFWSTPRTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1218] G1-AA/SS1mAb(具有LALA)的重链和轻链的氨基酸序列

[1219] SEQ ID NO:167 重链(具有LALA)

[1220] *QVQLQQSGPELEKPGASVKISCKASGYSFTGYTMNWVKQSHGKSLEWIGLITPYNGASSYNQKFRG KATLTVDKSSSTAYMDLLSLTSEDSAVYFCARGGYDGRGFDYWGSGTPVTVSS*ASTKGPSVFPLAPSSKST SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

[1221] SEQ ID NO:168 轻链

[1222] DIELTQSPAIMSASPGEKVTMTCSASSSVSYMHWYQQKSGTSPKRWIYDTSKLASGVPGRFSGSGSGNS YSLTISSVEAEDDATYYCQQWSKHPLTFGSGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[1223] MSLN-His-Avi

[1224] 间皮素(无MPF和C末端)(显示)

[1225] His和Avi标签(未显示)

[1226] SEQ ID NO:169 人

[1227] EVEKTACPSGKKAREIDESLIFYKKWELEACVDAALLATQMDRVNAIPFTYEQLDVLKHKLDELYPQGYPESVIQHLGYLFLKMSPEDIRKWNVTSLETLKALLEVNKGHEMSPQVATLIDRFVKGRGQLDKDTLDTLTAFYPGYLCSLSPEELSSVPPSSIWAVRPQDLDTCDPRQLDVLYPKARLAFQNMNGSEYFVKIQSFLGGAPTEDLKALSQQNVSMDLATFMKLRTDAVLPLTVAEVQKLLGPHVEGLKAEERHRPVRDWILRQRQDDLDTLGLGLQGGIPNGYLVLDLSMQEALS

[1228] SEQ ID NO:170 猕猴

[1229] DVERTTCPPEKEVHEIDESLIFYKKRELEACVDAALLAAQMDRVDAIPFTYEQLDVLKHKLDELYPQGYPESVIRHLGHLFLKMSPEDIRKWNVTSLETLKALLKVSKGHEMSAQVATLIDRVVVGRGQLDKDTADTLTAFCPGCLCSLSPERLSSVPPSIIGAVRPQDLDTCGPRQLDVLYPKARLAFQNMSGSEYFVKIRPFLGGAPTEDLKALSQQNVSMDLATFMKLRREAVLPLSVAEVQKLLGPHVEGLKVEEQHSPVRDWILKQRQDDLDTLGLGLQGGIPNGYLILDLSVREALS

[1230] SEQ ID NO:171 小鼠

[1231] DAEQKACPPGKEPYKVDEDLIFYQNWELEACVDGTMLARQMDLVNEIPFTYEQLSIFKHKLDKTYPQGYPESLIQQLGHFFRYVSPEDIHQWNVTSPDTVKTLLKVSKGQKMNAQAIALVACYLRGGGQLDEDMVKALGDIPLSYLCDFSPQDLHSVPSSVMWLVGPQDLDKCSQRHLGLLYQKACSAFQNVSGLEYFEKIKTFLGGASVKDLRALSQHNVSMDIATFKRLQVDSLVGLSVAEVQKLLGPNIVDLKTEEDKSPVRDWLFRQHQKDLDRLGLGLQGGIPNGYLVLDFNVREAFS

[1232] 野生型CH3结构域的氨基酸序列

[1233] SEQ ID NO:172

[1234] GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[1235] 包含LALA突变的CH2结构域的氨基酸序列

[1236] (LALA突变用粗体和下划线表示)

[1237] SEQ ID NO:173

[1238] APE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK

[1239] 包含LALA-PA突变的CH2结构域的氨基酸序列

[1240] (LALA-PA突变以粗体和下划线显示)

[1241] SEQ ID NO:174

[1242] APE**AA**GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL**A**APIEKTISKAK

[1243] Fcab FS22-172-003CH3结构域结构环序列的氨基酸序列

[1244] FS22-172-003第一序列-PYIIPPY(SEQ ID NO:198)

[1245] FS22-172-003第二序列-GADRWLE(SEQ ID NO:199)

[1246] FS22-172-003-AA/FS28-256-271的轻链氨基酸和cDNA序列

[1247] SEQ ID NO:200 轻链

[1248] AAEIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGS GSGTDFTLTISRLEPEDFAVYYCQQTVPYPYTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLL NNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLS

[1249] SPVTKSFNRGEC

[1250] SEQ ID NO:201 重链AA(具有LALA)

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[1253] 本说明书中提及的所有文件均通过引用整体并入本文。

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100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

[0008] Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys

305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

[0009] Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 5
<211> 445
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS28-024 mAb的重链

<400> 5

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Tyr Ser
20 25 30

Ser Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Phe Ile Thr Pro Ser Thr Gly Tyr Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ala Leu Thr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

[0010]

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

[0011]

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 6
<211> 1335
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS28-024 mAb的重链

<400> 6
gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccctcagt tattcttcta tgtcatgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcttt attactccgt ctactggcta tacccactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acagcaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagacgggcg 300

ctgacgttcg actactgggg ccagggaacc ttggtcaccg tctcgagtgc tagcactaag 360

ggcccgtcgg tgttcccgct ggccccatcg tccaagagca catcaggggg taccgccgcc 420

ctgggctgcc ttgtgaagga ttactttccc gagcccgtca cagtgtcctg gaacagcgga 480

gccctgacct ccggagtgca tactttcccg gctgtgcttc agtcctctgg cctgtactca 540

ttgtcctccg tggtcaccgt cccttcgtcc tccctgggca cccagaccta tatctgtaat 600

gtcaaccata agccctcgaa caccaaggtc gacaagaagg tcgagccgaa gtcgtgcgac 660

aagactcaca cttgcccgcc ttgcccagcc ccggaactgc tgggtggtcc ttcggtgttc 720

ctcttcccgc ccaagccgaa ggataccctg atgatctcac ggacccccga agtgacctgt 780

gtggtggtgg acgtgtccca cgaggacccg gaagtgaaat tcaattggta cgtggatgga 840

gtggaagtgc acaacgccaa gaccaagcca cgggaagaac agtacaactc tacctaccgc 900

[0012]

gtggtgtccg tgctcactgt gctgcaccaa gactggctga acgggaagga gtacaagtgc 960

aaagtgtcca acaaggcgct gcctgcccca attgagaaaa ctatctcgaa agccaaggga 1020

cagcctcgag agcctcaagt gtacaccctg cctccctctc gggacgagct gaccaagaac 1080

caagtctccc tgacctgtct ggtcaaggga ttctacccat cggatatcgc cgtggaatgg 1140

gaaagcaacg gacagcccga gaacaactac aagacgactc cgcccgtgct ggattccgac 1200

gggagcttct tcttgtactc caagctgacc gtcgacaaga gcagatggca gcagggaaac 1260

gtgttctcct gctccgtgat gcatgaggcg ctgcacaacc actacactca gaagagcttg 1320

tccctgtcgc ccgga 1335

<210> 7
<211> 1335
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS28-024 mAb的重链

<400> 7
gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccctcagt tattcttcta tgtcatgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcttt attactccgt ctactggcta tacccactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acagcaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagacgggcg 300

ctgacgttcg actactgggg ccagggaacc ttggtcaccg tctcgagtgc tagcactaag 360

ggcccgtcgg tgttcccgct ggccccatcg tccaagagca catcaggggg taccgccgcc 420

ctgggctgcc ttgtgaagga ttactttccc gagcccgtca cagtgtcctg gaacagcgga 480

gccctgacct ccggagtgca tactttcccg gctgtgcttc agtcctctgg cctgtactca 540

ttgtcctccg tggtcaccgt cccttcgtcc tccctgggca cccagaccta tatctgtaat 600

gtcaaccata agccctcgaa caccaaggtc gacaagaagg tcgagccgaa gtcgtgcgac 660

aagactcaca cttgcccgcc ttgcccagcc ccggaagctg ccggtggtcc ttcggtgttc 720

ctcttcccgc ccaagccgaa ggataccctg atgatctcac ggacccccga agtgacctgt 780

gtggtggtgg acgtgtccca cgaggacccg gaagtgaaat tcaattggta cgtggatgga 840

gtggaagtgc acaacgccaa gaccaagcca cgggaagaac agtacaactc tacctaccgc 900

[0013] gtggtgtccg tgctcactgt gctgcaccaa gactggctga acgggaagga gtacaagtgc 960

aaagtgtcca acaaggcgct gcctgcccca attgagaaaa ctatctcgaa agccaaggga 1020

cagcctcgag agcctcaagt gtacaccctg cctccctctc gggacgagct gaccaagaac 1080

caagtctccc tgacctgtct ggtcaaggga ttctacccat cggatatcgc cgtggaatgg 1140

gaaagcaacg gacagcccga gaacaactac aagacgactc cgcccgtgct ggattccgac 1200

gggagcttct tcttgtactc caagctgacc gtcgacaaga gcagatggca gcagggaaac 1260

gtgttctcct gctccgtgat gcatgaggcg ctgcacaacc actacactca gaagagcttg 1320

tccctgtcgc ccgga 1335

<210> 8
<211> 116
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024 mAb 可变结构域

<400> 8

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Tyr Ser
20 25 30

Ser Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Phe Ile Thr Pro Ser Thr Gly Tyr Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ala Leu Thr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

[0014] Thr Val Ser Ser
115

<210> 9
<211> 348
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024 mAb可变结构域

<400> 9
gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccctcagt tattcttcta tgtcatgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcttt attactccgt ctactggcta tacccactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acagcaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagacgggcg 300

ctgacgttcg actactgggg ccagggaacc ttggtcaccg tctcgagt 348

<210> 10
<211> 8
<212> PRT

<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024 mAb CDR1 (IMGT)

<400> 10

Gly Phe Thr Leu Ser Tyr Ser Ser
1 5

<210> 11
<211> 8
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024 mAb CDR2 (IMGT)

<400> 11

Ile Thr Pro Ser Thr Gly Tyr Thr
1 5

<210> 12
<211> 9
[0015] <212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024 mAb CDR3 (IMGT)

<400> 12

Ala Arg Arg Ala Leu Thr Phe Asp Tyr
1 5

<210> 13
<211> 5
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024 mAb CDR1 (Kabat)

<400> 13

Tyr Ser Ser Met Ser
1 5

<210> 14
<211> 17
<212> PRT

<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024 mAb CDR2 (Kabat)

<400> 14

Phe Ile Thr Pro Ser Thr Gly Tyr Thr His Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 15
<211> 7
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024 mAb CDR3 (Kabat)

<400> 15

Arg Ala Leu Thr Phe Asp Tyr
1 5

[0016]

<210> 16
<211> 215
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024 mAb的轻链

<400> 16

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu

65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ala Ser Ser Tyr Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165 170 175

[0017] Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 17
<211> 645
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024 mAb的轻链

<400> 17
gaaattgtgc tgacccagtc tccgggcacg ttatctctga gccctggtga gcgcgccact 60

ctgtcatgcc gggcttctca aagtgttagc agtagctacc tggcgtggta tcagcaaaaa 120

ccgggccagg ccccgcgtct gctgatttac ggtgcatcca gccgtgccac cggcattcca 180

gatcgttttt ccggtagtgg ttctgggacg gacttcactc tgacaatctc acgcctggaa 240

ccggaggatt ttgcggtgta ttactgccag caagcttctt cttatcctct cacgttcggc 300

caagggacca aggtggaaat caaacgtact gtggccgctc ctagcgtgtt catttttccg 360

ccatccgacg agcagctcaa gtccggcacc gcctccgtgg tctgcctgct caacaacttc 420

taccctcgcg aagctaaggt ccagtggaag gtcgacaatg ccctgcagtc cggaaactcg 480

caggaaagcg tgactgaaca ggactccaag gactccacct attcactgtc ctcgactctg 540

accctgagca aggcggatta cgaaaagcac aaagtgtacg catgcgaagt gacccaccag 600

ggtctttcgt cccccgtgac caagagcttc aacagaggag agtgt 645

<210> 18
<211> 108
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024 mAb的可变结构域

<400> 18

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

[0018]

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ala Ser Ser Tyr Pro
85 90 95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 19
<211> 324
<212> DNA

<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024 mAb的可变结构域

<400> 19
gaaattgtgc tgacccagtc tccgggcacg ttatctctga gccctggtga gcgcgccact 60

ctgtcatgcc gggcttctca aagtgttagc agtagctacc tggcgtggta tcagcaaaaa 120

ccgggccagg ccccgcgtct gctgatttac ggtgcatcca gccgtgccac cggcattcca 180

gatcgttttt ccggtagtgg ttctgggacg gacttcactc tgacaatctc acgcctggaa 240

ccggaggatt ttgcggtgta ttactgccag caagcttctt cttatcctct cacgttcggc 300

caagggacca aggtggaaat caaa 324

<210> 20
<211> 7
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024 mAb (IMGT) CDR1

[0019] <400> 20

Gln Ser Val Ser Ser Ser Tyr
1 5

<210> 21
<211> 3
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024 mAb (IMGT) CDR2

<400> 21

Gly Ala Ser
1

<210> 22
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024 mAb (IMGT) CDR3

<400> 22

Gln Gln Ala Ser Ser Tyr Pro Leu Thr
1 5

<210> 23
<211> 12
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024 mAb (Kabat) CDR1

<400> 23

Arg Ala Ser Gln Ser Val Ser Ser Ser Tyr Leu Ala
1 5 10

<210> 24
<211> 7
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024 mAb (Kabat) CDR2

<400> 24

[0020]

Gly Ala Ser Ser Arg Ala Thr
1 5

<210> 25
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256 mAb CDR3 (IMGT)

<400> 25

Gln Gln Ser Tyr Tyr Tyr Pro Ile Thr
1 5

<210> 26
<211> 445
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS28-024-051mAb重链

<400> 26

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Tyr Ser
20 25 30

Ser Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Phe Ile Thr Pro Ser Thr Gly Tyr Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ala Leu Ile Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

[0021]

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

[0022]

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 27
<211> 1335
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS28-024-051 mAb重链

<400> 27

[0023]

gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccctcagt tattcttcta tgtcatgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcttt attactccgt ctactggcta tacccactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acagcaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagacgggcg 300

ctgattttcg actactgggg ccagggaacc ctggtcaccg tctcgagtgc tagcactaag 360

ggcccgtcgg tgttcccgct ggccccatcg tccaagagca catcaggggg taccgccgcc 420

ctgggctgcc ttgtgaagga ttactttccc gagcccgtca cagtgtcctg gaacagcgga 480

gccctgacct ccggagtgca tactttcccg gctgtgcttc agtcctctgg cctgtactca 540

ttgtcctccg tggtcaccgt cccttcgtcc tccctgggca cccagaccta tatctgtaat 600

gtcaaccata agccctcgaa caccaaggtc gacaagaagg tcgagccgaa gtcgtgcgac 660

aagactcaca cttgcccgcc ttgcccagcc ccggaactgc tgggtggtcc ttcggtgttc 720

ctcttcccgc ccaagccgaa ggataccctg atgatctcac ggacccccga agtgacctgt 780

gtggtggtgg acgtgtccca cgaggacccg gaagtgaaat tcaattggta cgtggatgga 840

gtggaagtgc acaacgccaa gaccaagcca cgggaagaac agtacaactc tacctaccgc 900

gtggtgtccg tgctcactgt gctgcaccaa gactggctga acgggaagga gtacaagtgc 960

aaagtgtcca acaaggcgct gcctgcccca attgagaaaa ctatctcgaa agccaaggga 1020

cagcctcgag agcctcaagt gtacaccctg cctccctctc gggacgagct gaccaagaac 1080

caagtctccc tgacctgtct ggtcaaggga ttctacccat cggatatcgc cgtggaatgg 1140

gaaagcaacg gacagcccga gaacaactac aagacgactc cgcccgtgct ggattccgac 1200

gggagcttct tcttgtactc caagctgacc gtcgacaaga gcagatggca gcagggaaac 1260

gtgttctcct gctccgtgat gcatgaggcg ctgcacaacc actacactca gaagagcttg 1320

tccctgtcgc ccgga 1335

<210> 28
<211> 445
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS28-024-051 mAb重链

