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(54)名稱

針對 LAG-3 之工程化抗體及自其製備之雙特異性 PD-1/LAG-3 結合蛋白

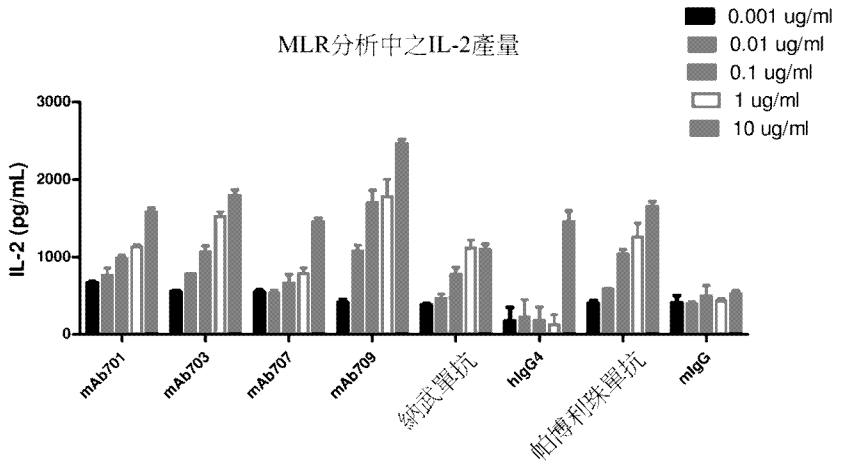
(57)摘要

本發明揭示識別計劃性死亡配位體-1 (PD-1)及淋巴球活化基因 3 蛋白(LAG-3)之高親和力抗體。將來自人類化抗 PD-1 抗體及抗 LAG-3 抗體之結合位點併入串聯 Fab 免疫球蛋白格式中而不顯著損失結合親和力，且所得雙特異性多價結合蛋白能夠同時與 PD-1 及 LAG-3 兩者結合。此類雙特異性 FIT-Ig 結合蛋白適用於治療癌症。

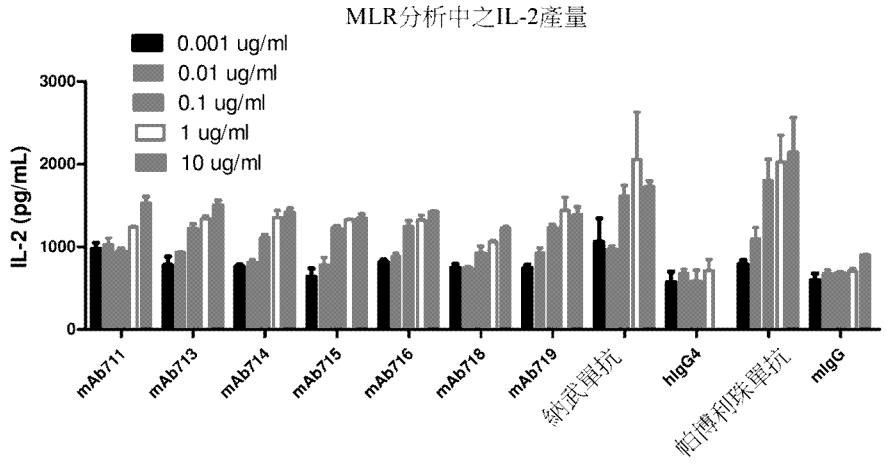
High-affinity antibodies recognizing Programmed Death Ligand-1 (PD-1) and Lymphocyte Activation Gene 3 protein (LAG-3) are disclosed. Binding sites from humanized anti-PD-1 and anti-LAG-3 antibodies are incorporated into a Fabs-in-Tandem Immunoglobulin format without significant loss of binding affinity, and the resultant bispecific, multivalent binding proteins are able to bind to both PD-1 and LAG-3 simultaneously. Such bispecific FIT-Ig binding proteins are useful for treatment of cancer.

指定代表圖：

A


MLR分析中之IL-2產量
0.001 ug/ml
0.01 ug/ml
0.1 ug/ml
1 ug/ml
10 ug/ml
IL-2 (pg/mL)
3000
2000
1000
0
mAb701
mAb703
mAb707
mAb709
紐武單抗
hIgG4
帕博利珠單抗
mIgG

B


MLR分析中之IL-2產量
0.001 ug/ml
0.01 ug/ml
0.1 ug/ml
1 ug/ml
10 ug/ml
IL-2 (pg/mL)
3000
2000
1000
0
mAb711
mAb713
mAb714
mAb715
mAb716
mAb718
mAb719
紐武單抗
hIgG4
帕博利珠單抗
mIgG

【圖1】

公告本

I784190

【發明摘要】

【中文發明名稱】

針對LAG-3之工程化抗體及自其製備之雙特異性PD-1/LAG-3結合蛋白

【英文發明名稱】

ENGINEERED ANTIBODIES TO LAG-3 AND BISPECIFIC PD-1/LAG-3 BINDING PROTEINS MADE THEREFROM

【中文】

本發明揭示識別計劃性死亡配位體-1 (PD-1)及淋巴球活化基因3蛋白(LAG-3)之高親和力抗體。將來自人類化抗PD-1抗體及抗LAG-3抗體之結合位點併入串聯Fab免疫球蛋白格式中而不顯著損失結合親和力，且所得雙特異性多價結合蛋白能夠同時與PD-1及LAG-3兩者結合。此類雙特異性FIT-Ig結合蛋白適用於治療癌症。

【英文】

High-affinity antibodies recognizing Programmed Death Ligand-1 (PD-1) and Lymphocyte Activation Gene 3 protein (LAG-3) are disclosed. Binding sites from humanized anti-PD-1 and anti-LAG-3 antibodies are incorporated into a Fabs-in-Tandem Immunoglobulin format without significant loss of binding affinity, and the resultant bispecific, multivalent binding proteins are able to bind to both PD-1 and LAG-3 simultaneously. Such bispecific FIT-Ig binding proteins are useful for treatment of cancer.

【指定代表圖】

圖1A

【代表圖之符號簡單說明】

無

【發明說明書】

【中文發明名稱】

針對LAG-3之工程化抗體及自其製備之雙特異性PD-1/LAG-3結合蛋白

【英文發明名稱】

ENGINEERED ANTIBODIES TO LAG-3 AND BISPECIFIC PD-1/LAG-3 BINDING PROTEINS MADE THEREFROM

【技術領域】

【0001】 本發明係關於識別淋巴球活化基因3蛋白(LAG-3)之新穎抗體及使用彼等抗體製備之雙特異性PD-1/LAG-3結合蛋白，諸如FIT-Ig結合蛋白。該等抗體及雙特異性結合蛋白適用於治療免疫疾病及血液癌症。

【先前技術】

【0002】

計劃性細胞死亡蛋白1 (PD-1)

計劃性細胞死亡蛋白1 (PD1，CD279)為CD28受體家族之成員，該家族包括CD28、CTLA-4、ICOS、PD-1及BTLA。在免疫細胞，諸如T細胞、B細胞、單核球及自然殺手(NK)細胞中經常存在PD-1之表現。PD-1及類似家族成員為I型跨膜醣蛋白，其含有類似於負責配位體結合之Ig可變域及負責信號傳導分子之結合的胞質尾區的免疫球蛋白樣域。PD-1之胞質尾區含有兩個基於酪胺酸之信號傳導基元，ITIM (基於免疫受體酪胺酸之抑制基元)及ITSM (基於免疫受體酪胺酸之開關基元)。Vivier等人, *Immunol. Today*, 18:286-291 (1997)及Chemnitz等人, *J. Immunol.*, 173:945-954 (2004)。

【0003】 已鑑別出PD-1之兩種細胞表面糖蛋白配位體計劃性死亡配位體1 (PD-L1，CD274，B7-H1)及PD-L2 (CD273，B7-DC)，且已顯示其誘導抑制CD3-及CD28-介導的T細胞活化的胞內信號轉導。Riley, *Immunol. Rev.*, 229:114-125 (2009)。T細胞活化之此下調轉而引起T細胞增殖、IL-2分泌、IFN-γ分泌及其他生長因子與細胞介素之分泌降低。Freeman等人, *J. Exp. Med.*, 192:1027-1034 (2000)；Latchman等人, *Nat. Immunol.*, 2:261-8 (2001)；Carter等人, *Eur. J. Immunol.*, 32:634-43 (2002)；Ohigashi等人, *Clin. Cancer Res.*, 11:2947-53 (2005)。咸信經由PD-1/PD-L1相互作用的信號傳導會在免疫系統中藉由負性調節T細胞反應來提供重要的非冗餘功能。此調節與胸腺中之T細胞發育、慢性發炎反應之調節及周邊耐受性及免疫赦免兩者之維持有關。此等功能之關鍵性質在呈現自體免疫表型之PD-1缺乏小鼠中例示。C57BL/6小鼠中之PD-1缺乏引起慢性進展性狼瘡樣腎絲球腎炎及關節炎。在Balb/c小鼠中，PD-1缺乏由於存在心臟組織特異性自體反應性抗體而引起嚴重心肌病。

【0004】 在T細胞刺激之後，PD-1將酪胺酸磷酸酶SHP-2募集至其胞質尾區內之ITSM基元，引起與CD3 T細胞信號傳導級聯有關之效應分子(諸如CD3-ζ、PKC-θ及ZAP70)之去磷酸化。由於PD-1及CTLA-4兩種分子調節重疊組之信號傳導蛋白質，PD-1下調T細胞反應之機制與CTLA-4的類似但又有所不同。Parry等人, *Mol. Cell Biol.*, 25:9543-9553 (2005)。一般而言，PD-1介導的抑制性信號在免疫耐受性中起重要作用。Bour-Jordan等人, *Immunol. Rev.*, 241:180-205 (2011)。

【0005】 在腫瘤浸潤性淋巴球(TIL)中發現增加的PD-1表現，且已在多種不同組織(包括肺、肝、胃、腎臟、乳房、卵巢、胰臟、黑素細胞

及食道)癌症中報導在腫瘤細胞中表現PD-1配位體。一般而言，腫瘤細胞上表現之PD-1配位體與在多個腫瘤類型中，癌症患者之不良預後有關。Okazaki and Honjo, *Int. Immunol.*, 19:813-824 (2007)。

【0006】 阻斷PD-1/PD-L1相互作用可引起腫瘤特異性T細胞免疫性增強，且因此有助於藉由免疫系統清除腫瘤細胞。在侵襲性胰臟癌之鼠類模型中，T. Nomi等人表明PD-1/PD-L1阻斷之治療功效，顯示投與抗PD-1或抗PD-L1抗體顯著地抑制腫瘤生長。Nomi等人, *Clin. Cancer Res.*, 13:2151-2157 (2007)。抗體阻斷有效促進腫瘤反應性CD8+ T細胞浸潤至腫瘤中，引起包括IFN-γ、顆粒酶B及穿孔蛋白之抗腫瘤效應子上調。在另一研究中，使用小鼠鱗狀細胞癌模型，PD-1或PD-L1之抗體阻斷顯著地抑制腫瘤生長。Tsushima等人, *Oral Oncol.*, 42:268-274 (2006)。

【0007】 近年來，已顯示，PD-1在來自HIV感染個體之T細胞上高度表現，且顯示，受體表現與減弱的T細胞功能及疾病進展相關。Day等人, *Nature*, 443:350-354 (2006)；Trautmann等人, *Nat. Med.*, 12:1198-1202 (2006)。在兩個研究中，配位體PD-L1之阻斷顯著增加活體外HIV特異性產生IFN-γ之細胞之擴增。

【0008】 因此，拮抗劑分子對PD-1信號傳導之治療性調節可恢復免疫細胞之耐受性且使其再活化以根除癌症及慢性病毒感染。

【0009】

淋巴球活化基因3 (LAG-3)

淋巴球活化基因3蛋白(LAG-3，CD223)為一種調節T細胞穩態、增殖及活化之負性共刺激受體。Sierro等人, *Expert Opin. Ther. Targets*, 15:91-101 (2010)。免疫球蛋白超家族成員LAG-3為一種CD4樣蛋白，其類

似CD4，與MHC II類分子結合但具有高兩倍之親和力且在與CD4不同的位點。Huard等人, *Proc. Natl Acad. Sci. USA*, 94:5744-9 (1997)。LAG-3表現於活化CD8+ T細胞、γδ T細胞、自然殺手細胞、B細胞、漿細胞樣樹突狀細胞及調節性T細胞(Treg)上。LAG-3作為T細胞反應之負調節劑之作用係基於利用LAG-3基因剔除小鼠及在模型中活體外及活體內系統使用阻斷性抗LAG-3抗體的研究。Sierro等人 (2010), *op. cit.*；Hannier等人, *J. Immunol.*, 161:4058-65 (1998)；Macon-Lemaitre 等人, *Immunology*, 115:170-8 (2005)；Workman等人, *Eur. J. Immunol.*, 33:970-9 (2003)。天然及誘導性Treg兩者均表現增加的LAG-3，此為該等Treg之最大抑制功能所需。Camisaschi等人, *J. Immunol.*, 184:6545-6551 (2010)；Huang, 等人, *Immunity*, 21:503-513 (2004)。此外，CD4+ 效應T細胞上異位表現LAG-3降低其增殖能力且賦予其針對第三方T細胞之調節潛能。Huang, *ibid*。近期研究亦已顯示，在耗盡淋巴球性脈絡叢腦膜炎病毒(LCMV)-特異性CD8+ T細胞上之高LAG-3表現有助於其無反應性狀態且限制CD8+ T細胞抗腫瘤反應。Blackburn等人, *Nat. Immunol.*, 10:29-37 (2009)及Grosso等人, *J. Clin. Invest.*, 117:3383-3392 (2007)。

【0010】 LAG-3在抗腫瘤免疫反應及針對感染之免疫反應中所起之重要作用使得其成為免疫療法之受關注目標。已提出將利用拮抗劑(包括單株抗體)阻斷LAG-3來治療某些癌症及慢性病毒感染。Turnis等人, *Eur. J. Immunol.*, 45:1892-1905 (2015)。

【0011】 由於PD-1-及LAG-3-介導的信號傳導之重要性變得更好理解，持續不斷地需求發現可有效地改變T細胞功能性或增加腫瘤細胞針對免疫效應細胞之反應性之新穎抑制性抗PD-1及抗LAG-3抗體。此外，可

將PD-1及LAG-3抑制效果組合之雙特異性分子之設計亦將為對於癌症治療之治療方法的所需改良。

【發明內容】

【0012】 本發明提供以高親和力與LAG-3結合之新穎工程改造抗體。本發明亦提供可與PD-1及LAG-3兩者反應之PD-1/LAG-3雙特異性串聯Fab免疫球蛋白(FIT-Ig)。本發明之抗體及雙特異性結合蛋白可阻斷TIL上之LAG-3降低腫瘤浸潤的Treg細胞群體或使TIL恢復細胞毒性表型。另外，本發明之雙特異性結合蛋白可用於抑制PD-1/PD-L1信號傳導，以便使腫瘤浸潤的細胞毒性T細胞再活化。本文所描述之雙特異性多價結合蛋白將適用作PD-1/LAG-3雙特異性抑制劑，以提供協同組合效果來克服抗腫瘤免疫抑制，且因此改良甚至對於單獨抗PD-1或抗LAG-3療法無反應或已終止反應之患者的結果。

【0013】 本發明亦提供製備及使用本文所描述之抗LAG-3抗體及PD-1/LAG-3雙特異性結合蛋白之方法，以及可用於偵測樣本中之PD-1及/或LAG-3之方法中或可用於治療或預防個體之與LAG-3或PD-1及LAG-3活性相關之病症之方法中的各種組合物。

【0014】 在又一實施例中，本發明提供一種雙特異性串聯Fab免疫球蛋白(FIT-Ig)結合蛋白，其包含第一、第二及第三多肽鏈，

其中該第一多肽鏈自胺基端至羧基端包含：(i) VL_A-CL-VH_B-CH1-Fc，其中CL直接與VH_B融合；或(ii) VH_B-CH1-VL_A-CL-Fc，其中CH1直接與VL_A融合；

其中該第二多肽鏈自胺基端至羧基端包含VH_A-CH1；及

其中該第三多肽鏈自胺基端至羧基端包含VL_B-CL；

其中VL為輕鏈可變域，CL為輕鏈恆定域，VH為重鏈可變域，CH1為重鏈恆定域，Fc為免疫球蛋白Fc區，A為PD-1或LAG-3之抗原決定位且B為PD-1或LAG-3之抗原決定位，其限制條件為A與B不同。根據本發明，此類FIT-Ig結合蛋白與PD-1及LAG-3兩者結合。

【0015】 在較佳實施例中，此類FIT-Ig結合蛋白之Fab片段併入來自與靶向PD-1或LAG-3之抗原中之一者結合之一種親本抗體的VL_A-CL域及VH_A-CH1域，且其併入來自與靶向PD-1及LAG-3之另一種抗原結合之不同親本抗體的VL_B-CL域及VH_B-CH1域。因此，VH-CH1/VL-CL配對將產生識別PD-1及LAG-3之串聯Fab部分。

【0016】 根據本發明，PD-1/LAG-3 FIT-Ig結合蛋白可宜包含第一、第二及第三多肽鏈，其中該第一多肽鏈自胺基端至羧基端包含VL_{PD-1}-CL-VH_{LAG-3}-CH1-Fc，其中CL直接與VH_{LAG-3}融合；其中該第二多肽鏈自胺基端至羧基端包含VH_{PD-1}-CH1；且其中該第三多肽鏈自胺基端至羧基端包含VL_{LAG-3}-CL；其中VL_{PD-1}為抗PD-1抗體之輕鏈可變域，CL為輕鏈恆定域，VH_{PD-1}為抗PD-1抗體之重鏈可變域，CH1為重鏈恆定域，VL_{LAG-3}為抗LAG-3抗體之輕鏈可變域，VH_{LAG-3}為抗LAG-3抗體之重鏈可變域且Fc為免疫球蛋白Fc區。有利地，在第一多肽鏈中，VL_{PD-1}-CL域與抗PD-1親本抗體之輕鏈相同，VH_{PD-1}-CH1域與抗PD-1親本抗體之重鏈可變域及重鏈恆定域相同，VL_{LAG-3}-CL域與抗LAG-3親本抗體之輕鏈相同，且VH_{LAG-3}-CH1域與抗LAG-3親本抗體之重鏈可變域及重鏈恆定域相同。