<400> 28

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Tyr Ser
20 25 30

Ser Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Phe Ile Thr Pro Ser Thr Gly Tyr Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[0024] 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ala Leu Ile Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu

180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

[0025] Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp

405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 29
<211> 1335
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS28-024-051 mAb重链

<400> 29

[0026]

gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccctcagt tattcttcta tgtcatgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcttt attactccgt ctactggcta tacccactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acagcaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagacgggcg 300

ctgattttcg actactgggg ccagggaacc ctggtcaccg tctcgagtgc tagcactaag 360

ggcccgtcgg tgttcccgct ggccccatcg tccaagagca catcaggggg taccgccgcc 420

ctgggctgcc ttgtgaagga ttactttccc gagcccgtca cagtgtcctg gaacagcgga 480

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gtcaaccata agccctcgaa caccaaggtc gacaagaagg tcgagccgaa gtcgtgcgac 660

aagactcaca cttgcccgcc ttgcccagcc ccggaagctg ccggtggtcc ttcggtgttc 720

ctcttcccgc ccaagccgaa ggataccctg atgatctcac ggacccccga agtgacctgt 780

gtggtggtgg acgtgtccca cgaggacccg gaagtgaaat tcaattggta cgtggatgga 840

gtggaagtgc acaacgccaa gaccaagcca cgggaagaac agtacaactc tacctaccgc 900

gtggtgtccg tgctcactgt gctgcaccaa gactggctga acgggaagga gtacaagtgc 960

aaagtgtcca acaaggcgct gcctgcccca attgagaaaa ctatctcgaa agccaaggga 1020

cagcctcgag agcctcaagt gtacaccctg cctccctctc gggacgagct gaccaagaac 1080

caagtctccc tgacctgtct ggtcaaggga ttctacccat cggatatcgc cgtggaatgg 1140

gaaagcaacg gacagcccga gaacaactac aagacgactc cgcccgtgct ggattccgac 1200

gggagcttct tcttgtactc caagctgacc gtcgacaaga gcagatggca gcagggaaac 1260

gtgttctcct gctccgtgat gcatgaggcg ctgcacaacc actacactca gaagagcttg 1320

tccctgtcgc ccgga 1335

<210> 30
<211> 116
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024-051 mAb可变结构域

<400> 30

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Tyr Ser
20 25 30

[0027]

Ser Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Phe Ile Thr Pro Ser Thr Gly Tyr Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ala Leu Ile Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 31
<211> 348
<212> DNA

<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024-051 mAb可变结构域

<400> 31
gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccctcagt tattcttcta tgtcatgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcttt attactccgt ctactggcta tacccactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acagcaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagacgggcg 300

ctgattttcg actactgggg ccagggaacc ctggtcaccg tctcgagt 348

<210> 32
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024-051 mAb CDR3 (IMGT)

[0028] <400> 32

Ala Arg Arg Ala Leu Ile Phe Asp Tyr
1 5

<210> 33
<211> 7
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024-051 mAb CDR3 (Kabat)

<400> 33

Arg Ala Leu Ile Phe Asp Tyr
1 5

<210> 34
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-001 mAb CDR3 (IMGT) 和 (Kabat)

<400> 34

Gln Gln His Asn Gln Tyr Pro Asn Thr
1 5

<210> 35
<211> 445
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS28-024-052 mAb重链

<400> 35

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Tyr Ser
20 25 30

Ser Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

[0029] Ser Phe Ile Thr Pro Ser Thr Gly Tyr Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ala Leu Leu Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser

165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

[0030] Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp

385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 36
<211> 1335
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS28-024-052 mAb重链

<400> 36

[0031]

gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccctcagt tattcttcta tgtcatgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcttt attactccgt ctactggcta tacccactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acagcaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagacgggcg 300

ctgcttttcg actactgggg ccagggaacc ctggtcaccg tctcgtcggc tagcactaag 360

ggcccgtcgg tgttcccgct ggccccatcg tccaagagca catcaggggg taccgccgcc 420

ctgggctgcc ttgtgaagga ttactttccc gagcccgtca cagtgtcctg gaacagcgga 480

gccctgacct ccggagtgca tactttcccg gctgtgcttc agtcctctgg cctgtactca 540

ttgtcctccg tggtcaccgt cccttcgtcc tccctgggca cccagaccta tatctgtaat 600

gtcaaccata agccctcgaa caccaaggtc gacaagaagg tcgagccgaa gtcgtgcgac 660

aagactcaca cttgcccgcc ttgcccagcc ccggaactgc tgggtggtcc ttcggtgttc 720

ctcttcccgc ccaagccgaa ggataccctg atgatctcac ggacccccga agtgacctgt 780

gtggtggtgg acgtgtccca cgaggacccg gaagtgaaat tcaattggta cgtggatgga 840

gtggaagtgc acaacgccaa gaccaagcca cgggaagaac agtacaactc tacctaccgc 900

gtggtgtccg tgctcactgt gctgcaccaa gactggctga acgggaagga gtacaagtgc 960

aaagtgtcca acaaggcgct gcctgcccca attgagaaaa ctatctcgaa agccaaggga 1020

cagcctcgag agcctcaagt gtacaccctg cctccctctc gggacgagct gaccaagaac 1080

caagtctccc tgacctgtct ggtcaaggga ttctacccat cggatatcgc cgtggaatgg 1140

gaaagcaacg gacagcccga gaacaactac aagacgactc cgcccgtgct ggattccgac 1200

gggagcttct tcttgtactc caagctgacc gtcgacaaga gcagatggca gcagggaaac 1260

gtgttctcct gctccgtgat gcatgaggcg ctgcacaacc actacactca gaagagcttg 1320

tccctgtcgc ccgga 1335

〈210〉 37
〈211〉 445
〈212〉 PRT
〈213〉 人工序列(Artificial Sequence)

〈220〉
〈223〉 具有LALA的FS28-024-052 mAb重链

〈400〉 37

[0032]

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Tyr Ser
20 25 30

Ser Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Phe Ile Thr Pro Ser Thr Gly Tyr Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ala Leu Leu Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

[0033]

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 38
<211> 1335
<212> DNA
[0034] <213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS28-024-052 mAb重链

<400> 38
gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccctcagt tattcttcta tgtcatgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcttt attactccgt ctactggcta tacccactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acagcaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagacgggcg 300

ctgcttttcg actactgggg ccagggaacc ctggtcaccg tctcgtcggc tagcactaag 360

ggcccgtcgg tgttcccgct ggccccatcg tccaagagca catcaggggg taccgccgcc 420

ctgggctgcc ttgtgaagga ttactttccc gagcccgtca cagtgtcctg gaacagcgga 480

gccctgacct ccggagtgca tactttcccg gctgtgcttc agtcctctgg cctgtactca 540

ttgtcctccg tggtcaccgt cccttcgtcc tccctgggca cccagaccta tatctgtaat 600

gtcaaccata agccctcgaa caccaaggtc gacaagaagg tcgagccgaa gtcgtgcgac 660

aagactcaca cttgcccgcc ttgcccagcc ccggaagctg ccggtggtcc ttcggtgttc 720

ctcttcccgc ccaagccgaa ggataccctg atgatctcac ggacccccga agtgacctgt 780

gtggtggtgg acgtgtccca cgaggacccg gaagtgaaat tcaattggta cgtggatgga 840

gtggaagtgc acaacgccaa gaccaagcca cgggaagaac agtacaactc tacctaccgc 900

gtggtgtccg tgctcactgt gctgcaccaa gactggctga acgggaagga gtacaagtgc 960

aaagtgtcca acaaggcgct gcctgcccca attgagaaaa ctatctcgaa agccaaggga 1020

cagcctcgag agcctcaagt gtacaccctg cctccctctc gggacgagct gaccaagaac 1080

caagtctccc tgacctgtct ggtcaaggga ttctacccat cggatatcgc cgtggaatgg 1140

gaaagcaacg gacagcccga gaacaactac aagacgactc cgcccgtgct ggattccgac 1200

gggagcttct tcttgtactc caagctgacc gtcgacaaga gcagatggca gcagggaaac 1260

gtgttctcct gctccgtgat gcatgaggcg ctgcacaacc actacactca gaagagcttg 1320

tccctgtcgc ccgga 1335

[0035]

<210> 39
<211> 116
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024-052 mAb可变结构域

<400> 39

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Tyr Ser
20 25 30

Ser Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Phe Ile Thr Pro Ser Thr Gly Tyr Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

85 90 95

Ala Arg Arg Ala Leu Leu Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 40
<211> 348
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024-052 mAb可变结构域

<400> 40
gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccctcagt tattcttcta tgtcatgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcttt attactccgt ctactggcta tacccactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acagcaagaa cacgctgtac 240

[0036] ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagacgggcg 300

ctgcttttcg actactgggg ccagggaacc ctggtcaccg tctcgtcg 348

<210> 41
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024-052 mAb CDR3 (IMGT)

<400> 41

Ala Arg Arg Ala Leu Leu Phe Asp Tyr
1 5

<210> 42
<211> 7
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024-052 mAb CDR3 (Kabat)

<400> 42

Arg Ala Leu Leu Phe Asp Tyr
1 5

<210> 43
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-005 mAb CDR3 (IMGT) 和 (Kabat)

<400> 43

Gln Gln Ala Leu Gly Tyr Pro His Thr
1 5

<210> 44
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-027 mAb CDR3 (IMGT) 和(Kabat)

<400> 44

[0037]

Gln Gln Thr Val Pro Tyr Pro Tyr Thr
1 5

<210> 45
<211> 445
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS28-024-053 mAb重链

<400> 45

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Tyr Ser
20 25 30

Ser Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Phe Ile Thr Pro Ser Thr Gly Tyr Thr His Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ala Leu Val Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

[0038] Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr

275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

[0039] Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 46
<211> 1335
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS28-024-053 mAb重链

<400> 46
gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccctcagt tattcttcta tgtcatgggt gcgtcaggct 120

[0040]

ccgggcaaag gtctggaatg ggttagcttt attactccgt ctactggcta tacccactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acagcaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagacgggcg 300

ctggtgttcg actactgggg ccagggaacc ctggtcaccg tctcgtcggc tagcactaag 360

ggcccgtcgg tgttcccgct ggccccatcg tccaagagca catcaggggg taccgccgcc 420

ctgggctgcc ttgtgaagga ttactttccc gagcccgtca cagtgtcctg gaacagcgga 480

gccctgacct ccggagtgca tactttcccg gctgtgcttc agtcctctgg cctgtactca 540

ttgtcctccg tggtcaccgt cccttcgtcc tccctgggca cccagaccta tatctgtaat 600

gtcaaccata agccctcgaa caccaaggtc gacaagaagg tcgagccgaa gtcgtgcgac 660

aagactcaca cttgcccgcc ttgcccagcc ccggaactgc tgggtggtcc ttcggtgttc 720

ctcttcccgc ccaagccgaa ggataccctg atgatctcac ggacccccga agtgacctgt 780

gtggtggtgg acgtgtccca cgaggacccg gaagtgaaat tcaattggta cgtggatgga 840

gtggaagtgc acaacgccaa gaccaagcca cgggaagaac agtacaactc tacctaccgc 900

gtggtgtccg tgctcactgt gctgcaccaa gactggctga acgggaagga gtacaagtgc 960

aaagtgtcca acaaggcgct gcctgcccca attgagaaaa ctatctcgaa agccaaggga 1020

cagcctcgag agcctcaagt gtacaccctg cctccctctc gggacgagct gaccaagaac 1080

caagtctccc tgacctgtct ggtcaaggga ttctacccat cggatatcgc cgtggaatgg 1140

gaaagcaacg gacagcccga gaacaactac aagacgactc cgcccgtgct ggattccgac 1200

gggagcttct tcttgtactc caagctgacc gtcgacaaga gcagatggca gcagggaaac 1260

gtgttctcct gctccgtgat gcatgaggcg ctgcacaacc actacactca gaagagcttg 1320

tccctgtcgc ccgga 1335

<210> 47
<211> 445
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的 FS28-024-053 mAb重链

<400> 47

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Tyr Ser
20 25 30

Ser Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Phe Ile Thr Pro Ser Thr Gly Tyr Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ala Leu Val Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

[0041]

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

[0042]

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 48
<211> 1335
<212> DNA

<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS28-024-053 mAb重链

<400> 48

[0043]

gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccctcagt tattcttcta tgtcatgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcttt attactccgt ctactggcta tacccactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acagcaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagacgggcg 300

ctggtgttcg actactgggg ccagggaacc ctggtcaccg tctcgtcggc tagcactaag 360

ggcccgtcgg tgttcccgct ggccccatcg tccaagagca catcaggggg taccgccgcc 420

ctgggctgcc ttgtgaagga ttactttccc gagcccgtca cagtgtcctg gaacagcgga 480

gccctgacct ccggagtgca tactttcccg gctgtgcttc agtcctctgg cctgtactca 540

ttgtcctccg tggtcaccgt cccttcgtcc tccctgggca cccagaccta tatctgtaat 600

gtcaaccata agccctcgaa caccaaggtc gacaagaagg tcgagccgaa gtcgtgcgac 660

aagactcaca cttgcccgcc ttgcccagcc ccggaagctg ccggtggtcc ttcggtgttc 720

ctcttcccgc ccaagccgaa ggataccctg atgatctcac ggacccccga agtgacctgt 780

gtggtggtgg acgtgtccca cgaggacccg gaagtgaaat tcaattggta cgtggatgga 840

gtggaagtgc acaacgccaa gaccaagcca cgggaagaac agtacaactc tacctaccgc 900

gtggtgtccg tgctcactgt gctgcaccaa gactggctga acgggaagga gtacaagtgc 960

aaagtgtcca acaaggcgct gcctgcccca attgagaaaa ctatctcgaa agccaaggga 1020

cagcctcgag agcctcaagt gtacaccctg cctccctctc gggacgagct gaccaagaac 1080

caagtctccc tgacctgtct ggtcaaggga ttctacccat cggatatcgc cgtggaatgg 1140

gaaagcaacg gacagcccga gaacaactac aagacgactc cgcccgtgct ggattccgac 1200

gggagcttct tcttgtactc caagctgacc gtcgacaaga gcagatggca gcagggaaac 1260

gtgttctcct gctccgtgat gcatgaggcg ctgcacaacc actacactca gaagagcttg 1320

tccctgtcgc ccgga 1335

<210> 49
<211> 116
<212> PRT

<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024-053 mAb 可变结构域

<400> 49

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Tyr Ser
20 25 30

Ser Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Phe Ile Thr Pro Ser Thr Gly Tyr Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

[0044] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ala Leu Val Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 50
<211> 348
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024-053 mAb可变结构域

<400> 50
gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccctcagt tattcttcta tgtcatgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcttt attactccgt ctactggcta tacccactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acagcaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagacgggcg 300

ctggtgttcg actactgggg ccagggaacc ctggtcaccg tctcgtcg 348

<210> 51
<211> 9
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024-053 mAb CDR3 (IMGT)

<400> 51

Ala Arg Arg Ala Leu Val Phe Asp Tyr
1 5

<210> 52
<211> 7
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-024-053 mAb CDR3 (Kabat)

[0045] <400> 52

Arg Ala Leu Val Phe Asp Tyr
1 5

<210> 53
<211> 108
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-005 mAb 可变结构域

<400> 53

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser

50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ala Leu Gly Tyr Pro
85 90 95

His Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 54
<211> 324
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-005 mAb 可变结构域