【0017】 在替代實施例中，PD-1/LAG-3 FIT-Ig結合蛋白可宜包含第一、第二及第三多肽鏈，其中該第一多肽鏈自胺基端至羧基端包含

VL_{LAG-3}-CL-VH_{PD-1}-CH1-Fc，其中CL直接與VH_{PD-1}融合；其中該第二多肽鏈自胺基端至羧基端包含VH_{LAG-3}-CH1；且其中該第三多肽鏈自胺基端至羧基端包含VL_{PD-1}-CL；其中VL_{PD-1}為抗PD-1抗體之輕鏈可變域，CL為輕鏈恆定域，VH_{PD-1}為抗PD-1抗體之重鏈可變域，CH1為重鏈恆定域，VL_{LAG-3}為抗LAG-3抗體之輕鏈可變域，VH_{LAG-3}為抗LAG-3抗體之重鏈可變域且Fc為免疫球蛋白Fc區。有利地，在第一多肽鏈中，VL_{LAG-3}-CL域與抗LAG-3親本抗體之輕鏈相同，VH_{LAG-3}-CH1域與抗LAG-3親本抗體之重鏈可變域及重鏈恆定域相同，VL_{PD-1}-CL域與抗PD-1親本抗體之輕鏈相同，且VH_{PD-1}-CH1域與抗PD-1親本抗體之重鏈可變域及重鏈恆定域相同。

【0018】 在替代實施例中，PD-1/LAG-3 FIT-Ig結合蛋白可宜包含第一、第二及第三多肽鏈，其中該第一多肽鏈自胺基端至羧基端包含VH_{LAG-3}-CH1-VL_{PD-1}-CL-Fc，其中CH1直接與VL_{PD-1}融合；其中該第二多肽鏈自胺基端至羧基端包含VL_{LAG-3}-CL；且其中該第三多肽鏈自胺基端至羧基端包含VH_{PD-1}-CH1；其中VL_{PD-1}為抗PD-1抗體之輕鏈可變域，CL為輕鏈恆定域，VH_{PD-1}為抗PD-1抗體之重鏈可變域，CH1為重鏈恆定域，VL_{LAG-3}為抗LAG-3抗體之輕鏈可變域，VH_{LAG-3}為抗LAG-3抗體之重鏈可變域且Fc為免疫球蛋白Fc區。有利地，在第一多肽鏈中，VL_{LAG-3}-CL域與抗LAG-3親本抗體之輕鏈相同，VH_{LAG-3}-CH1域與抗LAG-3親本抗體之重鏈可變域及重鏈恆定域相同，VL_{PD-1}-CL域與抗PD-1親本抗體之輕鏈相同，且VH_{PD-1}-CH1域與抗PD-1親本抗體之重鏈可變域及重鏈恆定域相同。

【0019】 在替代實施例中，PD-1/LAG-3 FIT-Ig結合蛋白可宜包含

第一、第二及第三多肽鏈，其中該第一多肽鏈自胺基端至羧基端包含VH_{PD-1}-CH1-VL_{LAG-3}-CL-Fc，其中CH1直接與VL_{LAG-3}融合；其中該第二多肽鏈自胺基端至羧基端包含VL_{PD-1}-CL；且其中該第三多肽鏈自胺基端至羧基端包含VH_{LAG-3}-CH1；其中VL_{PD-1}為抗PD-1抗體之輕鏈可變域，CL為輕鏈恆定域，VH_{PD-1}為抗PD-1抗體之重鏈可變域，CH1為重鏈恆定域，VL_{LAG-3}為抗LAG-3抗體之輕鏈可變域，VH_{LAG-3}為抗LAG-3抗體之重鏈可變域且Fc為免疫球蛋白Fc區。有利地，在第一多肽鏈中，VL_{LAG-3}-CL域與抗LAG-3親本抗體之輕鏈相同，VH_{LAG-3}-CH1域與抗LAG-3親本抗體之重鏈可變域及重鏈恆定域相同，VL_{PD-1}-CL域與抗PD-1親本抗體之輕鏈相同，且VH_{PD-1}-CH1域與抗PD-1親本抗體之重鏈可變域及重鏈恆定域相同。

【0020】 在FIT-Ig結合蛋白之第一多肽鏈之前述式中，Fc區可為原生或變異Fc區。在特定實施例中，Fc區為來自IgG1、IgG2、IgG3、IgG4、IgA、IgM、IgE或IgD之人類Fc區。在特定實施例中，Fc為來自IgG1之人類Fc或經修飾之人類Fc，諸如下文表6中所闡述的(SEQ ID NO:28)。

【0021】 在本發明之一實施例中，本發明之FIT-Ig結合蛋白保留親本抗體之一或多個特性，自該等親本抗體中使用其Fab片段之序列且併入FIT-Ig結構中。在較佳實施例中，FIT-Ig將針對目標抗原(亦即LAG-3及PD-1)，保留與親本抗體之結合親和力相當的結合親和力，意謂FIT-Ig結合蛋白針對PD-1及LAG-3抗原目標之結合親和力與親本抗體針對其各別目標抗原之結合親和力相比相差不大於10倍，如藉由表面電漿子共振或生物層干涉法所量測。

【0022】在一個實施例中，本發明之FIT-Ig結合蛋白結合PD-1及LAG-3，且包含：第一多肽鏈，其包含SEQ ID NO:140之胺基酸序列23-679、基本上由其組成或由其組成；第二多肽鏈，其包含SEQ ID NO:144之胺基酸序列、基本上由其組成或由其組成；及第三多肽鏈，其包含SEQ ID NO:146之胺基酸序列、基本上由其組成或由其組成。(參見FIT107-1-6a-1；表41。)

【0023】在又一實施例中，本發明之FIT-Ig結合蛋白結合PD-1及LAG-3，且包含：第一多肽鏈，其包含SEQ ID NO:147之胺基酸序列23-684、基本上由其組成或由其組成；第二多肽鏈，其包含SEQ ID NO:151之胺基酸序列、基本上由其組成或由其組成；及第三多肽鏈，其包含SEQ ID NO:153之胺基酸序列、基本上由其組成或由其組成。(參見FIT-107-1-6b-1；表42。)

【0024】在又一實施例中，本發明之FIT-Ig結合蛋白結合PD-1及LAG-3，且包含：第一多肽鏈，其包含SEQ ID NO:154之胺基酸序列23-679、基本上由其組成或由其組成；第二多肽鏈，其包含SEQ ID NO:158之胺基酸序列、基本上由其組成或由其組成；及第三多肽鏈，其包含SEQ ID NO:160之胺基酸序列、基本上由其組成或由其組成。(參見FIT-107-1-6a-2；表43。)

【0025】在又一實施例中，本發明之FIT-Ig結合蛋白結合PD-1及LAG-3，且包含：第一多肽鏈，其包含SEQ ID NO:161之胺基酸序列23-684、基本上由其組成或由其組成；第二多肽鏈，其包含SEQ ID NO:165之胺基酸序列、基本上由其組成或由其組成；及第三多肽鏈，其包含SEQ ID NO:167之胺基酸序列、基本上由其組成或由其組成。(參見FIT-107-1-

6b-2；表44。)

【0026】在又一實施例中，本發明之FIT-Ig結合蛋白結合PD-1及LAG-3，且包含：第一多肽鏈，其包含SEQ ID NO:168之胺基酸序列23-679、基本上由其組成或由其組成；第二多肽鏈，其包含SEQ ID NO:172之胺基酸序列、基本上由其組成或由其組成；及第三多肽鏈，其包含SEQ ID NO:174之胺基酸序列、基本上由其組成或由其組成。(參見FIT-107-1-6a-3；表45。)

【0027】在又一實施例中，本發明之FIT-Ig結合蛋白結合PD-1及LAG-3，且包含：第一多肽鏈，其包含SEQ ID NO:175之胺基酸序列23-684、基本上由其組成或由其組成；第二多肽鏈，其包含SEQ ID NO:179之胺基酸序列、基本上由其組成或由其組成；及第三多肽鏈，其包含SEQ ID NO:181之胺基酸序列、基本上由其組成或由其組成。(參見FIT-107-1-6b-3；表46。)

【0028】在又一實施例中，本發明之FIT-Ig結合蛋白結合PD-1及LAG-3，且包含：第一多肽鏈，其包含SEQ ID NO:182之胺基酸序列23-679、基本上由其組成或由其組成；第二多肽鏈，其包含SEQ ID NO:186之胺基酸序列、基本上由其組成或由其組成；及第三多肽鏈，其包含SEQ ID NO:188之胺基酸序列、基本上由其組成或由其組成。(參見FIT-107-1-7a-1；表47。)