<400> 54
gaaattgtgc tgacccagtc tccgggcacg ttatctctga gccctggtga gcgcgccact 60

ctgtcatgcc gggcttctca aagtgttagc agtagctacc tggcgtggta tcagcaaaaa 120

[0046] ccgggccagg ccccgcgtct gctgatttac ggtgcatcca gccgtgccac cggcattcca 180

gatcgttttt ccggtagtgg ttctgggacg gacttcactc tgacaatctc acgcctggaa 240

ccggaggatt ttgcggtgta ttactgccag caagctttgg gttatcctca tacgttcggc 300

caagggacca aggtggaaat caaa 324

<210> 55
<211> 445
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS28-024-060 mAb重链

<400> 55

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Tyr Ser
20 25 30

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

35 40 45

Ser Phe Ile Thr Pro Ser Thr Gly Tyr Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ala Leu Trp Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

[0047] Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val

260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

[0048] Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 56
<211> 108
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-027 mAb可变结构域

<400> 56

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Thr Val Pro Tyr Pro
85 90 95

Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

[0049]

<210> 57
<211> 324
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-027 mAb可变结构域

<400> 57
gaaattgtgc tgacccagtc tccgggcacg ttatctctga gccctggtga gcgcgccact 60

ctgtcatgcc gggcttctca aagtgttagc agtagctacc tggcgtggta tcagcaaaaa 120

ccgggccagg ccccgcgtct gctgatttac ggtgcatcca gccgtgccac cggcattcca 180

gatcgttttt ccggtagtgg ttctgggacg gacttcactc tgacaatctc acgcctggaa 240

ccggaggatt ttgcggtgta ttactgccag caaactgtgc cgtatccgta tacgttcggc 300

caagggacca aggtggaaat caaa 324

<210> 58
<211> 445
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-026 mAb（具有LALA）重链

<400> 58

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Thr Pro Tyr Tyr Ser Lys Thr Asp Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

[0050]

Ala Arg Asn Trp Tyr Arg Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

[0051]

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 59
<211> 215
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-026 mAb轻链

<400> 59

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

[0052] Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Ser Tyr Pro
85 90 95

Ile Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu

165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 60
<211> 445
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS28-091 mAb重链

<400> 60

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

[0053]

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asn Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Lys Pro Tyr Asp Gly Asn Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asn Arg Trp Val Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

[0054]

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 61
<211> 215
<212> PRT
[0055] <213> 人工序列(Artificial Sequence)

<220>
<223> FS28-091 mAb轻链

<400> 61

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Ser Ser Pro

85 90 95

Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

[0056] Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 62
<211> 452
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS28-185 mAb重链

<400> 62

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Thr Ser
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Arg Ile Asn Pro Tyr Glu Gly Glu Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Trp Ser Ile Ala Thr Tyr Tyr Lys Ser Ala Met Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
115 120 125

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
130 135 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145 150 155 160

[0057]

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
165 170 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
180 185 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
195 200 205

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
210 215 220

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
225 230 235 240

Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
245 250 255

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
260 265 270

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
275 280 285

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
290 295 300

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305 310 315 320

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
325 330 335

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
340 345 350

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
355 360 365

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
370 375 380

[0058]

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
385 390 395 400

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
405 410 415

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
420 425 430

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
435 440 445

Leu Ser Pro Gly
450

<210> 63
<211> 119
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-001 mAb 可变结构域

<400> 63

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Glu Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

[0059] Ala Arg Tyr Asn Ser Tyr Gln Gly Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 64
<211> 357
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-001 mAb 可变结构域

<400> 64
gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccttcact gagacttata tgagctgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcaat atttctccga cttatagcac taccaactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acagcaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagatacaac 300

tcttaccagg gtggcttgga ctactggggc cagggaacct tggtcaccgt ctcgagt 357

<210> 65
<211> 448
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS28-256 mAb重链

<400> 65

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asn Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

[0060] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ser Tyr Gln Gly Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

[0061] Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys

405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 66
<211> 1344
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS28-256 mAb重链

<400> 66

[0062]

gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccttcact aacacttata tgagctgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcaat atttctccga cttatagcac taccaactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acagcaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagatacaac 300

tcttaccagg gtggcttgga ctactggggc cagggaacct tggtcaccgt ctcgagtgct 360

agcactaagg gcccgtcggt gttcccgctg gccccatcgt ccaagagcac atcagggggt 420

accgccgccc tgggctgcct tgtgaaggat tactttcccg agcccgtcac agtgtcctgg 480

aacagcggag ccctgacctc cggagtgcat actttcccgg ctgtgcttca gtcctctggc 540

ctgtactcat tgtcctccgt ggtcaccgtc ccttcgtcct ccctgggcac ccagacctat 600

atctgtaatg tcaaccataa gccctcgaac accaaggtcg acaagaaggt cgagccgaag 660

tcgtgcgaca agactcacac ttgcccgcct tgcccagccc cggaactgct gggtggtcct 720

tcggtgttcc tcttcccgcc caagccgaag gataccctga tgatctcacg gacccccgaa 780

gtgacctgtg tggtggtgga cgtgtcccac gaggacccgg aagtgaaatt caattggtac 840

gtggatggag tggaagtgca caacgccaag accaagccac gggaagaaca gtacaactct 900

acctaccgcg tggtgtccgt gctcactgtg ctgcaccaag actggctgaa cgggaaggag 960

tacaagtgca aagtgtccaa caaggcgctg cctgccccaa ttgagaaaac tatctcgaaa 1020

gccaagggac agcctcgaga gcctcaagtg tacaccctgc ctccctctcg ggacgagctg 1080

accaagaacc aagtctccct gacctgtctg gtcaagggat tctacccatc ggatatcgcc 1140

gtggaatggg aaagcaacgg acagcccgag aacaactaca agacgactcc gcccgtgctg 1200

gattccgacg ggagcttctt cttgtactcc aagctgaccg tcgacaagag cagatggcag 1260

cagggaaacg tgttctcctg ctccgtgatg catgaggcgc tgcacaacca ctacactcag 1320

aagagcttgt ccctgtcgcc cgga 1344

〈210〉 67
〈211〉 448
〈212〉 PRT
〈213〉 人工序列(Artificial Sequence)

〈220〉
〈223〉 具有LALA的FS28-256 mAb重链

〈400〉 67

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asn Thr
20 25 30

[0063]

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ser Tyr Gln Gly Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

[0064]

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 68
<211> 1344
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS28-256 mAb重链

[0065]

<400> 68
gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccttcact aacacttata tgagctgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcaat atttctccga cttatagcac taccaactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acagcaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagatacaac 300

tcttaccagg gtggcttgga ctactggggc cagggaacct tggtcaccgt ctcgagtgct 360

agcactaagg gcccgtcggt gttcccgctg gccccatcgt ccaagagcac atcagggggt 420

accgccgccc tgggctgcct tgtgaaggat tactttcccg agcccgtcac agtgtcctgg 480

aacagcggag ccctgacctc cggagtgcat actttcccgg ctgtgcttca gtcctctggc 540

ctgtactcat tgtcctccgt ggtcaccgtc ccttcgtcct ccctgggcac ccagacctat 600

atctgtaatg tcaaccataa gccctcgaac accaaggtcg acaagaaggt cgagccgaag 660

tcgtgcgaca agactcacac ttgcccgcct tgcccagccc cggaagctgc cggtggtcct 720

tcggtgttcc tcttcccgcc caagccgaag gataccctga tgatctcacg gacccccgaa 780

gtgacctgtg tggtggtgga cgtgtcccac gaggacccgg aagtgaaatt caattggtac 840

gtggatggag tggaagtgca caacgccaag accaagccac gggaagaaca gtacaactct 900

acctaccgcg tggtgtccgt gctcactgtg ctgcaccaag actggctgaa cgggaaggag 960

tacaagtgca aagtgtccaa caaggcgctg cctgccccaa ttgagaaaac tatctcgaaa 1020

gccaagggac agcctcgaga gcctcaagtg tacaccctgc ctccctctcg ggacgagctg 1080

accaagaacc aagtctccct gacctgtctg gtcaagggat tctacccatc ggatatcgcc 1140

gtggaatggg aaagcaacgg acagcccgag aacaactaca agacgactcc gcccgtgctg 1200

gattccgacg ggagcttctt cttgtactcc aagctgaccg tcgacaagag cagatggcag 1260

cagggaaacg tgttctcctg ctccgtgatg catgaggcgc tgcacaacca ctacactcag 1320

aagagcttgt ccctgtcgcc cgga 1344

<210> 69
<211> 119
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256 mAb可变结构域

[0066]

<400> 69

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asn Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ser Tyr Gln Gly Gly Leu Asp Tyr Trp Gly Gln Gly

100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 70
<211> 357
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256 mAb 可变结构域

<400> 70
gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccttcact aacacttata tgagctgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcaat atttctccga cttatagcac taccaactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acagcaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagatacaac 300

tcttaccagg gtggcttgga ctactggggc cagggaacct tggtcaccgt ctcgagt 357

[0067]

<210> 71
<211> 8
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256 mAb CDR1 (IMGT)

<400> 71

Gly Phe Thr Phe Thr Asn Thr Tyr
1 5

<210> 72
<211> 5
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256 mAb CDR1 (Kabat)

<400> 72

Asn Thr Tyr Met Ser
1 5

<210> 73
<211> 8
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256 mAb CDR2 (IMGT)

<400> 73

Ile Ser Pro Thr Tyr Ser Thr Thr
1 5

<210> 74
<211> 17
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256 mAb CDR2 (Kabat)

<400> 74

Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val Lys
1 5 10 15

[0068]

Gly

<210> 75
<211> 12
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256 mAb CDR3 (IMGT)

<400> 75

Ala Arg Tyr Asn Ser Tyr Gln Gly Gly Leu Asp Tyr
1 5 10

<210> 76
<211> 10
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256 mAb CDR3 (Kabat)

<400> 76

Tyr Asn Ser Tyr Gln Gly Gly Leu Asp Tyr
1 5 10

<210> 77
<211> 215
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256 mAb 轻链

<400> 77

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

[0069] Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Tyr Tyr Tyr Pro
85 90 95

Ile Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu

165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 78
<211> 645
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256 mAb 轻链

<400> 78

[0070]

gaaattgtgc tgacccagtc tccgggcacg ttatctctga gccctggtga gcgcgccact 60

ctgtcatgcc gggcttctca aagtgttagc agtagctacc tggcgtggta tcagcaaaaa 120

ccgggccagg ccccgcgtct gctgatttac ggtgcatcca gccgtgccac cggcattcca 180

gatcgttttt ccggtagtgg ttctgggacg gacttcactc tgacaatctc acgcctggaa 240

ccggaggatt ttgcggtgta ttactgccag caatcttatt attatcctat cacgttcggc 300

caagggacca aggtggaaat caaacgtact gtggccgctc ctagcgtgtt catttttccg 360

ccatccgacg agcagctcaa gtccggcacc gcctccgtgg tctgcctgct caacaacttc 420

taccctcgcg aagctaaggt ccagtggaag gtcgacaatg ccctgcagtc cggaaactcg 480

caggaaagcg tgactgaaca ggactccaag gactccacct attcactgtc ctcgactctg 540

accctgagca aggcggatta cgaaaagcac aaagtgtacg catgcgaagt gacccaccag 600

ggtctttcgt cccccgtgac caagagcttc aacagaggag agtgt 645

<210> 79
<211> 108
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256 mAb可变结构域

<400> 79

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Tyr Tyr Tyr Pro
85 90 95

Ile Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

[0071]

<210> 80
<211> 324
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256 mAb 可变结构域

<400> 80
gaaattgtgc tgacccagtc tccgggcacg ttatctctga gccctggtga gcgcgccact 60

ctgtcatgcc gggcttctca aagtgttagc agtagctacc tggcgtggta tcagcaaaaa 120

ccgggccagg ccccgcgtct gctgatttac ggtgcatcca gccgtgccac cggcattcca 180

gatcgttttt ccggtagtgg ttctgggacg gacttcactc tgacaatctc acgcctggaa 240

ccggaggatt ttgcggtgta ttactgccag caatcttatt attatcctat cacgttcggc 300

caagggacca aggtggaaat caaa 324

<210> 81
<211> 448
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS28-256-001 mAb重链

<400> 81

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Glu Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

[0072]

Ala Arg Tyr Asn Ser Tyr Gln Gly Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

[0073]

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 82
<211> 1344
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS28-256-001 mAb重链

<400> 82

[0074]

gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccttcact gagacttata tgagctgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcaat atttctccga cttatagcac taccaactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acagcaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagatacaac 300

tcttaccagg gtggcttgga ctactggggc cagggaacct tggtcaccgt ctcgagtgct 360

agcactaagg gcccgtcggt gttcccgctg gccccatcgt ccaagagcac atcagggggt 420

accgccgccc tgggctgcct tgtgaaggat tactttcccg agcccgtcac agtgtcctgg 480

aacagcggag ccctgacctc cggagtgcat actttcccgg ctgtgcttca gtcctctggc 540

ctgtactcat tgtcctccgt ggtcaccgtc ccttcgtcct ccctgggcac ccagacctat 600

atctgtaatg tcaaccataa gccctcgaac accaaggtcg acaagaaggt cgagccgaag 660

tcgtgcgaca agactcacac ttgcccgcct tgcccagccc cggaactgct gggtggtcct 720

tcggtgttcc tcttcccgcc caagccgaag gataccctga tgatctcacg gacccccgaa 780

gtgacctgtg tggtggtgga cgtgtcccac gaggacccgg aagtgaaatt caattggtac 840

gtggatggag tggaagtgca caacgccaag accaagccac gggaagaaca gtacaactct 900

acctaccgcg tggtgtccgt gctcactgtg ctgcaccaag actggctgaa cgggaaggag 960

tacaagtgca aagtgtccaa caaggcgctg cctgccccaa ttgagaaaac tatctcgaaa 1020

gccaagggac agcctcgaga gcctcaagtg tacaccctgc ctccctctcg ggacgagctg 1080

accaagaacc aagtctccct gacctgtctg gtcaagggat tctacccatc ggatatcgcc 1140

gtggaatggg aaagcaacgg acagcccgag aacaactaca agacgactcc gcccgtgctg 1200

gattccgacg ggagcttctt cttgtactcc aagctgaccg tcgacaagag cagatggcag 1260

cagggaaacg tgttctcctg ctccgtgatg catgaggcgc tgcacaacca ctacactcag 1320

aagagcttgt ccctgtcgcc cgga 1344

<210> 83
<211> 215
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-001 mAb 轻链

<400> 83

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

[0075] Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Asn Gln Tyr Pro
85 90 95

Asn Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu

165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 84
<211> 1344
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS28-256-001 mAb重链

<400> 84

[0076]

gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccttcact gagacttata tgagctgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcaat atttctccga cttatagcac taccaactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acagcaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagatacaac 300

tcttaccagg gtggcttgga ctactggggc cagggaacct tggtcaccgt ctcgagtgct 360

agcactaagg gcccgtcggt gttcccgctg gccccatcgt ccaagagcac atcagggggt 420

accgccgccc tgggctgcct tgtgaaggat tactttcccg agcccgtcac agtgtcctgg 480

aacagcggag ccctgacctc cggagtgcat actttcccgg ctgtgcttca gtcctctggc 540

ctgtactcat tgtcctccgt ggtcaccgtc ccttcgtcct ccctgggcac ccagacctat 600

atctgtaatg tcaaccataa gccctcgaac accaaggtcg acaagaaggt cgagccgaag 660

tcgtgcgaca agactcacac ttgcccgcct tgcccagccc cggaagctgc cggtggtcct 720

tcggtgttcc tcttcccgcc caagccgaag gataccctga tgatctcacg gacccccgaa 780

gtgacctgtg tggtggtgga cgtgtcccac gaggacccgg aagtgaaatt caattggtac 840

gtggatggag tggaagtgca caacgccaag accaagccac gggaagaaca gtacaactct 900

acctaccgcg tggtgtccgt gctcactgtg ctgcaccaag actggctgaa cgggaaggag 960

tacaagtgca aagtgtccaa caaggcgctg cctgccccaa ttgagaaaac tatctcgaaa 1020

gccaagggac agcctcgaga gcctcaagtg tacaccctgc ctccctctcg ggacgagctg 1080

accaagaacc aagtctccct gacctgtctg gtcaagggat tctacccatc ggatatcgcc 1140

gtggaatggg aaagcaacgg acagcccgag aacaactaca agacgactcc gcccgtgctg 1200

gattccgacg ggagcttctt cttgtactcc aagctgaccg tcgacaagag cagatggcag 1260

cagggaaacg tgttctcctg ctccgtgatg catgaggcgc tgcacaacca ctacactcag 1320

aagagcttgt ccctgtcgcc cgga 1344

<210> 85
<211> 8
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-001 mAb CDR1 (IMGT)

<400> 85

Gly Phe Thr Phe Thr Glu Thr Tyr
1 5

[0077]

<210> 86
<211> 5
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-001 mAb CDR1 (Kabat)

<400> 86

Glu Thr Tyr Met Ser
1 5

<210> 87
<211> 448
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS28-256-005 mAb重链

<400> 87

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Glu Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ser Tyr Gln Gly Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

[0078]

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

[0079]

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 88
<211> 1344
<212> DNA

<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS28-256-005 mAb重链

<400> 88

[0080]

gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccttcact gagacttata tgagctgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcaat atttctccga cttatagcac taccaactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acagcaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagatacaac 300

tcttaccagg gtggcttgga ctactggggc cagggaacct tggtcaccgt ctcgagtgct 360

agcactaagg gcccgtcggt gttcccgctg gccccatcgt ccaagagcac atcagggggt 420

accgccgccc tgggctgcct tgtgaaggat tactttcccg agcccgtcac agtgtcctgg 480

aacagcggag ccctgacctc cggagtgcat actttcccgg ctgtgcttca gtcctctggc 540

ctgtactcat tgtcctccgt ggtcaccgtc ccttcgtcct ccctgggcac ccagacctat 600

atctgtaatg tcaaccataa gccctcgaac accaaggtcg acaagaaggt cgagccgaag 660

tcgtgcgaca agactcacac ttgcccgcct tgcccagccc cggaactgct gggtggtcct 720

tcggtgttcc tcttcccgcc caagccgaag gataccctga tgatctcacg gacccccgaa 780

gtgacctgtg tggtggtgga cgtgtcccac gaggacccgg aagtgaaatt caattggtac 840

gtggatggag tggaagtgca caacgccaag accaagccac gggaagaaca gtacaactct 900

acctaccgcg tggtgtccgt gctcactgtg ctgcaccaag actggctgaa cgggaaggag 960

tacaagtgca aagtgtccaa caaggcgctg cctgccccaa ttgagaaaac tatctcgaaa 1020

gccaagggac agcctcgaga gcctcaagtg tacaccctgc ctccctctcg ggacgagctg 1080

accaagaacc aagtctccct gacctgtctg gtcaagggat tctacccatc ggatatcgcc 1140

gtggaatggg aaagcaacgg acagcccgag aacaactaca agacgactcc gcccgtgctg 1200

gattccgacg ggagcttctt cttgtactcc aagctgaccg tcgacaagag cagatggcag 1260

cagggaaacg tgttctcctg ctccgtgatg catgaggcgc tgcacaacca ctacactcag 1320

aagagcttgt ccctgtcgcc cgga 1344

<210> 89
<211> 448
<212> PRT

<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS28-256-005 mAb重链

<400> 89

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Glu Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

[0081] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ser Tyr Gln Gly Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

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

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

[0082] Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

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

420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 90
<211> 215
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-005 mAb轻链

<400> 90

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

[0083]

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ala Leu Gly Tyr Pro
85 90 95

His Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 91
<211> 645
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-005 mAb 轻链

<400> 91
gaaattgtgc tgacccagtc tccgggcacg ttatctctga gccctggtga gcgcgccact 60

[0084] ctgtcatgcc gggcttctca aagtgttagc agtagctacc tggcgtggta tcagcaaaaa 120

ccgggccagg ccccgcgtct gctgatttac ggtgcatcca gccgtgccac cggcattcca 180

gatcgttttt ccggtagtgg ttctgggacg gacttcactc tgacaatctc acgcctggaa 240

ccggaggatt ttgcggtgta ttactgccag caagctttgg gttatcctca tacgttcggc 300

caagggacca aggtggaaat caaacgtact gtagcagctc cttccgtgtt catctttccg 360

cccagtgatg agcagctgaa gtcaggtact gcttccgtgg tttgcctgct caacaacttt 420

taccccagag aagccaaagt ccagtggaaa gtggacaatg cgttgcaaag cgggaactct 480

caggaatccg tcacagagca ggactctaag gactccacct atagcctctc tagtacgctg 540

acactgagca aagccgatta cgagaagcac aaggtgtatg cctgtgaggt tacccatcaa 600

ggccttagct caccagtgac caagagcttc aatagggggag aatgc 645

<210> 92
<211> 645
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-021 mAb轻链

<400> 92
gaaattgtgc tgacccagtc tccgggcacg ttatctctga gccctggtga gcgcgccact 60

ctgtcatgcc gggcttctca aagtgttagc agtagctacc tggcgtggta tcagcaaaaa 120

ccgggccagg ccccgcgtct gctgatttac ggtgcatcca gccgtgccac cggcattcca 180

gatcgttttt ccggtagtgg ttctgggacg gacttcactc tgacaatctc acgcctggaa 240

ccggaggatt ttgcggtgta ttactgccag caacataatc agtatccgaa tacgttcggc 300

caagggacca aggtggaaat caaacgtact gtagcagctc cttccgtgtt catctttccg 360

cccagtgatg agcagctgaa gtcaggtact gcttccgtgg tttgcctgct caacaacttt 420

taccccagag aagccaaagt ccagtggaaa gtggacaatg cgttgcaaag cgggaactct 480

caggaatccg tcacagagca ggactctaag gactccacct atagcctctc tagtacgctg 540

acactgagca aagccgatta cgagaagcac aaggtgtatg cctgtgaggt tacccatcaa 600

ggccttagct caccagtgac caagagcttc aatagggggag aatgc 645

<210> 93
<211> 108
<212> PRT
[0085] <213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-021 mAb 可变结构域

<400> 93

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Asn Gln Tyr Pro

85 90 95

Asn Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 94
<211> 324
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-021 mAb 可变结构域

<400> 94
gaaattgtgc tgacccagtc tccgggcacg ttatctctga gccctggtga gcgcgccact 60

ctgtcatgcc gggcttctca aagtgttagc agtagctacc tggcgtggta tcagcaaaaa 120

ccgggccagg ccccgcgtct gctgatttac ggtgcatcca gccgtgccac cggcattcca 180

gatcgttttt ccggtagtgg ttctgggacg gacttcactc tgacaatctc acgcctggaa 240

ccggaggatt ttgcggtgta ttactgccag caacataatc agtatccgaa tacgttcggc 300

caagggacca aggtggaaat caaa 324

[0086]

<210> 95
<211> 215
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-027 mAb 轻链

<400> 95

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu

65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Thr Val Pro Tyr Pro
85 90 95

Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165 170 175

[0087] Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 96
<211> 645
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-027 mAb 轻链

<400> 96
gaaattgtgc tgacccagtc tccgggcacg ttatctctga gccctggtga gcgcgccact 60

ctgtcatgcc gggcttctca aagtgttagc agtagctacc tggcgtggta tcagcaaaaa 120

ccgggccagg ccccgcgtct gctgatttac ggtgcatcca gccgtgccac cggcattcca 180

gatcgttttt ccggtagtgg ttctgggacg gacttcactc tgacaatctc acgcctggaa 240

ccggaggatt ttgcggtgta ttactgccag caaactgtgc cgtatccgta tacgttcggc 300

caagggacca aggtggaaat caaacgtact gtggccgctc ctagcgtgtt catttttccg 360

ccatccgacg agcagctcaa gtccggcacc gcctccgtgg tctgcctgct caacaacttc 420

taccctcgcg aagctaaggt ccagtggaag gtcgacaatg ccctgcagtc cggaaactcg 480

caggaaagcg tgactgaaca ggactccaag gactccacct attcactgtc ctcgactctg 540

accctgagca aggcggatta cgaaaagcac aaagtgtacg catgcgaagt gacccaccag 600

ggtctttcgt cccccgtgac caagagcttc aacagaggag agtgt 645

<210> 97
<211> 5
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-271 mAb CDR1 (Kabat)

<400> 97

His Thr Tyr Met Ser
1 5

[0088]

<210> 98
<211> 8
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-271 mAb CDR1 (IMGT)

<400> 98

Gly Phe Thr Phe Thr His Thr Tyr
1 5

<210> 99
<211> 12
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-271 mAb CDR3 (IMGT)

<400> 99

Ala Arg Tyr Asn Ala Tyr His Ala Ala Leu Asp Tyr
1 5 10

<210> 100
<211> 10
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-271 mAb CDR3 (Kabat)

<400> 100

Tyr Asn Ala Tyr His Ala Ala Leu Asp Tyr
1 5 10

<210> 101
<211> 8
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-018 mAb CDR1 (IMGT)

<400> 101

Gly Phe Thr Phe Thr Gln Thr Tyr
1 5

[0089]

<210> 102
<211> 5
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-018 mAb CDR1 (Kabat)

<400> 102

Gln Thr Tyr Met Ser
1 5

<210> 103
<211> 12
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-018 mAb CDR3 (IMGT)

<400> 103

Ala Arg Tyr Asn Ala Tyr Gln Ile Gly Leu Asp Tyr
1 5 10

<210> 104
<211> 10
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-018 mAb CDR3 (Kabat)

<400> 104

Tyr Asn Ala Tyr Gln Ile Gly Leu Asp Tyr
1 5 10

<210> 105
<211> 448
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS28-256-021 mAb重链

<400> 105

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

[0090]

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr His Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Asn Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr His Ala Ala Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240

[0091]

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 106
<211> 1344
<212> DNA
[0092] <213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的 FS28-256-021 mAb重链

<400> 106
gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccttcact catacttata tgagctgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcaat atttctccga cttatagcac taccaactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acaacaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagatacaac 300

gcgtatcatg ctgctctgga ctactggggc cagggaaccc tggtcaccgt ctcgagtgct 360

agcactaagg gcccgtcggt gttcccgctg gccccatcgt ccaagagcac atcagggggt 420

accgccgccc tgggctgcct tgtgaaggat tactttcccg agcccgtcac agtgtcctgg 480

aacagcggag ccctgacctc cggagtgcat actttcccgg ctgtgcttca gtcctctggc 540

ctgtactcat tgtcctccgt ggtcaccgtc ccttcgtcct ccctgggcac ccagacctat 600

atctgtaatg tcaaccataa gccctcgaac accaaggtcg acaagaaggt cgagccgaag 660

tcgtgcgaca agactcacac ttgcccgcct tgcccagccc cggaactgct gggtggtcct 720

tcggtgttcc tcttcccgcc caagccgaag gataccctga tgatctcacg gacccccgaa 780

gtgacctgtg tggtggtgga cgtgtcccac gaggacccgg aagtgaaatt caattggtac 840

gtggatggag tggaagtgca caacgccaag accaagccac gggaagaaca gtacaactct 900

acctaccgcg tggtgtccgt gctcactgtg ctgcaccaag actggctgaa cgggaaggag 960

tacaagtgca aagtgtccaa caaggcgctg cctgccccaa ttgagaaaac tatctcgaaa 1020

gccaagggac agcctcgaga gcctcaagtg tacaccctgc ctccctctcg ggacgagctg 1080

accaagaacc aagtctccct gacctgtctg gtcaagggat tctacccatc ggatatcgcc 1140

gtggaatggg aaagcaacgg acagcccgag aacaactaca agacgactcc gcccgtgctg 1200

gattccgacg ggagcttctt cttgtactcc aagctgaccg tcgacaagag cagatggcag 1260

cagggaaacg tgttctcctg ctccgtgatg catgaggcgc tgcacaacca ctacactcag 1320

aagagcttgt ccctgtcgcc cgga 1344

[0093]

<210> 107
<211> 448
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS28-256-021 mAb重链

<400> 107

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr His Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Asn Lys Asn Thr Leu Tyr
65 70 75 80

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

85 90 95

Ala Arg Tyr Asn Ala Tyr His Ala Ala Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

[0094] Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

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

305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

[0095] Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 108
<211> 1344
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS28-256-021 mAb重链

<400> 108
gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccttcact catacttata tgagctgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcaat atttctccga cttatagcac taccaactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acaacaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagatacaac 300

gcgtatcatg ctgctctgga ctactggggc cagggaaccc tggtcaccgt ctcgagtgct 360

[0096]

agcactaagg gcccgtcggt gttcccgctg gccccatcgt ccaagagcac atcagggggt 420

accgccgccc tgggctgcct tgtgaaggat tactttcccg agcccgtcac agtgtcctgg 480

aacagcggag ccctgacctc cggagtgcat actttcccgg ctgtgcttca gtcctctggc 540

ctgtactcat tgtcctccgt ggtcaccgtc ccttcgtcct ccctgggcac ccagacctat 600

atctgtaatg tcaaccataa gccctcgaac accaaggtcg acaagaaggt cgagccgaag 660

tcgtgcgaca agactcacac ttgcccgcct tgcccagccc cggaagctgc cggtggtcct 720

tcggtgttcc tcttcccgcc caagccgaag gataccctga tgatctcacg gacccccgaa 780

gtgacctgtg tggtggtgga cgtgtcccac gaggacccgg aagtgaaatt caattggtac 840

gtggatggag tggaagtgca caacgccaag accaagccac gggaagaaca gtacaactct 900

acctaccgcg tggtgtccgt gctcactgtg ctgcaccaag actggctgaa cgggaaggag 960

tacaagtgca aagtgtccaa caaggcgctg cctgccccaa ttgagaaaac tatctcgaaa 1020

gccaagggac agcctcgaga gcctcaagtg tacaccctgc ctccctctcg ggacgagctg 1080

accaagaacc aagtctccct gacctgtctg gtcaagggat tctacccatc ggatatcgcc 1140

gtggaatggg aaagcaacgg acagcccgag aacaactaca agacgactcc gcccgtgctg 1200

gattccgacg ggagcttctt cttgtactcc aagctgaccg tcgacaagag cagatggcag 1260

cagggaaacg tgttctcctg ctccgtgatg catgaggcgc tgcacaacca ctacactcag 1320

aagagcttgt ccctgtcgcc cgga 1344

<210> 109
<211> 119
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-021 mAb 可变结构域

<400> 109

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr His Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Asn Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr His Ala Ala Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 110
<211> 357
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
[0097] <223> FS28-256-021 mAb 可变结构域

<400> 110
gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccttcact catacttata tgagctgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcaat atttctccga cttatagcac taccaactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acaacaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagatacaac 300

gcgtatcatg ctgctctgga ctactggggc cagggaaccc tggtcaccgt ctcgagt 357

<210> 111
<211> 8
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-014 mAb CDR1 (IMGT)

<400> 111

Gly Phe Thr Phe Thr Asp Thr Tyr
1 5

<210> 112
<211> 5
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-014 mAb CDR1 (Kabat)

<400> 112

Asp Thr Tyr Met Ser
1 5

<210> 113
<211> 12
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-014 mAb CDR3 (IMGT)

<400> 113

Ala Arg Tyr Asn Ala Tyr Ala Ala Gly Leu Asp Tyr
1 5 10

[0098]

<210> 114
<211> 10
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-014 mAb CDR3 (Kabat)

<400> 114

Tyr Asn Ala Tyr Ala Ala Gly Leu Asp Tyr
1 5 10

<210> 115
<211> 119
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-014 mAb 可变结构域

<400> 115

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asp Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr Ala Ala Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

[0099]

<210> 116
<211> 357
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-014 mAb 可变结构域