【0029】在又一實施例中，本發明之FIT-Ig結合蛋白結合PD-1及LAG-3，且包含：第一多肽鏈，其包含SEQ ID NO:189之胺基酸序列23-687、基本上由其組成或由其組成；第二多肽鏈，其包含SEQ ID NO:193之胺基酸序列、基本上由其組成或由其組成；及第三多肽鏈，其包含SEQ

ID NO:195之胺基酸序列、基本上由其組成或由其組成。(參見FIT-107-1-7b-1；表48。)

【0030】在又一實施例中，本發明之FIT-Ig結合蛋白結合PD-1及LAG-3，且包含：第一多肽鏈，其包含SEQ ID NO:196之胺基酸序列23-679、基本上由其組成或由其組成；第二多肽鏈，其包含SEQ ID NO:200之胺基酸序列、基本上由其組成或由其組成；及第三多肽鏈，其包含SEQ ID NO:202之胺基酸序列、基本上由其組成或由其組成。(參見FIT-107-1-7a-2；表49。)

【0031】在又一實施例中，本發明之FIT-Ig結合蛋白結合PD-1及LAG-3，且包含：第一多肽鏈，其包含SEQ ID NO:203之胺基酸序列23-687、基本上由其組成或由其組成；第二多肽鏈，其包含SEQ ID NO:207之胺基酸序列、基本上由其組成或由其組成；及第三多肽鏈，其包含SEQ ID NO:209之胺基酸序列、基本上由其組成或由其組成。(參見FIT-107-1-7b-2；表50。)

【0032】在又一實施例中，本發明之FIT-Ig結合蛋白結合PD-1及LAG-3，且包含：第一多肽鏈，其包含SEQ ID NO:210之胺基酸序列23-679、基本上由其組成或由其組成；第二多肽鏈，其包含SEQ ID NO:214之胺基酸序列、基本上由其組成或由其組成；及第三多肽鏈，其包含SEQ ID NO:216之胺基酸序列、基本上由其組成或由其組成。(參見FIT-107-1-7a-3；表51。)

【0033】在又一實施例中，本發明之FIT-Ig結合蛋白結合PD-1及LAG-3，且包含：第一多肽鏈，其包含SEQ ID NO:217之胺基酸序列23-687、基本上由其組成或由其組成；第二多肽鏈，其包含SEQ ID NO:221

之胺基酸序列、基本上由其組成或由其組成；及第三多肽鏈，其包含SEQ ID NO:223之胺基酸序列、基本上由其組成或由其組成。(參見FIT-107-1-7b-3；表52。)

【0034】 本發明亦提供能夠結合人類LAG-3之新穎抗體，其中抗體之抗原結合域包含一組六個CDR，亦即CDR-H1、CDR-H2、CDR-H3、CDR-L1、CDR-L2及CDR-L3，該等CDR選自以下定義之CDR組的群組：

CDR組編號	CDR	CDR 胺基酸序列	SEQ ID NO:
1	CDR-H1	DFNIKDDYMH	SEQ ID NO:114之殘基26-35
	CDR-H2	WIVPENGNTEYASKFQG	SEQ ID NO:114之殘基50-66
	CDR-H3	YGDY	SEQ ID NO:114之殘基99-102
	CDR-L1	RASQEISGYLS	SEQ ID NO:117之殘基24-34
	CDR-L2	AASTLDS	SEQ ID NO:117之殘基50-56
	CDR-L3	LQYASYPLT	SEQ ID NO:117之殘基89-97
2	CDR-H1	DDYMH	SEQ ID NO:72之殘基31-35
	CDR-H2	WIVPENGNTEYASKFQG	SEQ ID NO:72之殘基50-66
	CDR-H3	YGDY	SEQ ID NO:72之殘基99-102
	CDR-L1	RASQEISGYLS	SEQ ID NO:77之殘基24-34
	CDR-L2	AASTLDS	SEQ ID NO:77之殘基50-56
	CDR-L3	LQYASYPLT	SEQ ID NO:77之殘基89-97
3	CDR-H1	DDYMH	SEQ ID NO:119之殘基30-34
	CDR-H2	WIVPENGNTVYASKFQG	SEQ ID NO:119之殘基48-64
	CDR-H3	YGDY	SEQ ID NO:119之殘基95-98
	CDR-L1	RASQEISGYLS	SEQ ID NO:120之殘基24-34
	CDR-L2	AASALDS	SEQ ID NO:120之殘基50-56
	CDR-L3	LQYASYPLT	SEQ ID NO:120之殘基89-97
4	CDR-H1	DDYMH	SEQ ID NO:121之殘基31-35
	CDR-H2	WIVPENGNTEYASKFQG	SEQ ID NO:121之殘基50-66
	CDR-H3	YGDY	SEQ ID NO:121之殘基99-102
	CDR-L1	RAMQEISGYLS	SEQ ID NO:122之殘基24-34
	CDR-L2	AASTLDS	SEQ ID NO:122之殘基50-56
	CDR-L3	LQYAYYPLT	SEQ ID NO:122之殘基89-97
5	CDR-H1	DDYMH	SEQ ID NO:123之殘基31-35
	CDR-H2	WIVPENGNTEYASKFQG	SEQ ID NO:123之殘基50-66

CDR組編號	CDR	CDR胺基酸序列	SEQ ID NO:
	CDR-H3	YGDY	SEQ ID NO:123之殘基99-102
	CDR-L1	RASQEISGYLS	SEQ ID NO:124之殘基24-34
	CDR-L2	AASHLDS	SEQ ID NO:124之殘基50-56
	CDR-L3	LQYASYPLT	SEQ ID NO:124之殘基89-97
6	CDR-H1	DDYMH	SEQ ID NO:125之殘基31-35
	CDR-H2	WIVPENGLTEYASKFQG	SEQ ID NO:125之殘基50-66
	CDR-H3	YGDY	SEQ ID NO:125之殘基99-102
	CDR-L1	RASQEISGYLS	SEQ ID NO:126之殘基24-34
	CDR-L2	ATSTLDS	SEQ ID NO:126之殘基50-56
	CDR-L3	LQYASYPLT	SEQ ID NO:126之殘基89-97
7	CDR-H1	DDYMH	SEQ ID NO:127之殘基31-35
	CDR-H2	WIVPENGKTEYASKFQG	SEQ ID NO:127之殘基50-66
	CDR-H3	YGDY	SEQ ID NO:127之殘基99-102
	CDR-L1	RASQEISGYLS	SEQ ID NO:128之殘基24-34
	CDR-L2	AAMTLDS	SEQ ID NO:128之殘基50-56
	CDR-L3	LQYASYPLT	SEQ ID NO:128之殘基89-97
8	CDR-H1	DDYMH	SEQ ID NO:129之殘基31-35
	CDR-H2	WIVPENGNTHYASKFQG	SEQ ID NO:129之殘基50-66
	CDR-H3	YGDY	SEQ ID NO:129之殘基99-102
	CDR-L1	RASQEISGYLS	SEQ ID NO:130之殘基24-34
	CDR-L2	EASTLDS	SEQ ID NO:130之殘基50-56
	CDR-L3	LQYASYPLT	SEQ ID NO:130之殘基89-97
9	CDR-H1	DDYMH	SEQ ID NO:131之殘基31-35
	CDR-H2	WIVPRNGNTMYASKFQG	SEQ ID NO:131之殘基50-66
	CDR-H3	YGDY	SEQ ID NO:131之殘基99-102
	CDR-L1	RASQEISGYLS	SEQ ID NO:132之殘基24-34
	CDR-L2	AASTLDL	SEQ ID NO:132之殘基50-56
	CDR-L3	LQYASYPLT	SEQ ID NO:132之殘基89-97
10	CDR-H1	DDYMH	SEQ ID NO:135之殘基31-35
	CDR-H2	WIVPENANTVYASKFQG	SEQ ID NO:224
	CDR-H3	YGDY	SEQ ID NO:135之殘基99-102
	CDR-L1	RASQEISGYLS	SEQ ID NO:138之殘基24-34
	CDR-L2	AASALDS	SEQ ID NO:138之殘基50-56
	CDR-L3	LQYASYPLT	SEQ ID NO:138之殘基89-97
11	CDR-H1	DDYMH	SEQ ID NO:136之殘基31-35
	CDR-H2	WIVPRNANTVYASKFQG	SEQ ID NO:225
	CDR-H3	YGDY	SEQ ID NO:136之殘基99-102

CDR組編號	CDR	CDR胺基酸序列	SEQ ID NO:
	CDR-L1	RASQEISGYLS	SEQ ID NO:139之殘基24-34
	CDR-L2	AASALDL	SEQ ID NO:139之殘基50-56
	CDR-L3	LQYASYPLT	SEQ ID NO:139之殘基89-97
12	CDR-H1	DDYMH	SEQ ID NO:136之殘基31-35
	CDR-H2	WIVPRNANTVYASKFQG	SEQ ID NO:225
	CDR-H3	YGDY	SEQ ID NO:136之殘基99-102
	CDR-L1	RASQEISGYLS	SEQ ID NO:117之殘基24-34
	CDR-L2	AASTLDS	SEQ ID NO:117之殘基50-56
	CDR-L3	LQYASYPLT	SEQ ID NO:117之殘基89-97

在一個實施例中，根據本發明之結合蛋白為雙特異性多價免疫球蛋白結合蛋白，其包含兩個或更多個抗原結合位點，其中至少一個抗原結合位點包含選自以上CDR組10、11及12之抗LAG-3 CDR組，且至少一個抗原結合位點包含選自以下CDR組13及14之抗PD-1 CDR組：

CDR組編號	CDR	CDR胺基酸序列	SEQ ID NO:
13	CDR-H1	FYTMS	SEQ ID NO:8之殘基31-35
	CDR-H2	TISGGGRDTYYPDSVKG	SEQ ID NO:8之殘基50-66
	CDR-H3	QGGNYLFAY	SEQ ID NO:8之殘基99-107
	CDR-L1	KASQDVNTVVA	SEQ ID NO:9之殘基24-34
	CDR-L2	WASTRHT	SEQ ID NO:9之殘基50-56
	CDR-L3	QQHYTTPYT	SEQ ID NO:9之殘基89-97
14	CDR-H1	DYGMH	SEQ ID NO:10之殘基31-35
	CDR-H2	YISSGSYTIYYADTVKG	SEQ ID NO:10之殘基50-66
	CDR-H3	RGGSSHVNVMDY	SEQ ID NO:10之殘基99-110
	CDR-L1	KASDHINNWLA	SEQ ID NO:11之殘基24-34
	CDR-L2	GATSLET	SEQ ID NO:11之殘基50-56
	CDR-L3	QQYWSPPYT	SEQ ID NO:11之殘基89-97

【0035】 在又一實施例中，根據本發明之抗LAG-3抗體包含VH及VL域，其中該兩個可變域包含選自由以下組成之群之胺基酸序列：

SEQ ID NO:121及SEQ ID NO:122	SEQ ID NO:123及SEQ ID NO:124
SEQ ID NO:125及SEQ ID NO:126	SEQ ID NO:127及SEQ ID NO:128
SEQ ID NO:129及SEQ ID NO:130	SEQ ID NO:131及SEQ ID NO:132
SEQ ID NO:135及SEQ ID NO:138	SEQ ID NO:136及SEQ ID NO:139
SEQ ID NO:136及SEQ ID NO:117	SEQ ID NO:226*及SEQ ID NO:138

SEQ ID NO:227*及SEQ ID NO:139	SEQ ID NO:227*及SEQ ID NO:117

*其中SEQ ID NO:226與SEQ ID NO:135相同，不同之處在於在胺基酸56處為Ala (A)而非Gly (G) (G55A取代，Kabat編號)；及SEQ ID NO:227與SEQ ID NO:136相同，不同之處在於在胺基酸56處為Ala (A)而非Gly(G) (G55A取代，Kabat編號)。

【0036】 在另一實施例中，本文所描述之抗LAG-3抗體可用於藉由本領域中良好確立之技術製備識別相同目標抗原之衍生結合蛋白。此種衍生物可為例如單鏈抗體(scFv)、Fab片段(Fab)、Fab'片段、$F(ab')_2$、Fv及二硫鍵聯Fv。

【0037】 在本發明之另一態樣中，本文所描述之抗體或雙特異性結合蛋白能夠調節LAG-3或PD-1與LAG-3兩者之生物功能。在另一態樣中，如本文所描述之抗PD-1抗體特異性能夠抑制PD-1/PD-L1信號傳導。信號抑制可在混合淋巴球反應分析中量測，諸如在下文之工作實例中進行。在另一態樣中，如本文所描述之抗LAG-3抗體特異性能夠抑制MHC II類/LAG-3相互作用。此類抑制可在PBMC SEB活化分析分析中量測，諸如在下文之工作實例中進行。在另一態樣中，本文所描述之雙特異性PD-1/LAG-3 FIT-Ig結合蛋白能夠抑制PD-1/PD-L1信號傳導及MHC II類/LAG-3相互作用兩者。

【0038】 在一實施例中，本文所描述之抗LAG-3抗體或其抗原結合片段對於人類LAG-3具有以下之締合速率常數(k_{on})：至少$5 \times 10^3\ M^{-1}s^{-1}$、至少$7 \times 10^3\ M^{-1}s^{-1}$、至少$1 \times 10^4\ M^{-1}s^{-1}$、至少$3 \times 10^4\ M^{-1}s^{-1}$、至少$5 \times 10^4\ M^{-1}s^{-1}$、至少$7 \times 10^4\ M^{-1}s^{-1}$、至少$1 \times 10^5\ M^{-1}s^{-1}$或至少$2 \times 10^5\ M^{-1}s^{-1}$或更高，如藉由表面電漿子共振或生物層干涉法所量測。

【0039】 在另一實施例中，本文所描述之抗LAG-3抗體或其抗原結

合片段對於人類LAG-3具有以下之解離速率常數(k_{off})：低於1.5 × $10^{-3}s^{-1}$、低於1 × $10^{-3}s^{-1}$、低於8 × $10^{-4}s^{-1}$、低於6 × $10^{-4}s^{-1}$、低於4 × $10^{-4}s^{-1}$、低於2 × $10^{-4}s^{-1}$、低於1 × $10^{-4}s^{-1}$、低於9 × $10^{-5}s^{-1}$、低於8 × $10^{-5}s^{-1}$、低於7 × $10^{-5}s^{-1}$、低於5 × $10^{-5}s^{-1}$、低於4 × $10^{-5}s^{-1}$、低於2 × $10^{-5}s^{-1}$或低於1 × $10^{-5}s^{-1}$，如藉由表面電漿子共振或生物層干涉法所量測。

【0040】 在另一實施例中，本文所描述之抗LAG-3抗體或其抗原結合片段對於LAG-3具有以下之解離常數(K_D)：低於5 × 10^{-7} M、低於2 × 10^{-7} M、低於1 × 10^{-7} M、低於8 × 10^{-8} M、低於6 × 10^{-8} M、低於4 × 10^{-8} M、低於2 × 10^{-8} M、低於1 × 10^{-8} M、低於8 × 10^{-9} M、低於6 × 10^{-9} M、低於4 × 10^{-9} M、低於2 × 10^{-9} M或低於1 × 10^{-9} M。

【0041】 在一實施例中，根據本發明之能夠結合PD-1及LAG-3之雙特異性FIT-Ig結合蛋白對於人類PD-1具有以下之締合速率常數(k_{on})：至少5 × 10^3 $M^{-1}s^{-1}$、至少1 × 10^4 $M^{-1}s^{-1}$、至少5 × 10^4 $M^{-1}s^{-1}$、至少1 × 10^5 $M^{-1}s^{-1}$、至少3 × 10^5 $M^{-1}s^{-1}$或至少5 × 10^5 $M^{-1}s^{-1}$或更高；且相同結合蛋白對於人類LAG-3具有以下之締合速率常數(k_{on})：至少5 × 10^3 $M^{-1}s^{-1}$、至少1 × 10^4 $M^{-1}s^{-1}$、至少5 × 10^4 $M^{-1}s^{-1}$、至少1 × 10^5 $M^{-1}s^{-1}$、至少3 × 10^5 $M^{-1}s^{-1}$或至少5 × 10^5 $M^{-1}s^{-1}$或更高，如藉由表面電漿子共振或生物層干涉法所量測。在其他實施例中，如本文所描述之能夠結合PD-1及LAG-3之雙特異性FIT-Ig結合蛋白對於人類PD-1將具有以下之締合速率常數(k_{on})，該締合速率常數比親本抗PD-1抗體針對PD-1之k_{on}低不大於10倍且比親本抗LAG-3抗體針對LAG-3之k_{on}低不大於10倍，分別自該等親本抗體中衍生FIT-Ig結合蛋白之抗PD-1及抗LAG-3特異性。換言之，FIT-Ig結合蛋白將保留針對各抗原(PD-1或LAG-3)之締合速率常數，亦即比由可與各別PD-1或

LAG-3抗原反應之親本抗體呈現之締合速率常數(k_{on})高、相同或低不大於一個數量級。如本文所揭示，與由親本抗體呈現之針對各別抗原之k_{on}相比，針對抗原之PD-1/LAG-3 FIT-Ig結合蛋白可顯示針對一種或兩種抗原之k_{on}改良，或針對一種或兩種抗原之k_{on}可基本上分別與由親本抗體所呈現的相同，或若與親本抗體相比，顯示FIT-Ig結合蛋白針對一種或兩種抗原之k_{on}降低，則降低不大於10倍降低。較佳地，與親本抗體針對特定抗原之k_{on}相比，FIT-Ig中針對該抗原之k_{on}的降低小於50%，更佳地小於25%降低。與親本抗體之k_{on}相比，雙特異性FIT-Ig中之此類高保留的k_{on}值為一個本領域中的出人意料的成就。