<400> 116
gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccttcact gatacttata tgagctgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcaat atttctccga cttatagcac taccaactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acagcaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagatacaac 300

gcgtatgcgg cgggtcttga ctactggggc cagggaaccc tggtcaccgt ctcgagt 357

<210> 117
<211> 448
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS28-256-014 mAb重链

<400> 117

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asp Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

[0100]

Ala Arg Tyr Asn Ala Tyr Ala Ala Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

[0101]

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 118
<211> 1344
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS28-256-014 mAb重链

<400> 118

[0102]

gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccttcact gatacttata tgagctgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcaat atttctccga cttatagcac taccaactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acagcaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagatacaac 300

gcgtatgcgg cgggtcttga ctactggggc cagggaaccc tggtcaccgt ctcgagtgct 360

agcactaagg gcccgtcggt gttcccgctg gccccatcgt ccaagagcac atcagggggt 420

accgccgccc tgggctgcct tgtgaaggat tactttcccg agcccgtcac agtgtcctgg 480

aacagcggag ccctgacctc cggagtgcat actttcccgg ctgtgcttca gtcctctggc 540

ctgtactcat tgtcctccgt ggtcaccgtc ccttcgtcct ccctgggcac ccagacctat 600

atctgtaatg tcaaccataa gccctcgaac accaaggtcg acaagaaggt cgagccgaag 660

tcgtgcgaca agactcacac ttgcccgcct tgcccagccc cggaactgct gggtggtcct 720

tcggtgttcc tcttcccgcc caagccgaag gataccctga tgatctcacg gacccccgaa 780

gtgacctgtg tggtggtgga cgtgtcccac gaggacccgg aagtgaaatt caattggtac 840

gtggatggag tggaagtgca caacgccaag accaagccac gggaagaaca gtacaactct 900

acctaccgcg tggtgtccgt gctcactgtg ctgcaccaag actggctgaa cgggaaggag 960

tacaagtgca aagtgtccaa caaggcgctg cctgccccaa ttgagaaaac tatctcgaaa 1020

gccaagggac agcctcgaga gcctcaagtg tacaccctgc ctccctctcg ggacgagctg 1080

accaagaacc aagtctccct gacctgtctg gtcaagggat tctacccatc ggatatcgcc 1140

gtggaatggg aaagcaacgg acagcccgag aacaactaca agacgactcc gcccgtgctg 1200

gattccgacg ggagcttctt cttgtactcc aagctgaccg tcgacaagag cagatggcag 1260

cagggaaacg tgttctcctg ctccgtgatg catgaggcgc tgcacaacca ctacactcag 1320

aagagcttgt ccctgtcgcc cgga 1344

<210> 119
<211> 448
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS28-256-014 mAb重链

<400> 119

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asp Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

[0103] Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr Ala Ala Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu

165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

[0104] Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu

385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 120
<211> 1344
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS28-256-014 mAb重链

<400> 120

[0105]

gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccttcact gatacttata tgagctgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcaat atttctccga cttatagcac taccaactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acagcaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagatacaac 300

gcgtatgcgg cgggtcttga ctactggggc cagggaaccc tggtcaccgt ctcgagtgct 360

agcactaagg gcccgtcggt gttcccgctg gccccatcgt ccaagagcac atcagggggt 420

accgccgccc tgggctgcct tgtgaaggat tactttcccg agcccgtcac agtgtcctgg 480

aacagcggag ccctgacctc cggagtgcat actttcccgg ctgtgcttca gtcctctggc 540

ctgtactcat tgtcctccgt ggtcaccgtc ccttcgtcct ccctgggcac ccagacctat 600

atctgtaatg tcaaccataa gccctcgaac accaaggtcg acaagaaggt cgagccgaag 660

tcgtgcgaca agactcacac ttgcccgcct tgcccagccc cggaagctgc cggtggtcct 720

tcggtgttcc tcttcccgcc caagccgaag gataccctga tgatctcacg gacccccgaa 780

gtgacctgtg tggtggtgga cgtgtcccac gaggacccgg aagtgaaatt caattggtac 840

gtggatggag tggaagtgca caacgccaag accaagccac gggaagaaca gtacaactct 900

acctaccgcg tggtgtccgt gctcactgtg ctgcaccaag actggctgaa cgggaaggag 960

tacaagtgca aagtgtccaa caaggcgctg cctgccccaa ttgagaaaac tatctcgaaa 1020

gccaagggac agcctcgaga gcctcaagtg tacaccctgc ctccctctcg ggacgagctg 1080

accaagaacc aagtctccct gacctgtctg gtcaagggat tctacccatc ggatatcgcc 1140

gtggaatggg aaagcaacgg acagcccgag aacaactaca agacgactcc gcccgtgctg 1200

gattccgacg ggagcttctt cttgtactcc aagctgaccg tcgacaagag cagatggcag 1260

cagggaaacg tgttctcctg ctccgtgatg catgaggcgc tgcacaacca ctacactcag 1320

aagagcttgt ccctgtcgcc cgga 1344

<210> 121
<211> 119
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-018 mAb可变结构域

<400> 121

[0106]

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Gln Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr Gln Ile Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 122
<211> 357
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-018 mAb 可变结构域

<400> 122
gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccttcact cagacttata tgagctgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcaat atttctccga cttatagcac taccaactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acagcaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagatacaac 300

gcttatcaga ttgggttgga ctactggggc cagggaaccc tggtcaccgt ctcgagt 357

<210> 123
<211> 448
<212> PRT
<213> 人工序列(Artificial Sequence)

[0107]

<220>
<223> 不含LALA的FS28-256-023 mAb重链

<400> 123

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Gln Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr Gln Ile Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

[0108]

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

[0109]

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 124
<211> 1344
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS28-256-023 mAb重链

<400> 124
gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccttcact cagacttata tgagctgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcaat atttctccga cttatagcac taccaactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acagcaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagatacaac 300

gcttatcaga ttgggttgga ctactggggc cagggaaccc tggtcaccgt ctcgagtgct 360

agcactaagg gcccgtcggt gttcccgctg gccccatcgt ccaagagcac atcagggggt 420

accgccgccc tgggctgcct tgtgaaggat tactttcccg agcccgtcac agtgtcctgg 480

aacagcggag ccctgacctc cggagtgcat actttcccgg ctgtgcttca gtcctctggc 540

ctgtactcat tgtcctccgt ggtcaccgtc ccttcgtcct ccctgggcac ccagacctat 600

atctgtaatg tcaaccataa gccctcgaac accaaggtcg acaagaaggt cgagccgaag 660

tcgtgcgaca agactcacac ttgcccgcct tgcccagccc cggaactgct gggtggtcct 720

tcggtgttcc tcttcccgcc caagccgaag gataccctga tgatctcacg gacccccgaa 780

gtgacctgtg tggtggtgga cgtgtcccac gaggacccgg aagtgaaatt caattggtac 840

gtggatggag tggaagtgca caacgccaag accaagccac gggaagaaca gtacaactct 900

acctaccgcg tggtgtccgt gctcactgtg ctgcaccaag actggctgaa cgggaaggag 960

tacaagtgca aagtgtccaa caaggcgctg cctgccccaa ttgagaaaac tatctcgaaa 1020

gccaagggac agcctcgaga gcctcaagtg tacaccctgc ctccctctcg ggacgagctg 1080

accaagaacc aagtctccct gacctgtctg gtcaagggat tctacccatc ggatatcgcc 1140

gtggaatggg aaagcaacgg acagcccgag aacaactaca agacgactcc gcccgtgctg 1200

gattccgacg ggagcttctt cttgtactcc aagctgaccg tcgacaagag cagatggcag 1260

[0110] cagggaaacg tgttctcctg ctccgtgatg catgaggcgc tgcacaacca ctacactcag 1320

aagagcttgt ccctgtcgcc cgga 1344

<210> 125
<211> 448
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS28-256-023 mAb重链

<400> 125

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Gln Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr Gln Ile Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

[0111] Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn

275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

[0112] Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 126
<211> 1344
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS28-256-023 mAb重链

<400> 126
gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccttcact cagacttata tgagctgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcaat atttctccga cttatagcac taccaactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acagcaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagatacaac 300

gcttatcaga ttgggttgga ctactggggc cagggaaccc tggtcaccgt ctcgagtgct 360

agcactaagg gcccgtcggt gttcccgctg gccccatcgt ccaagagcac atcagggggt 420

accgccgccc tgggctgcct tgtgaaggat tactttcccg agcccgtcac agtgtcctgg 480

aacagcggag ccctgacctc cggagtgcat actttcccgg ctgtgcttca gtcctctggc 540

ctgtactcat tgtcctccgt ggtcaccgtc ccttcgtcct ccctgggcac ccagacctat 600

atctgtaatg tcaaccataa gccctcgaac accaaggtcg acaagaaggt cgagccgaag 660

tcgtgcgaca agactcacac ttgcccgcct tgcccagccc cggaagctgc cggtggtcct 720

tcggtgttcc tcttcccgcc caagccgaag gataccctga tgatctcacg gacccccgaa 780

gtgacctgtg tggtggtgga cgtgtcccac gaggacccgg aagtgaaatt caattggtac 840

gtggatggag tggaagtgca caacgccaag accaagccac gggaagaaca gtacaactct 900

[0113] acctaccgcg tggtgtccgt gctcactgtg ctgcaccaag actggctgaa cgggaaggag 960

tacaagtgca aagtgtccaa caaggcgctg cctgccccaa ttgagaaaac tatctcgaaa 1020

gccaagggac agcctcgaga gcctcaagtg tacaccctgc ctccctctcg ggacgagctg 1080

accaagaacc aagtctccct gacctgtctg gtcaagggat tctacccatc ggatatcgcc 1140

gtggaatggg aaagcaacgg acagcccgag aacaactaca agacgactcc gcccgtgctg 1200

gattccgacg ggagcttctt cttgtactcc aagctgaccg tcgacaagag cagatggcag 1260

cagggaaacg tgttctcctg ctccgtgatg catgaggcgc tgcacaacca ctacactcag 1320

aagagcttgt ccctgtcgcc cgga 1344

<210> 127
<211> 453
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS22-053-008 / FS28-256-012 mAb2重链

<400> 127

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr His Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Asn Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr His Ala Ala Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

[0114]

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

[0115]

Leu Pro Pro Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn
355 360 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
370 375 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385 390 395 400

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
405 410 415

Leu Thr Val Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys
420 425 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly
450

<210> 128
<211> 453
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS22-053-008 / FS28-256-012 mAb2重链

<400> 128

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr His Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

[0116] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Asn Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr His Ala Ala Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

[0117] Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn
355 360 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
370 375 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385 390 395 400

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys

405 410 415

Leu Thr Val Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys
420 425 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly
450

<210> 129
<211> 453
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS22-053-008 / FS28-256-014mAb2重链

<400> 129

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

[0118]

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asp Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr Ala Ala Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240

[0119]

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn
355 360 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
370 375 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385 390 395 400

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
405 410 415

Leu Thr Val Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys
420 425 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly
450

[0120]

<210> 130
<211> 453
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS22-053-008 / FS28-256-014 mAb2重链

<400> 130

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asp Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr Ala Ala Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

[0121] Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val

290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn
355 360 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
370 375 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385 390 395 400

[0122] Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
405 410 415

Leu Thr Val Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys
420 425 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly
450

<210> 131
<211> 453
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS22-053-008 / FS28-256-018 mAb2重链

<400> 131

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Gln Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr Gln Ile Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

[0123]

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

[0124]

Leu Pro Pro Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn
355 360 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
370 375 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385 390 395 400

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
405 410 415

Leu Thr Val Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys
420 425 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly
450

<210> 132
<211> 453
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS22-053-008 / FS28-256-018 mAb2重链

<400> 132

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Gln Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

[0125] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr Gln Ile Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

[0126] Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn
355 360 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
370 375 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385 390 395 400

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys

405 410 415

Leu Thr Val Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys
420 425 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly
450

<210> 133
<211> 453
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的 FS22-053-008 / FS28-256-021 mAb2重链

<400> 133

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

[0127]

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr His Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Asn Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr His Ala Ala Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240

[0128]

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn
355 360 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
370 375 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385 390 395 400

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
405 410 415

Leu Thr Val Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys
420 425 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly
450

[0129]

<210> 134
<211> 453
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS22-053-008 / FS28-256-021 mAb2重链

<400> 134

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr His Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Asn Lys Asn Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr His Ala Ala Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

[0130] Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val

290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn
355 360 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
370 375 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385 390 395 400

[0131] Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
405 410 415

Leu Thr Val Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys
420 425 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly
450

<210> 135
<211> 453
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的 FS22-053-008 / FS28-256-023 mAb2重链

<400> 135

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Gln Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr Gln Ile Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

[0132]

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

[0133]

Leu Pro Pro Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn
355 360 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
370 375 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385 390 395 400

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
405 410 415

Leu Thr Val Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys
420 425 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly
450

<210> 136
<211> 453
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS22-053-008 / FS28-256-023 mAb2重链

<400> 136

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Gln Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

[0134] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr Gln Ile Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

[0135] Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn
355 360 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
370 375 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385 390 395 400

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys

405 410 415

Leu Thr Val Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys
420 425 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly
450

<210> 137
<211> 453
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS22-053-008 / FS28-256-024 mAb2重链

<400> 137

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

[0136]

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr His Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Asn Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr His Ala Ala Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240

[0137]

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn
355 360 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
370 375 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385 390 395 400

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
405 410 415

Leu Thr Val Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys
420 425 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly
450

[0138]

<210> 138
<211> 453
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS22-053-008 / FS28-256-024 mAb2

<400> 138

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr His Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Asn Lys Asn Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr His Ala Ala Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

[0139] Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val

290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn
355 360 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
370 375 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385 390 395 400

[0140] Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
405 410 415

Leu Thr Val Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys
420 425 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly
450

<210> 139
<211> 453
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的 FS22-053-008 / FS28-256-026 重链

<400> 139

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Gln Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr Gln Ile Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

[0141]

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

[0142]

Leu Pro Pro Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn
355 360 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
370 375 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385 390 395 400

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
405 410 415

Leu Thr Val Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys
420 425 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly
450

<210> 140
<211> 453
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的S22-053-008 / FS28-256-026重链

<400> 140

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Gln Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

[0143] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr Gln Ile Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

[0144] Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn
355 360 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
370 375 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385 390 395 400

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys

405 410 415

Leu Thr Val Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys
420 425 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly
450

<210> 141
<211> 453
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS22-053-008 / FS28-256-027 mAb2重链

<400> 141

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

[0145]

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr His Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Asn Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr His Ala Ala Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240

[0146]

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn
355 360 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
370 375 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385 390 395 400

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
405 410 415

Leu Thr Val Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys
420 425 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly
450

[0147]

<210> 142
<211> 453
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS22-053-008 / FS28-256-027 mAb2重链

<400> 142

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr His Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Asn Lys Asn Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr His Ala Ala Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

[0148] Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val

290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn
355 360 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
370 375 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385 390 395 400

[0149] Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
405 410 415

Leu Thr Val Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys
420 425 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly
450

<210> 143
<211> 450
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS22-053-008 / FS28-024 mAb2重链

<400> 143

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Tyr Ser
20 25 30

Ser Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Phe Ile Thr Pro Ser Thr Gly Tyr Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ala Leu Thr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

[0150]

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

[0151]

Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
405 410 415

Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly
450

<210> 144
<211> 450
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS22-053-008 / FS28-024 mAb2重链

<400> 144

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Tyr Ser
20 25 30

Ser Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Phe Ile Thr Pro Ser Thr Gly Tyr Thr His Tyr Ala Asp Ser Val
50 55 60

[0152] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ala Leu Thr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu

180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

[0153] Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val

405 410 415

Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly
450

<210> 145
<211> 450
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS22-053-008 / FS28-024-051 mAb2重链

<400> 145

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

[0154]

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Tyr Ser
20 25 30

Ser Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Phe Ile Thr Pro Ser Thr Gly Tyr Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ala Leu Ile Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225 230 235 240

[0155]

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
405 410 415

Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly
450

[0156]

<210> 146
<211> 450
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的 FS22-053-008 / FS28-024-051 mAb2重链

<400> 146

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Tyr Ser
20 25 30

Ser Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Phe Ile Thr Pro Ser Thr Gly Tyr Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ala Leu Ile Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

[0157] Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val

290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

[0158] Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
405 410 415

Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly
450

<210> 147
<211> 450
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS22-053-008 / FS28-024-052 mAb2重链（无LALA）

<400> 147

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Tyr Ser
20 25 30

Ser Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Phe Ile Thr Pro Ser Thr Gly Tyr Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ala Leu Leu Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

[0159]

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

[0160]

Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
405 410 415

Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly
450

<210> 148
<211> 450
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS22-053-008 / FS28-024-052 mAb2重链（含LALA）

<400> 148

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Tyr Ser
20 25 30

Ser Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Phe Ile Thr Pro Ser Thr Gly Tyr Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
[0161] 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ala Leu Leu Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu

180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

[0162] Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val

405 410 415

Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly
450

<210> 149
<211> 450
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的 FS22-053-008 / FS28-024-053 mAb2重链

<400> 149

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

[0163]

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Tyr Ser
20 25 30

Ser Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Phe Ile Thr Pro Ser Thr Gly Tyr Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ala Leu Val Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225 230 235 240

[0164]

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
405 410 415

Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly
450

[0165]

<210> 150
<211> 450
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的 FS22-053-008 / FS28-024-053 mAb2重链

<400> 150

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Tyr Ser
20 25 30

Ser Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Phe Ile Thr Pro Ser Thr Gly Tyr Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ala Leu Val Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

[0166] Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val

290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

[0167] Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
405 410 415

Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly
450

<210> 151
<211> 450
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS22-053-008-AA / FS28-024-060 mAb2重链

<400> 151

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Tyr Ser
20 25 30

Ser Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Phe Ile Thr Pro Ser Thr Gly Tyr Thr His Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ala Leu Trp Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

[0168]

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

[0169]

Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
405 410 415

Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly
450

<210> 152
<211> 450
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS22-053-008-AA / FS28-026 mAb2重链

<400> 152

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Thr Pro Tyr Tyr Ser Lys Thr Asp Tyr Ala Asp Ser Val
50 55 60

[0170] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asn Trp Tyr Arg Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu

180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

[0171] Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val

405 410 415

Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly
450

<210> 153
<211> 450
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS22-053-008-AA / FS28-091 mAb2重链

<400> 153

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

[0172]

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asn Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Lys Pro Tyr Asp Gly Asn Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asn Arg Trp Val Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

[0173]

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn Gln Val Ser
355 360 365

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
370 375 380

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
385 390 395 400

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
405 410 415

Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys Ser Val Met
420 425 430

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
435 440 445

Pro Gly
450

[0174]

<210> 154
<211> 457
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS22-053-008-AA / FS28-185 mAb2重链

<400> 154

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Thr Ser
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Arg Ile Asn Pro Tyr Glu Gly Glu Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Trp Ser Ile Ala Thr Tyr Tyr Lys Ser Ala Met Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
115 120 125

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
130 135 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145 150 155 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
165 170 175

[0175] Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
180 185 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
195 200 205

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
210 215 220

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala
225 230 235 240

Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
245 250 255

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
260 265 270

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
275 280 285

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

290 295 300

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305 310 315 320

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
325 330 335

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
340 345 350

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Asn Pro Pro Tyr
355 360 365

Leu Phe Ser Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
370 375 380

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
385 390 395 400

[0176] Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
405 410 415

Leu Tyr Ser Lys Leu Thr Val Asp Tyr Trp Arg Trp Leu Glu Gly Asn
420 425 430

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
435 440 445

Gln Lys Ser Leu Ser Leu Ser Pro Gly
450 455

<210> 155
<211> 453
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS22-053-008 / FS28-256 mAb2重链

<400> 155

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asn Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ser Tyr Gln Gly Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

[0177]

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

[0178]

Leu Pro Pro Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn
355 360 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
370 375 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385 390 395 400

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
405 410 415

Leu Thr Val Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys
420 425 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly
450

<210> 156
<211> 453
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS22-053-008 / FS28-256 mAb2重链

<400> 156

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Asn Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

[0179] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ser Tyr Gln Gly Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

[0180] Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn
355 360 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
370 375 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385 390 395 400

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys

405 410 415

Leu Thr Val Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys
420 425 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly
450

<210> 157
<211> 453
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS22-053-008 / FS28-256-001 mAb2重链

<400> 157

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

[0181]

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Glu Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ser Tyr Gln Gly Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240

[0182]

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn
355 360 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
370 375 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385 390 395 400

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
405 410 415

Leu Thr Val Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys
420 425 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly
450

[0183]

<210> 158
<211> 453
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS22-053-008 / FS28-256-001 mAb2重链

<400> 158

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Glu Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ser Tyr Gln Gly Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

[0184] Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val

290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn
355 360 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
370 375 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385 390 395 400

[0185] Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
405 410 415

Leu Thr Val Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys
420 425 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly
450

<210> 159
<211> 453
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS22-053-008 / FS28-256-005 mAb2重链

<400> 159

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Glu Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ser Tyr Gln Gly Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

[0186]

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

[0187]

Leu Pro Pro Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn
355 360 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
370 375 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385 390 395 400

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
405 410 415

Leu Thr Val Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys
420 425 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly
450

<210> 160
<211> 453
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS22-053-008 / FS28-256-005 mAb2重链

<400> 160

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr Glu Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

[0188] Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ser Tyr Gln Gly Gly Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

[0189] Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Asn Pro Pro Tyr Leu Phe Ser Asn
355 360 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
370 375 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385 390 395 400

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys

405 410 415

Leu Thr Val Asp Tyr Trp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys
420 425 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly
450

<210> 161
<211> 447
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28m-228 mAb（含有LALA）重链

<400> 161

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

[0190]

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30

Phe Met Val Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Met Ile Ser Pro Lys Ser Ser Asn Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Phe Thr Pro Ala Arg Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
130 135 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
225 230 235 240

[0191]

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
290 295 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
340 345 350

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 162
<211> 215
<212> PRT
[0192] <213> 人工序列(Artificial Sequence)

<220>
<223> FS28m-228 mAb 轻链

<400> 162

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Pro Phe Pro Phe Ser

85 90 95

Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

[0193] Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 163
<211> 447
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的FS22-063-AA / FS28m-228 mAb2重链

<400> 163

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30

Phe Met Val Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Met Ile Ser Pro Lys Ser Ser Asn Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Trp Phe Thr Pro Ala Arg Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
130 135 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160

[0194]

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
290 295 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
340 345 350

Pro Pro Ser Arg Asp Glu Pro Tyr Trp Ser Tyr Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

[0195]

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Met Asn Tyr
405 410 415

Arg Trp Glu Leu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 164
<211> 215
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS22-063-AA/FS28m-228 mAb2 轻链

<400> 164

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly

1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Pro Phe Pro Phe Ser
85 90 95

Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

[0196] Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205

Ser Phe Asn Arg Gly Glu Cys
210 215

〈210〉 165

<211> 445
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 具有LALA的G1-AA / HelD1.3 mAb重链

<400> 165

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Arg Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Ser Thr Phe Ser Gly Tyr
20 25 30

Gly Val Asn Trp Val Arg Gln Pro Pro Gly Arg Gly Leu Glu Trp Ile
35 40 45

Gly Met Ile Trp Gly Asp Gly Asn Thr Asp Tyr Asn Ser Ala Leu Lys
50 55 60

Ser Arg Val Thr Met Leu Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80

[0197]

Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Glu Arg Asp Tyr Arg Leu Asp Tyr Trp Gly Gln Gly Ser Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

[0198]

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 166
<211> 214
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> G1-AA/HelD1.3 mAb轻链

<400> 166

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Glu Thr Val Thr Ile Thr Cys Arg Ala Ser Gly Asn Ile His Asn Tyr
20 25 30

[0199] Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Val
35 40 45

Tyr Asn Ala Lys Thr Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Asn Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Gly Ser Tyr Tyr Cys Gln His Phe Trp Ser Thr Pro Arg
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln

145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 167
<211> 448
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> G1-AA / SS1 mAb（含LALA）重链

[0200] <400> 167

Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Glu Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Gly Tyr
20 25 30

Thr Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Leu Ile Thr Pro Tyr Asn Gly Ala Ser Ser Tyr Asn Gln Lys Phe
50 55 60

Arg Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Asp Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
85 90 95

Ala Arg Gly Gly Tyr Asp Gly Arg Gly Phe Asp Tyr Trp Gly Ser Gly
100 105 110

Thr Pro Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

[0201]

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

[0202]

<210> 168
<211> 213
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> G1-AA/SS1 mAb 轻链

<400> 168

Asp Ile Glu Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1 5 10 15

Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
20 25 30

His Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr
35 40 45

Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Gly Arg Phe Ser Gly Ser
50 55 60

Gly Ser Gly Asn Ser Tyr Ser Leu Thr Ile Ser Ser Val Glu Ala Glu

65 70 75 80

Asp Asp Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Lys His Pro Leu Thr
85 90 95

Phe Gly Ser Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
100 105 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
115 120 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
130 135 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145 150 155 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165 170 175

[0203] Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195 200 205

Asn Arg Gly Glu Cys
210

<210> 169
<211> 303
<212> PRT
<213> 智人(Homo sapiens) MSLN-His-Avi

<400> 169

Glu Val Glu Lys Thr Ala Cys Pro Ser Gly Lys Lys Ala Arg Glu Ile
1 5 10 15

Asp Glu Ser Leu Ile Phe Tyr Lys Lys Trp Glu Leu Glu Ala Cys Val
20 25 30

Asp Ala Ala Leu Leu Ala Thr Gln Met Asp Arg Val Asn Ala Ile Pro
35 40 45

Phe Thr Tyr Glu Gln Leu Asp Val Leu Lys His Lys Leu Asp Glu Leu
50 55 60

Tyr Pro Gln Gly Tyr Pro Glu Ser Val Ile Gln His Leu Gly Tyr Leu
65 70 75 80

Phe Leu Lys Met Ser Pro Glu Asp Ile Arg Lys Trp Asn Val Thr Ser
85 90 95

Leu Glu Thr Leu Lys Ala Leu Leu Glu Val Asn Lys Gly His Glu Met
100 105 110

Ser Pro Gln Val Ala Thr Leu Ile Asp Arg Phe Val Lys Gly Arg Gly
115 120 125

Gln Leu Asp Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly
130 135 140

Tyr Leu Cys Ser Leu Ser Pro Glu Glu Leu Ser Ser Val Pro Pro Ser
145 150 155 160

[0204]

Ser Ile Trp Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Asp Pro Arg
165 170 175

Gln Leu Asp Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn Met
180 185 190

Asn Gly Ser Glu Tyr Phe Val Lys Ile Gln Ser Phe Leu Gly Gly Ala
195 200 205

Pro Thr Glu Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met Asp
210 215 220

Leu Ala Thr Phe Met Lys Leu Arg Thr Asp Ala Val Leu Pro Leu Thr
225 230 235 240

Val Ala Glu Val Gln Lys Leu Leu Gly Pro His Val Glu Gly Leu Lys
245 250 255

Ala Glu Glu Arg His Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg
260 265 270

Gln Asp Asp Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro
275 280 285

Asn Gly Tyr Leu Val Leu Asp Leu Ser Met Gln Glu Ala Leu Ser
290 295 300

<210> 170
<211> 303
<212> PRT
<213> 猕猴(cynomolgus) MSLN-His-Avi

<400> 170

Asp Val Glu Arg Thr Thr Cys Pro Pro Glu Lys Glu Val His Glu Ile
1 5 10 15

Asp Glu Ser Leu Ile Phe Tyr Lys Lys Arg Glu Leu Glu Ala Cys Val
20 25 30

Asp Ala Ala Leu Leu Ala Ala Gln Met Asp Arg Val Asp Ala Ile Pro
35 40 45

[0205]

Phe Thr Tyr Glu Gln Leu Asp Val Leu Lys His Lys Leu Asp Glu Leu
50 55 60

Tyr Pro Gln Gly Tyr Pro Glu Ser Val Ile Arg His Leu Gly His Leu
65 70 75 80

Phe Leu Lys Met Ser Pro Glu Asp Ile Arg Lys Trp Asn Val Thr Ser
85 90 95

Leu Glu Thr Leu Lys Ala Leu Leu Lys Val Ser Lys Gly His Glu Met
100 105 110

Ser Ala Gln Val Ala Thr Leu Ile Asp Arg Val Val Val Gly Arg Gly
115 120 125

Gln Leu Asp Lys Asp Thr Ala Asp Thr Leu Thr Ala Phe Cys Pro Gly
130 135 140

Cys Leu Cys Ser Leu Ser Pro Glu Arg Leu Ser Ser Val Pro Pro Ser
145 150 155 160

Ile Ile Gly Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Gly Pro Arg
165 170 175

Gln Leu Asp Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn Met
180 185 190

Ser Gly Ser Glu Tyr Phe Val Lys Ile Arg Pro Phe Leu Gly Gly Ala
195 200 205

Pro Thr Glu Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met Asp
210 215 220

Leu Ala Thr Phe Met Lys Leu Arg Arg Glu Ala Val Leu Pro Leu Ser
225 230 235 240

Val Ala Glu Val Gln Lys Leu Leu Gly Pro His Val Glu Gly Leu Lys
245 250 255

Val Glu Glu Gln His Ser Pro Val Arg Asp Trp Ile Leu Lys Gln Arg
260 265 270

[0206]

Gln Asp Asp Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro
275 280 285

Asn Gly Tyr Leu Ile Leu Asp Leu Ser Val Arg Glu Ala Leu Ser
290 295 300

<210> 171
<211> 303
<212> PRT
<213> 小鼠(Murine) MSLN-His-Avi

<400> 171

Asp Ala Glu Gln Lys Ala Cys Pro Pro Gly Lys Glu Pro Tyr Lys Val
1 5 10 15

Asp Glu Asp Leu Ile Phe Tyr Gln Asn Trp Glu Leu Glu Ala Cys Val
20 25 30

Asp Gly Thr Met Leu Ala Arg Gln Met Asp Leu Val Asn Glu Ile Pro
35 40 45

Phe Thr Tyr Glu Gln Leu Ser Ile Phe Lys His Lys Leu Asp Lys Thr
50 55 60

Tyr Pro Gln Gly Tyr Pro Glu Ser Leu Ile Gln Gln Leu Gly His Phe
65 70 75 80

Phe Arg Tyr Val Ser Pro Glu Asp Ile His Gln Trp Asn Val Thr Ser
85 90 95

Pro Asp Thr Val Lys Thr Leu Leu Lys Val Ser Lys Gly Gln Lys Met
100 105 110

Asn Ala Gln Ala Ile Ala Leu Val Ala Cys Tyr Leu Arg Gly Gly Gly
115 120 125

Gln Leu Asp Glu Asp Met Val Lys Ala Leu Gly Asp Ile Pro Leu Ser
130 135 140

Tyr Leu Cys Asp Phe Ser Pro Gln Asp Leu His Ser Val Pro Ser Ser
145 150 155 160

[0207]

Val Met Trp Leu Val Gly Pro Gln Asp Leu Asp Lys Cys Ser Gln Arg
165 170 175

His Leu Gly Leu Leu Tyr Gln Lys Ala Cys Ser Ala Phe Gln Asn Val
180 185 190

Ser Gly Leu Glu Tyr Phe Glu Lys Ile Lys Thr Phe Leu Gly Gly Ala
195 200 205

Ser Val Lys Asp Leu Arg Ala Leu Ser Gln His Asn Val Ser Met Asp
210 215 220

Ile Ala Thr Phe Lys Arg Leu Gln Val Asp Ser Leu Val Gly Leu Ser
225 230 235 240

Val Ala Glu Val Gln Lys Leu Leu Gly Pro Asn Ile Val Asp Leu Lys
245 250 255

Thr Glu Glu Asp Lys Ser Pro Val Arg Asp Trp Leu Phe Arg Gln His
260 265 270

Gln Lys Asp Leu Asp Arg Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro
275 280 285