【0042】 在一實施例中，根據本發明之能夠結合PD-1及LAG-3之雙特異性FIT-Ig結合蛋白對於人類PD-1具有以下之解離速率常數(k_{off})：低於$2 \times 10^{-4}s^{-1}$、低於$1 \times 10^{-4}s^{-1}$、低於$5 \times 10^{-5}s^{-1}$、低於$3 \times 10^{-5}s^{-1}$、低於$2 \times 10^{-5}s^{-1}$、低於$1 \times 10^{-5}s^{-1}$或低於$8 \times 10^{-6}s^{-1}$；且相同結合蛋白對於人類LAG-3具有以下之解離速率常數(k_{off})：低於$2 \times 10^{-4}s^{-1}$、低於$1 \times 10^{-4}s^{-1}$、低於$5 \times 10^{-5}s^{-1}$、低於$3 \times 10^{-5}s^{-1}$、低於$2 \times 10^{-5}s^{-1}$、低於$1 \times 10^{-5}s^{-1}$或低於$8 \times 10^{-6}s^{-1}$，如藉由表面電漿子共振或生物層干涉法所量測。

【0043】 在另一實施例中，根據本發明之能夠結合PD-1及LAG-3之雙特異性FIT-Ig結合蛋白對於PD-1具有以下之解離常數(K_D)：低於2×10^{-8} M、低於1×10^{-8} M、低於5×10^{-9} M、低於1×10^{-9} M、低於6×10^{-10} M、低於5×10^{-10} M、低於3×10^{-10} M、低於2×10^{-10} M、低於1×10^{-10} M、低於8×10^{-11} M、低於6×10^{-11} M、低於4×10^{-11} M或低於1×10^{-11} M；且相同結合蛋白針對人類LAG-3具有以下之解離常數(K_D)：低於2×10^{-8} M、低於1×10^{-8} M、低於5×10^{-9} M、低於1×10^{-9} M、低於6×10^{-10}

M、低於5 × 10^{-10} M、低於3 × 10^{-10} M、低於2 × 10^{-10} M、低於1 × 10^{-10} M、低於8 × 10^{-11} M、低於6 × 10^{-11} M、低於4 × 10^{-11} M或低於1 × 10^{-11} M。在其他實施例中，如本文所描述之能夠結合PD-1及LAG-3之雙特異性FIT-Ig結合蛋白對於人類PD-1將具有以下之解離常數(K_D)，該解離常數與親本抗PD-1抗體針對PD-1之K_D相差不大於10倍，且與親本抗LAG-3抗體針對LAG-3之K_D相差不大於10倍，分別自該等親本抗體中衍生FIT-Ig結合蛋白之抗PD-1及抗LAG-3特異性。換言之，FIT-Ig結合蛋白將保留親本抗體針對各抗原(PD-1或LAG-3)之結合親和力，如由在可分別與PD-1或LAG-3抗原反應之親本抗體所呈現之K_D之一個數量級內的解離常數(K_D)指示。如本文所揭示，與由親本抗體呈現之針對一種或兩種抗原之K_D相比，PD-1/LAG-3 FIT-Ig結合蛋白可顯示針對各別抗原之K_D的改良(亦即具有更低K_D值；更緊密地結合)，或針對一種或兩種抗原之K_D可分別與由親本抗體所呈現的基本上相同，或與親本抗體之K_D相比，FIT-Ig結合蛋白顯示針對一種或兩種抗原之K_D可顯示降低(亦即具有更高K_D值，不那麼緊密地結合)，但若FIT-Ig結合蛋白與親本抗體之間的K_D存在差異，則該差異不大於10倍。較佳地，與由一種或兩種親本抗體呈現之針對一種或兩種抗原之K_D相比，PD-1/LAG-3 FIT-Ig結合蛋白針對各別抗原顯示更低的K_D (更緊密地結合)。保留K_D之親本抗PD-1及抗LAG-3抗體之結合親和力±10倍變化為一個本領域中之出人意料的成就。

【0044】 本發明亦提供醫藥組合物，其包含至少一種抗LAG-3抗體或其抗原結合片段及醫藥學上可接受之載劑。本發明亦提供醫藥組合物，其包含如本文中所描述之抗PD-1抗體與抗LAG-3抗體或其抗原結合片段之組合，及醫藥學上可接受之載劑。本發明亦提供可與PD-1及LAG-3兩

者反應之雙特異性多價免疫球蛋白結合蛋白，該等結合蛋白併入來自本文所描述之抗PD-1抗體及抗LAG-3抗體之VH/VL結合位點。特定言之，本發明提供醫藥組合物，其包含能夠結合PD-1及LAG-3之至少一種FIT-Ig結合蛋白及醫藥學上可接受之載劑。本發明之醫藥組合物可進一步包含至少一種額外活性成分。在一實施例中，此種額外成分包括(但不限於)：治療劑、顯影劑、細胞毒性劑、血管生成抑制劑、激酶抑制劑、共刺激分子阻斷劑、黏附分子阻斷劑、具有不同特異性之抗體或其功能片段、可偵測標記或報導子；針對特定細胞介素之促效劑或拮抗劑、麻醉藥、非類固醇抗炎藥(NSAID)、鎮痛劑、麻醉劑、鎮靜劑、局部麻醉劑、肌神經阻斷劑、抗微生物劑、皮質類固醇、同化類固醇、紅血球生成素、免疫原、免疫抑制劑、生長激素、激素置換藥物、放射性藥品、抗抑鬱劑、抗精神病藥、刺激劑(例如安非他明(amphetamine)、咖啡鹼等)、β促效劑、吸入性類固醇、腎上腺素或類似物、細胞介素。

【0045】 在另一實施例中，醫藥組合物進一步包含用於治療其中PD-1介導及/或LAG-3介導的信號傳導活性有害的病症的至少一種額外治療劑。

【0046】 在又一實施例中，本發明提供經分離核酸，其編碼本發明之抗LAG-3抗體或其抗原結合片段之一或多個胺基酸序列；且本發明進一步提供經分離核酸，其編碼能夠結合PD-1及LAG-3兩者之雙特異性串聯Fab免疫球蛋白(FIT-Ig)結合蛋白的一或多個胺基酸序列。可將此類核酸插入至載體中以用於進行各種遺傳分析或用於表現、表徵或改良本文所描述之抗體或結合蛋白之一或多個特性。載體可包含編碼本文所描述之抗體或結合蛋白之一或多個胺基酸序列之一或多個核酸分子，其中該一或多個

核酸分子與准許在攜帶載體(例如經載體轉染)之特定宿主細胞中表現抗體或結合蛋白的適當轉錄及/或轉譯序列可操作地連接。用於選殖或表現編碼本文所描述之結合蛋白之胺基酸序列之核酸之載體的實例包括(但不限於) pcDNA、pTT、pTT3、pEFBOS、pBV、pJV及pBJ及其衍生物。

【0047】 本發明亦提供一種宿主細胞，其包含含有編碼本文所描述之抗體或結合蛋白之一或多個胺基酸序列之核酸的載體。適用於本發明之宿主細胞可為原核或真核的。例示性原核宿主細胞為大腸桿菌(*Escherichia coli*)。適用作本發明中之宿主細胞之真核細胞包括原生生物細胞、動物細胞、植物細胞及真菌細胞。例示性真菌細胞為酵母細胞，包括釀酒酵母(*Saccharomyces cerevisiae*)。適用作根據本發明之宿主細胞之例示性動物細胞包括(但不限於)哺乳動物細胞、禽類細胞及昆蟲細胞。較佳的哺乳動物細胞包括(但不限於) CHO細胞、HEK細胞及COS細胞。適用作根據本發明之宿主細胞之昆蟲細胞為昆蟲Sf9細胞。

【0048】 在另一態樣中，本發明提供一種製造抗LAG-3抗體或其功能片段之方法，該方法包含在培養基中，在足以使得宿主細胞表現能夠結合LAG-3之抗體或片段之條件下，培養包含編碼抗體或功能片段之表現載體的宿主細胞。在另一態樣中，本發明提供一種製造能夠結合PD-1及LAG-3之雙特異性多價結合蛋白，特定言之結合PD-1及LAG-3之FIT-Ig結合蛋白之方法，該方法包含在培養基中，在足以使得宿主細胞表現能夠結合PD-1及LAG-3之結合蛋白之條件下，培養包含編碼FIT-Ig結合蛋白之表現載體的宿主細胞。如此製造之蛋白質可經分離，且用於本文所描述之各種組合物及方法中。