Asn Gly Tyr Leu Val Leu Asp Phe Asn Val Arg Glu Ala Phe Ser
290 295 300

<210> 172
<211> 107
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 野生型CH3 结构域

<400> 172

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
1 5 10 15

Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
20 25 30

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
[0208] 35 40 45

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
50 55 60

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
65 70 75 80

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
85 90 95

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
100 105

<210> 173
<211> 110
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 包含LALA突变的CH2结构域

<400> 173

Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
100 105 110

[0209]

<210> 174
<211> 110
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 包含LALA-PA突变的CH2结构域

<400> 174

Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
85 90 95

Ala Leu Ala Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
100 105 110

<210> 175
<211> 1901
<212> DNA
<213> 智人(Homo sapiens) MSLN 前蛋白

<400> 175
aagcttgaat tcgccgccac catggccctg cctaccgcta ggcctctgct cggatcctgc 60

ggcacacctg ccctgggaag cctcctgttc ctgctgttct ccctgggctg ggtgcagccc 120

tccagaacac tggccggcga aacaggacaa gaggctgccc ctctcgatgg cgtgctcgct 180

aaccccccca acatcagctc cctgtcccct aggcagctcc tgggctttcc ctgtgccgag 240

gtcagcggcc tctccaccga gagggtgagg gagctggctg tggccctggc tcagaagaac 300

gtgaaactga gcaccgagca actcaggtgc ctggctcata ggctgtccga gccccccgag 360

[0210] gatctggatg ccctgcctct cgacctgctg ctgttcctga accccgacgc ttttagcggc 420

ccccaggcct gcacaaggtt cttcagcaga atcaccaagg ccaacgtgga tctgctgccc 480

agaggcgctc ccgagaggca aagactgctg cccgccgctc tcgcctgttg gggcgtcaga 540

ggatccctgc tgagcgaggc cgacgtgaga gccctgggcg gcctggcttg tgatctgccc 600

ggcaggtttg tcgctgagag cgccgaagtg ctcctgccca gactggtgag ctgccctgga 660

cctctggacc aggatcaaca ggaggccgcc agagctgctc tgcagggagg aggacccccc 720

tacggacctc ctagcacctg gtccgtgagc acaatggacg ccctgagagg cctgctgcct 780

gtgctgggac agcccatcat taggagcatt ccccagggca ttgtggccgc ctggagacag 840

aggagcagca gggacccctc ctggaggcag cctgagagaa caatcctgag gcccagattc 900

agaagagagg tggagaaaac cgcctgccct agcggcaaga aggccagaga gattgacgag 960

agcctgatct tctataaaaa gtgggagctc gaagcctgcg tggatgctgc cctgctggcc 1020

acacagatgg acagggtgaa cgccatcccc ttcacctacg agcagctgga cgtcctgaag 1080

cacaagctcg atgagctgta cccccagggc taccccgagt ccgtgattca gcatctcggc 1140

tacctgttcc tgaaaatgag ccccgaagac atcaggaagt ggaacgtgac aagcctggag 1200

accctcaagg ccctgctgga agtgaacaag ggacacgaga tgagccccca ggtggccacc 1260

ctcatcgaca gatttgtgaa gggaagggga cagctggata aggacaccct cgacaccctg 1320

accgccttct accctggata cctctgcagc ctgtcccccg aagagctgtc cagcgtgcct 1380

ccctcctcca tctgggccgt cagaccccag gatctcgaca catgcgaccc cagacagctg 1440

gatgtgctgt accccaaggc taggctggcc ttccagaaca tgaacggatc cgaatatttc 1500

gtcaaaatcc agagctttct gggcggagcc cccacagagg acctcaaagc cctgagccag 1560

cagaacgtca gcatggacct ggccaccttt atgaaactga gaaccgacgc cgtcctccct 1620

ctgacagtgg ccgaagtgca gaagctcctg ggcccccatg tggaaggcct gaaggccgag 1680

gagagacaca gacccgtgag agactggatt ctgaggcaga ggcaggacga tctggatacc 1740

ctgggcctgg gactgcaggg cggcattcct aacggatacc tggtcctcga cctgagcatg 1800

caggaagccc tgagcggcac accttgtctg ctgggacctg gccctgtcct caccgtgctc 1860

gctctgctgc tggcttccac cctcgcctga tgagcggccg c 1901

[0211]

<210> 176
<211> 448
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS28-256-271 mAb重链

<400> 176

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr His Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Asn Lys Asn Thr Leu Tyr
65 70 75 80

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

85 90 95

Ala Arg Tyr Asn Ala Tyr His Ala Ala Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

[0212] Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

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

305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

[0213] Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 177
<211> 1344
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 不含LALA的FS28-256-271 mAb重链

<400> 177
gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccttcact catacttata tgagctgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcgcg atttctccga cttatagcac taccaactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acaacaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagatacaac 300

gcgtatcatg ctgctctgga ctactggggc cagggaaccc tggtcaccgt ctcgagtgct 360

[0214]

agcactaagg gcccgtcggt gttcccgctg gccccatcgt ccaagagcac atcagggggt 420

accgccgccc tgggctgcct tgtgaaggat tactttcccg agcccgtcac agtgtcctgg 480

aacagcggag ccctgacctc cggagtgcat actttcccgg ctgtgcttca gtcctctggc 540

ctgtactcat tgtcctccgt ggtcaccgtc ccttcgtcct ccctgggcac ccagacctat 600

atctgtaatg tcaaccataa gccctcgaac accaaggtcg acaagaaggt cgagccgaag 660

tcgtgcgaca agactcacac ttgcccgcct tgcccagccc cggaactgct gggtggtcct 720

tcggtgttcc tcttcccgcc caagccgaag gataccctga tgatctcacg gacccccgaa 780

gtgacctgtg tggtggtgga cgtgtcccac gaggacccgg aagtgaaatt caattggtac 840

gtggatggag tggaagtgca caacgccaag accaagccac gggaagaaca gtacaactct 900

acctaccgcg tggtgtccgt gctcactgtg ctgcaccaag actggctgaa cgggaaggag 960

tacaagtgca aagtgtccaa caaggcgctg cctgccccaa ttgagaaaac tatctcgaaa 1020

gccaagggcc agcctcgaga accacaggtg tacaccctgc ccccatcccg ggatgagctg 1080

accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 1140

gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 1200

gactccgacg gatccttctt cctctacagc aagctcaccg tggacaagag caggtggcag 1260

caggggaacg tcttctcctg cagcgtgatg catgaggctc tgcacaacca ctacacacag 1320

aagagcctct ccctgtctcc gggt 1344

<210> 178
<211> 448
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 含有LALA的FS28-256-271 mAb重链

<400> 178

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr His Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Asn Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr His Ala Ala Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

[0215]

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

[0216]

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 179
<211> 1344
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> 含有LALA的FS28-256-271 mAb重链

<400> 179
gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccttcact catacttata tgagctgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcgcg atttctccga cttatagcac taccaactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acaacaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagatacaac 300

gcgtatcatg ctgctctgga ctactggggc cagggaaccc tggtcaccgt ctcgagtgct 360

agcactaagg gcccgtcggt gttcccgctg gccccatcgt ccaagagcac atcagggggt 420

accgccgccc tgggctgcct tgtgaaggat tactttcccg agcccgtcac agtgtcctgg 480

aacagcggag ccctgacctc cggagtgcat actttcccgg ctgtgcttca gtcctctggc 540

ctgtactcat tgtcctccgt ggtcaccgtc ccttcgtcct ccctgggcac ccagacctat 600

atctgtaatg tcaaccataa gccctcgaac accaaggtcg acaagaaggt cgagccgaag 660

tcgtgcgaca agactcacac ttgcccgcct tgcccagccc cggaagctgc cggtggtcct 720

tcggtgttcc tcttcccgcc caagccgaag gataccctga tgatctcacg gacccccgaa 780

gtgacctgtg tggtggtgga cgtgtcccac gaggacccgg aagtgaaatt caattggtac 840

gtggatggag tggaagtgca caacgccaag accaagccac gggaagaaca gtacaactct 900

[0217] acctaccgcg tggtgtccgt gctcactgtg ctgcaccaag actggctgaa cgggaaggag 960

tacaagtgca aagtgtccaa caaggcgctg cctgccccaa ttgagaaaac tatctcgaaa 1020

gccaagggcc agcctcgaga accacaggtg tacaccctgc ccccatcccg ggatgagctg 1080

accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc 1140

gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg 1200

gactccgacg gatccttctt cctctacagc aagctcaccg tggacaagag caggtggcag 1260

caggggaacg tcttctcctg cagcgtgatg catgaggctc tgcacaacca ctacacacag 1320

aagagcctct ccctgtctcc gggt 1344

<210> 180
<211> 119
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-271 mAb 可变结构域

<400> 180

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr His Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Asn Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr His Ala Ala Leu Asp Tyr Trp Gly Gln Gly
100 105 110

[0218] Thr Leu Val Thr Val Ser Ser
115

<210> 181
<211> 357
<212> DNA
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-271 mAb 可变结构域
<400> 181
gaagtgcaac tgctggagtc cggtggtggt ctggtacagc cgggtggttc tctgcgtctg 60

agttgcgcgg ccagtggctt taccttcact catacttata tgagctgggt gcgtcaggct 120

ccgggcaaag gtctggaatg ggttagcgcg atttctccga cttatagcac taccaactat 180

gcggatagcg tgaaaggccg ttttaccatt tctcgcgaca acaacaagaa cacgctgtac 240

ctgcagatga actcactgcg tgccgaagat acggccgtgt attactgtgc gagatacaac 300

gcgtatcatg ctgctctgga ctactggggc cagggaaccc tggtcaccgt ctcgagt 357

<210> 182
<211> 17
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-256-271 mAb CDR2 (Kabat)

<400> 182

Ala Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 187
<211> 453
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 含有LALA的FS22-172-003-AA / FS28-256-271 mAb2重链

<400> 187

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr His Thr
[0219] 20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Asn Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr His Ala Ala Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu

130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

[0220] Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Pro Tyr Ile Ile Pro Pro Tyr Asn

355 360 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
370 375 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385 390 395 400

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
405 410 415

Leu Thr Val Gly Ala Asp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys
420 425 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly
450

[0221] <210> 188
<211> 215
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS22-172-003-AA/FS28-256-271 mAb2 轻链

<400> 188

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Thr Val Pro Tyr Pro
85 90 95

Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

[0222]

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 189
<211> 448
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 含有LALA的OX40（FS20-022-049）/ FS28-256-271 mAb2重链

<400> 189

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr His Thr
20 25 30

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

35 40 45

Ser Ala Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Asn Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr His Ala Ala Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

[0223] Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp

260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Tyr Trp Asp Gln Glu Val Ser Leu Thr
355 360 365

[0224] Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
370 375 380

Ser Asn Gly Asp Glu Gln Phe Ala Tyr Lys Thr Thr Pro Pro Val Leu
385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Gln
405 410 415

Tyr Arg Trp Asn Pro Ala Asp Tyr Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 190
<211> 215
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> OX40 (FS20-022-049)/FS28-256-271 mAb2 轻链

<400> 190

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Thr Val Pro Tyr Pro
85 90 95

Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

[0225]

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 191
<211> 445
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 含有LALA的FS22m-063-AA / HelD1.3 mAb2重链

<400> 191

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Arg Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Ser Thr Phe Ser Gly Tyr
20 25 30

Gly Val Asn Trp Val Arg Gln Pro Pro Gly Arg Gly Leu Glu Trp Ile
35 40 45

Gly Met Ile Trp Gly Asp Gly Asn Thr Asp Tyr Asn Ser Ala Leu Lys
50 55 60

[0226] Ser Arg Val Thr Met Leu Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80

Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Glu Arg Asp Tyr Arg Leu Asp Tyr Trp Gly Gln Gly Ser Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu

180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe
225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
275 280 285

[0227] Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
340 345 350

Ser Arg Asp Glu Pro Tyr Trp Ser Tyr Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Met Asn Tyr Arg Trp

405 410 415

Glu Leu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 192
<211> 214
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS22m-063-AA/HelD1.3 mAb2 轻链

<400> 192

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Glu Thr Val Thr Ile Thr Cys Arg Ala Ser Gly Asn Ile His Asn Tyr
20 25 30

[0228]

Leu Ala Trp Tyr Gln Gln Lys Gln Gly Lys Ser Pro Gln Leu Leu Val
35 40 45

Tyr Asn Ala Lys Thr Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Asn Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Gly Ser Tyr Tyr Cys Gln His Phe Trp Ser Thr Pro Arg
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> 193
<211> 447
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 含有LALA的FS22m-063-AA / 4420 mAb2重链

[0229]

<400> 193

Glu Val Lys Leu Asp Glu Thr Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Pro Met Lys Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Trp Met Asn Trp Val Arg Gln Ser Pro Glu Lys Gly Leu Glu Trp Val
35 40 45

Ala Gln Ile Arg Asn Lys Pro Tyr Asn Tyr Glu Thr Tyr Tyr Ser Asp
50 55 60

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Ser Ser
65 70 75 80

Val Tyr Leu Gln Met Asn Asn Leu Arg Val Glu Asp Met Gly Ile Tyr
85 90 95

Tyr Cys Thr Gly Ser Tyr Tyr Gly Met Asp Tyr Trp Gly Gln Gly Thr

100 105 110

Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
130 135 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205

[0230] Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
290 295 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr

325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
340 345 350

Pro Pro Ser Arg Asp Glu Pro Tyr Trp Ser Tyr Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Met Asn Tyr
405 410 415

Arg Trp Glu Leu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

[0231] Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 194
<211> 219
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS22m-063-AA/4420 mAb2轻链

<400> 194

Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Arg Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Lys Val Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Ser
85 90 95

Thr His Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

[0232]

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 195
<211> 216
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS28-185 mAb 轻链

<400> 195

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser

20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Ser Tyr Ser Ala
85 90 95

Pro Val Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val
100 105 110

Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys
115 120 125

[0233] Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
130 135 140

Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
145 150 155 160

Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser
165 170 175

Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys
180 185 190

Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
195 200 205

Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 196
<211> 447
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> 含有LALA的FS22m-063-AA / FS28m-228-010 mAb2重链

<400> 196

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30

Phe Met Val Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Met Ile Ser Pro Lys Ser Ser Asn Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

[0234]

Ala Arg Tyr His Ile Ser Pro Arg Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
115 120 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
130 135 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
290 295 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

[0235]

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
340 345 350

Pro Pro Ser Arg Asp Glu Pro Tyr Trp Ser Tyr Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385 390 395 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Met Asn Tyr
405 410 415

Arg Trp Glu Leu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

<210> 197
<211> 215
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS22m-063-AA/FS28m-228-010 mAb2轻链

<400> 197

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
[0236] 50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Pro Phe Pro Phe Ser
85 90 95

Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu

165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 198
<211> 7
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> Fcab FS22-172-003 CH3结构域结构环序列

<400> 198

Pro Tyr Ile Ile Pro Pro Tyr
1 5

[0237]

<210> 199
<211> 7
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> Fcab FS22-172-003 CH3结构域结构环序列

<400> 199

Gly Ala Asp Arg Trp Leu Glu
1 5

<210> 200
<211> 217
<212> PRT
<213> 人工序列(Artificial Sequence)

<220>
<223> FS22-172-003-AA/FS28-256-271 轻链

<400> 200

Ala Ala Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser
1 5 10 15

Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser
20 25 30

Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg
35 40 45

Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg
50 55 60

Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg
65 70 75 80

Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Thr Val Pro
85 90 95

Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu
115 120 125

[0238]

Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro
130 135 140

Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly
145 150 155 160

Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr
165 170 175

Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His
180 185 190

Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val
195 200 205

Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 201
<211> 453
<212> PRT

<213> 人工序列(Artificial Sequence)