【0049】 在另一實施例中，本發明提供用於治療有需要之個體之癌

症之方法，該方法包含向個體投與如本文中所描述之抗LAG-3抗體或其LAG-3結合片段，其中該抗體結合片段能夠在表現LAG-3之細胞中結合LAG-3且抑制MHC II類/LAG-3介導的信號傳導。在另一實施例中，本發明提供用於治療有需要之個體之癌症之方法，該方法包含向個體投與能夠結合如本文中所描述之LAG-3及PD-1之雙特異性FIT-Ig結合蛋白，其中該結合蛋白能夠在表現LAG-3之細胞中結合LAG-3及PD-1且抑制MHC II類/LAG-3介導的信號傳導，且能夠在表現PD-1之細胞中抑制PD-1/PD-L1或PD-1/PD-L2信號傳導。在又一實施例中，本發明之FIT-Ig結合蛋白結合PD-1及LAG-3，且包含：第一多肽鏈，其包含SEQ ID NO:189之胺基酸序列23-687、基本上由其組成或由其組成；第二多肽鏈，其包含SEQ ID NO:192之胺基酸序列20-235、基本上由其組成或由其組成；及第三多肽鏈，其包含SEQ ID NO:194之胺基酸序列23-236、基本上由其組成或由其組成。(參見FIT107-1-7b-1；表48。)

【0050】 在另一實施例中，本發明提供用於治療有需要之個體之自體免疫疾病或癌症之方法，其中該結合蛋白能夠結合LAG-3及PD-1，且其中該自體免疫疾病或癌症為通常對免疫療法有反應之自體免疫疾病或癌症。在另一實施例中，該癌症為與免疫療法不相關之癌症。在另一實施例中，該癌症為癌症，即難治性或復發性惡性疾病。在另一實施例中，結合蛋白抑制腫瘤細胞之生長或存活。在另一實施例中，該癌症係選自由以下組成之群：黑素瘤(例如轉移性惡性黑素瘤)、腎癌(例如透明細胞癌)、前列腺癌(例如激素抗性前列腺腺癌)、胰臟腺癌、乳癌、結腸癌、肺癌(例如非小細胞肺癌)、食道癌、頭頸部鱗狀細胞癌、肝癌、卵巢癌、宮頸癌、甲狀腺癌、神經膠母細胞瘤、神經膠瘤、白血病、淋巴瘤及其他贅生

性惡性疾病。

【0051】 本文所描述之治療方法可進一步包含向有需要之個體投與免疫刺激佐劑，諸如包含完全或部分磷酸二酯或硫代磷酸酯主鏈之CpG寡脫氧核苷酸(CpG ODN)。舉例而言，在本發明之治療方法中，可將免疫刺激佐劑併入包含本發明之抗體或FIT-Ig結合蛋白的組合物及向需要治療之個體投與的組合物中。在另一實施例中，本發明之治療方法可包含：向需要治療之個體投與本文所描述之抗體或FIT-Ig結合蛋白的步驟，及在向個體投與本發明之抗體或FIT-Ig結合蛋白之步驟之前、同時或之後，向該個體投與免疫刺激佐劑的獨立步驟。

【圖式簡單說明】

【0052】

圖1A及圖1B為顯示在混合淋巴球反應中之IL-2產量水準之條形圖，該混合淋巴球反應測試與由公開序列產生之兩種重組抗PD-1抗體(納武單抗(nivolumab)及帕博利珠單抗(pembrolizumab))及針對無關抗原之人類及鼠類對照抗體(「hIgG4」及「mIgG」)相比，本文所揭示之各種抗PD-1抗體的效果。圖1A及圖1B顯示使用來自不同供體之應答淋巴球之獨立MLR測試。

圖2A及圖2B為顯示在混合淋巴球反應中之γ干擾素(IFN-γ)產量水準之條形圖，該混合淋巴球反應測試與由公開序列產生之兩種重組抗PD-1抗體(納武單抗及帕博利珠單抗)及針對無關抗原之人類及鼠類對照抗體(「hIgG4」及「mIgG」)相比，本文所揭示之各種抗PD-1抗體的效果。圖2A及圖2B顯示使用來自不同供體之應答淋巴球之獨立MLR測試。

圖3顯示在混合淋巴球反應中之IL-2產量水準之條形圖，該混合淋巴

球反應測試與由公開序列產生之重組治療性抗PD-1抗體(納武單抗)及針對無關抗原之對照人類抗體(「HuF0323-1」)相比，本文所揭示之各種人類化抗PD-1抗體的效果。

圖4顯示在混合淋巴球反應中之IL-2產量水準之條形圖，該混合淋巴球反應測試與親本鼠類mAb709、由公開序列產生之重組治療性抗PD-1抗體(納武單抗)及針對無關抗原之對照人類抗體(「HuF0323-1」)相比，本文所揭示之各種人類化抗PD-1抗體的效果。

圖5顯示在混合淋巴球反應中之IL-2產量水準之條形圖，該混合淋巴球反應測試與具有親本鼠類mAb713可變域之嵌合體(mAb713c)、由公開序列產生之重組治療性抗PD-1抗體(納武單抗)及針對無關抗原之對照人類抗體(「HuF0323-1」)相比，本文所揭示之各種人類化抗PD-1抗體的效果。圖3、圖4及圖5顯示使用來自不同供體之應答淋巴球之獨立MLR測試。

圖6為顯示在SEB T細胞活化分析中之IL-2產量之條形圖，該SEB T細胞活化分析比較在本文所描述之兩種鼠類抗LAG-3抗體之不同濃度下的T細胞抑制效果的反轉。將本發明之抗LAG-3抗體(「3502-mAb746」及「3502-mAb747」)之功能性與以下各者進行比較：由公開序列產生之重組抗LAG-3 mAb (「BMS-986016」)、由公開序列產生之重組鼠類抗LAG-3抗體(「BAP050」)及針對無關抗原之人類及鼠類對照抗體(「hIgG4」及「mIgG」)。

圖7為顯示在SEB T細胞活化分析中之IL-2產量之條形圖，該SEB T細胞活化分析比較在本文所描述之FIT-Ig雙特異性結合蛋白FIT107-1-2a之不同濃度下的T細胞抑制效果的反轉。將FIT107-1-2a之功能性與以下

進行比較：已知序列之重組抗LAG-3 mAb (BMS-986016)與已知序列之重組抗PD-1 mAb (納武單抗)之組合，及單獨的人類化抗PD-1抗體(本文所揭示之HumAb709-8)。

圖8呈現顯示在混合淋巴球反應中之相對γ干擾素(IFN-g)產量水準的曲線，該混合淋巴球反應測試與已知序列之重組抗LAG-3 mAb (BMS-986016)與已知序列之重組抗PD-1 mAb (納武單抗)之組合，及人類化抗PD-1抗體(本文所揭示之HumAb709-8)相比，在不同濃度下之FIT107-1-2a雙特異性FIT-Ig結合蛋白的效果。

圖9為顯示在SEB T細胞活化分析中之IL-2產量之條形圖，該SEB T細胞活化分析比較在嵌合抗LAG-3抗體mAb747c及人類化抗LAG-3抗體HumAb747-60之不同濃度下的T細胞抑制效果的反轉。參見實例13。將本發明之人類化抗LAG-3抗體(HumAb747-60)之功能性與以下各者進行比較：使用本文所描述之鼠類可變域產生之嵌合抗LAG-3 mAb，及針對無關抗原之人類抗體(「hIgG4」，對照)。

圖10為顯示在SEB T細胞活化分析中之IL-2產量之條形圖，該SEB T細胞活化分析比較在嵌合抗LAG-3抗體mAb747c及在親和力成熟實驗之後併入所指示突變之人類化抗LAG-3抗體HumAb747-60之高親和力變體之不同濃度下的T細胞抑制效果的反轉。參見實例14。將本發明之抗LAG-3變體抗體(HumAb747V-66至HumAb747V-73)之功能性與以下各者進行比較：使用本文所描述之鼠類可變域產生之嵌合抗LAG-3 mAb，及針對無關抗原之人類抗體(「hIgG4」，對照)。

圖11為顯示在SEB T細胞活化分析中之IL-2產量之條形圖，該SEB T細胞活化分析比較在對LAG-3及PD-1目標兩者具有特異性之FIT-Ig結合蛋

白之不同濃度下的T細胞抑制效果的反轉。參見實例16.2。將本發明之PD-1/LAG-3 FIT-Ig雙特異性抗體之功能性與以下各者進行比較：根據公開序列製備之重組抗PD-1單株抗體與抗LAG-3單株抗體之組合(「納武單抗+ BMS 986016」)，及針對無關抗原之人類抗體(「hIgG」，對照)。

圖12為顯示受體阻斷分析之結果之條形圖，該受體阻斷分析顯示根據本發明之抗LAG-3抗體(HumAb747V-67)及根據本發明之PD-1/LAG-3 FIT-Ig結合蛋白(FIT107-1-7b-1)能夠阻斷人類LAG-3與血纖維蛋白原樣蛋白1 (FGL1)之間的相互作用。參見實例16.5。

圖13為評價與T細胞上表現之PD-1及LAG-3之細胞表面結合之一系列曲線。結果顯示，雙特異性FIT-Ig蛋白FIT107-1-7b-1識別T細胞上之PD-1及LAG-3表面蛋白質兩者。