<220>
<223> 含有LALA的FS22-172-003-AA / FS28-256-271重链

<400> 201

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Thr His Thr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Pro Thr Tyr Ser Thr Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Asn Lys Asn Thr Leu Tyr
65 70 75 80

[0239] Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Tyr Asn Ala Tyr His Ala Ala Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

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

195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

[0240] Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Pro Tyr Ile Ile Pro Pro Tyr Asn
355 360 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
370 375 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385 390 395 400

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
405 410 415

Leu Thr Val Gly Ala Asp Arg Trp Leu Glu Gly Asn Val Phe Ser Cys

420 425 430

[0241] Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
435 440 445

Ser Leu Ser Pro Gly
450

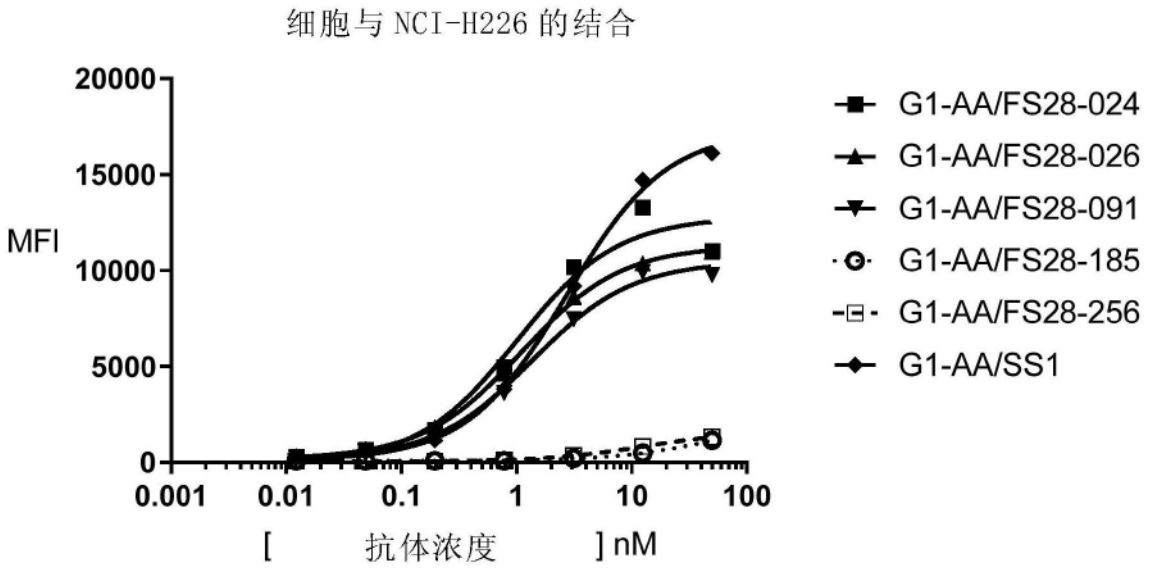
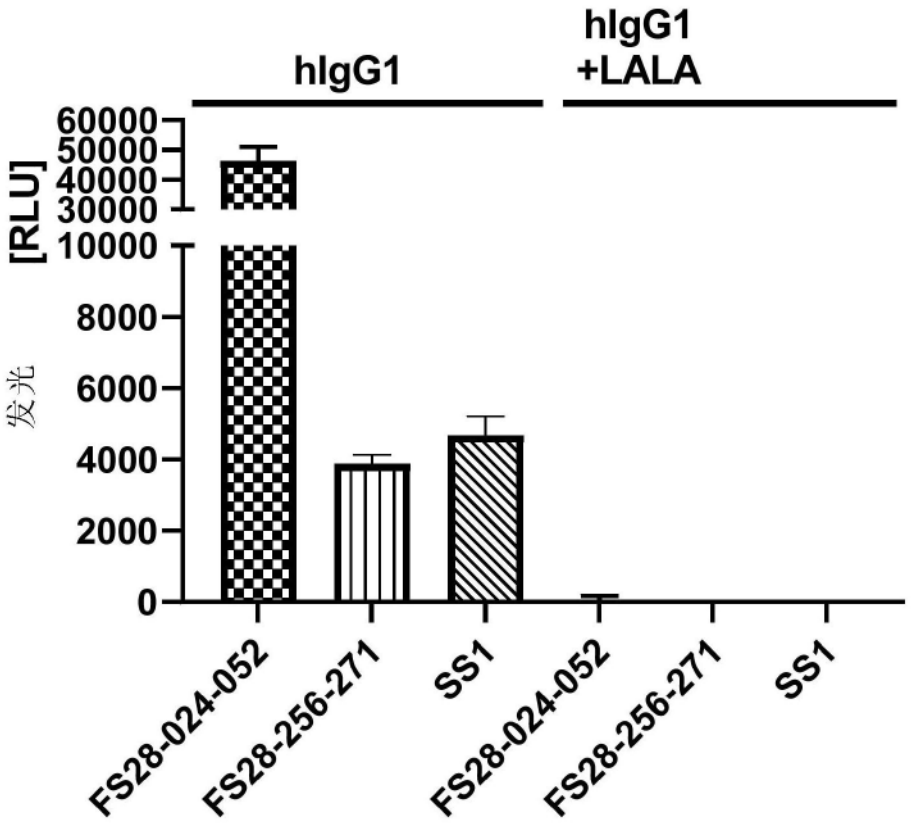

细胞与 NCI-H226 的结合
MFI
20000
15000
10000
5000
0
0.001
0.01
0.1
1
10
100
[抗体浓度] nM
G1-AA/FS28-024
G1-AA/FS28-026
G1-AA/FS28-091
G1-AA/FS28-185
G1-AA/FS28-256
G1-AA/SS1

图1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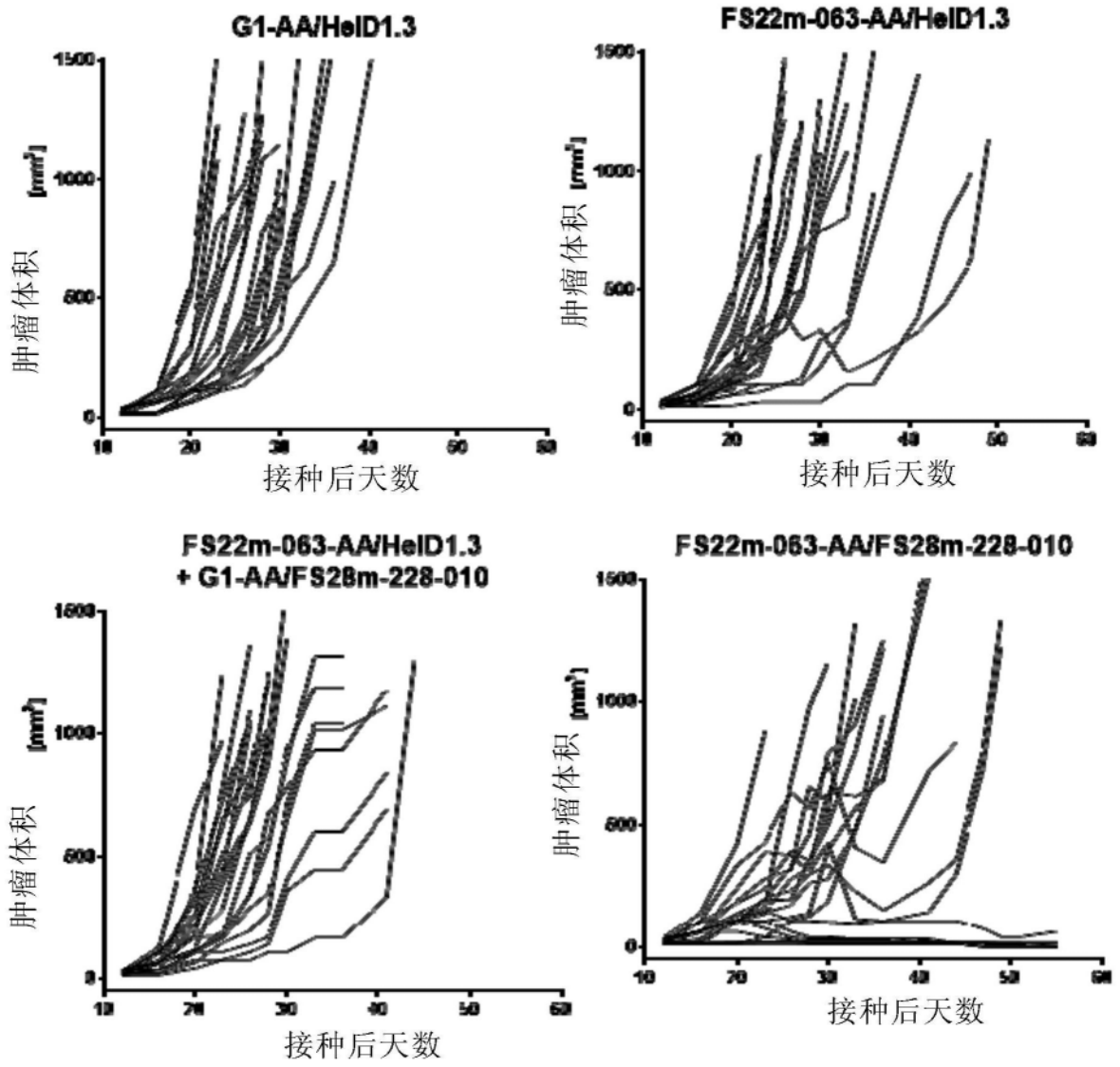
hIgG1
+LALA
发光 [RLU]
60000
50000
40000
30000
10000
8000
6000
4000
2000
0
FS28-024-052
FS28-256-271
SS1
FS28-024-052
FS28-256-271
SS1

图2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FS22m-063-AA/HelD1.3
FS22m-063-AA/HelD1.3
+ G1-AA/FS28m-228-010
FS22m-063-AA/FS28m-228-010
肿瘤体积 [mm³]
接种后天数
1500
1000
500
0
10
20
30
40
50
60

图3

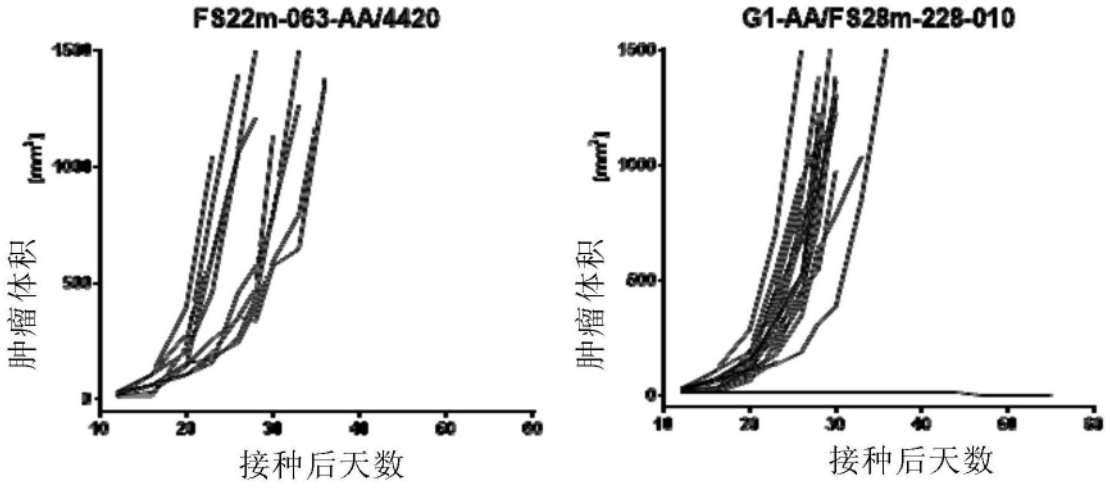
FS22m-063-AA/4420
G1-AA/FS28m-228-010
肿瘤体积
[mm³]
接种后天数

图3(续)

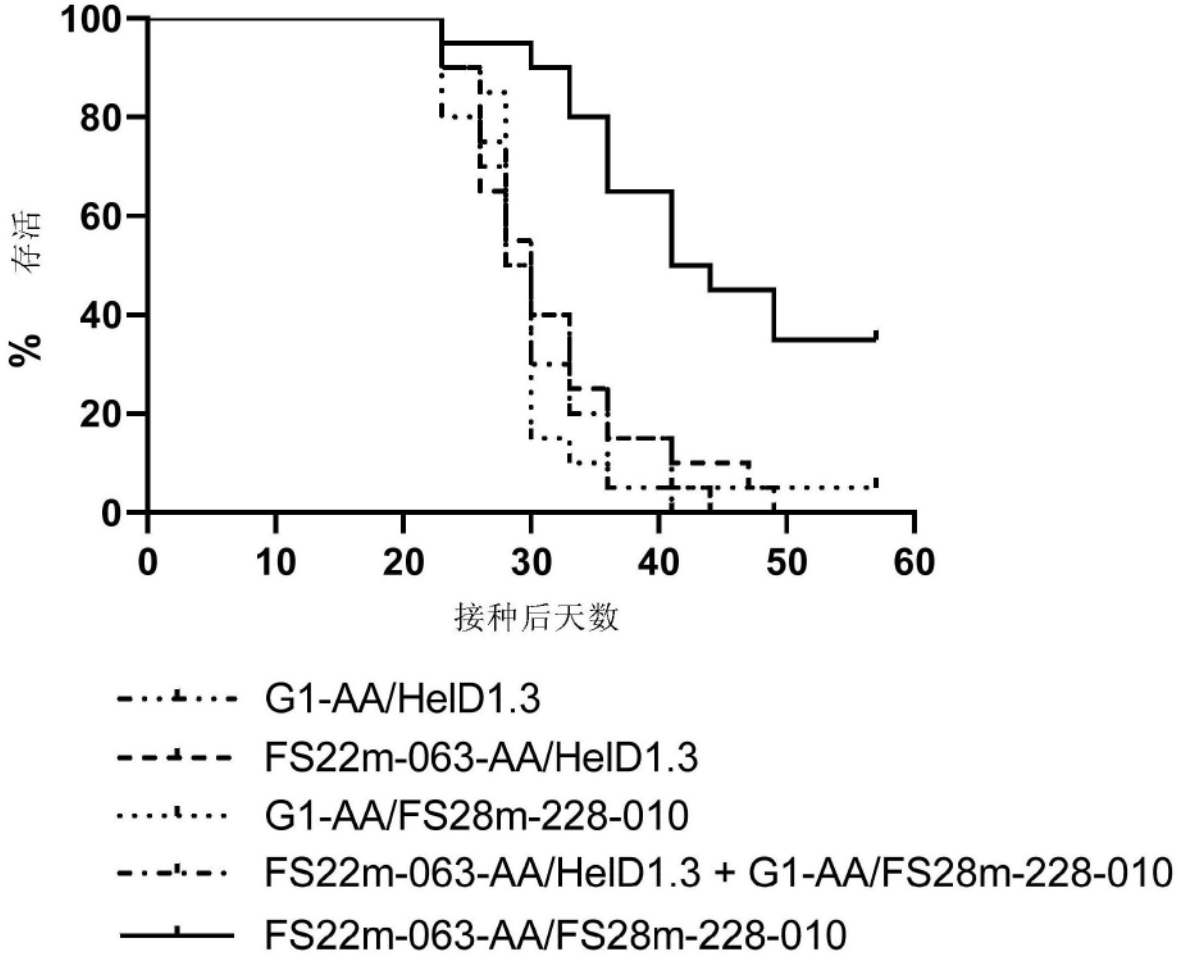
100
80
60
40
20
0
% 存活
0
10
20
30
40
50
60
接种后天数
G1-AA/HelD1.3
FS22m-063-AA/HelD1.3
G1-AA/FS28m-228-010
FS22m-063-AA/HelD1.3 + G1-AA/FS28m-228-010
FS22m-063-AA/FS28m-228-010

图4