【實施方式】

【0053】 本發明係關於新穎抗LAG-3抗體、其抗原結合部分及多價雙特異性結合蛋白，諸如均與PD-1及LAG-3目標結合之串聯Fab免疫球蛋白(FIT-Ig)。本發明之各種態樣係關於抗LAG-3抗體及抗體片段、與人類PD-1及人類LAG-3結合之多價FIT-Ig結合蛋白及自其製得之醫藥組合物，以及用於製備此類抗體、功能抗體片段及多價結合蛋白之核酸、重組表現載體及宿主細胞。本發明亦涵蓋使用本發明之抗體、功能抗體片段及雙特異性結合蛋白來偵測人類PD-1、人類LAG-3或兩者的方法；活體外或活體內抑制人類LAG-3或人類PD-1及人類LAG-3活性的方法；及治療由PD-1及/或LAG-3與其各別配位體(亦即PD-L1及MHC II類)結合介導的疾病(尤其癌症)的方法。

【0054】 除非本文中另外定義，否則結合本發明使用之科學與技術

術語應具有由一般熟習此項技術者通常理解之含義。術語之含義及範疇應為清楚的，然而，在任何潛在不明確性之情況下，本文所提供之定義優先於任何字典或外部定義。此外，除非上下文另外需要，否則單數術語應包括複數且複數術語應包括單數。在本申請案中，除非另外陳述，否則使用「或」意謂「及/或」。此外，術語「包括(including)」以及其他形式(諸如「包括(includes)」及「包括(included)」)之使用不具限制性。此外，除非另外特定陳述，否則諸如「元件」或「組件」之術語涵蓋包含一個單元之元件及組件以及包含多於一個次單元之元件及組件兩者。

【0055】 一般而言，本文中所描述之與細胞及組織培養、分子生物學、免疫學、微生物學、遺傳學及蛋白與核酸化學及雜交結合使用的命名法及其技術為此項技術中熟知且常用者。除非另外指示，否則本發明之方法及技術通常根據此項技術中熟知之習知方法且如本說明書通篇所引用及討論之各種一般及更特定文獻中所描述來進行。酶促反應及純化技術係根據製造商之說明書如此項技術中通常所實現或如本文所描述執行。本文所描述之與分析化學、合成有機化學及藥物與醫藥化學結合使用的命名法及其實驗室程序及技術為在此項技術中熟知且常用者。標準技術用於化學合成、化學分析、醫藥製備、調配及遞送以及患者治療。

【0056】 為了可更容易地理解本發明，下文定義所選術語。

【0057】 術語「多肽」係指胺基酸之任何聚合鏈。術語「肽」及「蛋白質」可與術語多肽互換使用且亦指胺基酸之聚合鏈。術語「多肽」涵蓋原生或人工蛋白質、蛋白質片段及蛋白質胺基酸序列之多肽類似物。除非上下文矛盾，否則術語「多肽」涵蓋片段及其變體(包括變體之片段)。對於抗原性多肽，多肽片段視情況含有至少一個連續或非線性之多

肽抗原決定位。至少一個抗原決定位片段之精確邊界可使用此項技術中之一般技術確認。片段包含至少約5個連續胺基酸，諸如至少約10個連續胺基酸，至少約15個連續胺基酸或至少約20個連續胺基酸。如本文描述多肽變體。

【0058】 術語「經分離蛋白質」或「經分離多肽」為如下蛋白質或多肽：根據其來源或衍生源而不與其在天然狀態中所伴隨的天然結合組分結合；實質上不含來自同一物種之其他蛋白質；由來自不同物種之細胞表現；或在自然界中不存在。因此，化學合成或在不同於其天然來源的細胞之細胞系統中合成之多肽將與其天然結合組分「分離」。蛋白質亦可藉由使用此項技術中熟知之蛋白質純化技術進行分離而使得實質上不含天然結合組分。

【0059】 術語「回收」係指藉由例如使用此項技術中熟知之蛋白質純化技術進行分離，使得諸如多肽之化學物種實質上不含天然結合組分之過程。

【0060】 術語「生物活性」係指本文所描述之抗PD-1或抗LAG-3抗體之所有固有生物特性。抗PD-1抗體之生物特性包括(但不限於)與PD-1蛋白結合；抗LAG-3抗體之生物特性包括(但不限於)與MHC II類蛋白結合。

【0061】 提及抗體、結合蛋白或肽與第二化學物種之相互作用，術語「特異性結合(specific binding/specifically binding)」意謂，該相互作用取決於第二化學物種上之特定結構(例如抗原決定子或抗原決定位)之存在。舉例而言，抗體識別且結合於特定蛋白質結構而非一般蛋白質。若抗體對抗原決定位「A」具有特異性，則在含有經標記「A」及該抗體之反

應中，含有抗原決定位A (或未經標記之游離A)之分子的存在將減少與該抗體結合之經標記A的量。

【0062】 術語「抗體」廣義地係指包含四條多肽鏈(兩條重(H)鏈及兩條輕(L)鏈)之任何免疫球蛋白(Ig)分子，或保留Ig分子之基本抗原決定位結合特徵的其任何功能片段、突變體、變體或衍生物。此類突變體、變體或衍生物抗體形式為此項技術中已知的。下文論述其非限制性實施例。

【0063】 在全長抗體中，各重鏈包含重鏈可變區(本文中縮寫為VH)及重鏈恆定區。重鏈恆定區包含三個域：CH1、CH2及CH3。各輕鏈包含輕鏈可變區(本文中縮寫為VL)及輕鏈恆定區。輕鏈恆定區包含一個域CL。VH及VL區可進一步細分成高變區，稱為互補決定區(CDR)，穿插有稱為構架區(FR)之更保守區。各VH及VL包含按以下次序自胺基端至羧基端排列的三個CDR及四個FR：FR1、CDR1、FR2、CDR2、FR3、CDR3、FR4。VH域之第一、第二及第三CDR通常列為CDR-H1、CDR-H2及CDR-H3；同樣，VL域之第一、第二及第三CDR通常列為CDR-L1、CDR-L2及CDR-L3。免疫球蛋白分子可具有任何類型(例如，IgG、IgE、IgM、IgD、IgA及IgY)、類別(例如，IgG1、IgG2、IgG3、IgG4、IgA1及IgA2)或子類別。

【0064】 術語「Fc區」用於定義免疫球蛋白重鏈之C端區，其可藉由番木瓜蛋白酶消化完整抗體產生。Fc區可為原生序列Fc區或變異Fc區。免疫球蛋白之Fc區一般包含兩個恆定域，亦即CH2域及CH3域，且視情況包含CH4域，例如如在IgM及IgE抗體之Fc區的情況下。IgG、IgA及IgD抗體之Fc區包含鉸鏈區、CH2域及CH3域。相比之下，IgM及IgE抗體之Fc區缺少鉸鏈區但包含CH2域、CH3域及CH4域。在Fc部分中置換胺基

酸殘基以改變抗體效應功能之變體Fc區為此項技術中已知的(參見例如Winter等人，美國專利第5,648,260號及第5,624,821號)。抗體之Fc部分介導若干重要效應功能，例如細胞介素誘導、ADCC、吞噬作用、補體依賴性細胞毒性(CDC)及抗體與抗原-抗體複合物之半衰期/清除率。在一些情況下，此等效應功能係治療性抗體所需的，但在其他情況下，取決於治療目的，可能為不必要的或甚至有害的。某些人類IgG同型，尤其IgG1及IgG3，分別經由與FcγR及互補序列C1q結合來介導ADCC及CDC。在再一實施例中，抗體之恆定區(例如抗體之Fc區)中之至少一個胺基酸殘基發生置換，使得抗體之效應功能改變。免疫球蛋白之兩條一致重鏈之二聚化係由CH3域之二聚化介導的，且藉由將CH1恆定域與Fc恆定域(例如CH2及CH3)連接之鉸鏈區內的二硫鍵穩定。IgG之消炎活性完全取決於IgG Fc片段之N-連接聚糖之唾液酸化。已測定消炎活性之精確聚糖需求，使得可產生適當IgG1 Fc片段，從而產生效能極大增強的完全重組唾液酸化IgG1 Fc (參見Anthony等人, *Science*, 320:373-376 (2008))。

【0065】 術語抗體之「抗原結合部分」及「抗原結合片段」或「功能片段」可互換地使用，且係指保留與抗原，亦即與衍生該部分或片段之全長抗體相同的抗原(例如PD-1、LAG-3)特異性結合之能力的抗體的一或多個片段。經顯示，抗體之抗原結合功能可由全長抗體之片段執行。此類抗體實施例亦可為雙特異性、雙重特異性或多特異性形式；與兩種或更多種不同抗原(例如PD-1及不同抗原，諸如LAG-3)特異性結合。涵蓋在術語抗體之「抗原結合部分」內之結合片段之實例包括：(i) Fab片段，一種由VL、VH、CL及CH1域組成的一價片段；(ii) $F(ab')_2$片段，一種包含在鉸鏈區處藉由二硫橋鍵連接之兩個Fab片段的二價片段；(iii) Fd片段，其由

VH及CH1域組成；(iv) Fv片段，其由抗體單臂之VL及VH域組成；(v) dAb片段(Ward等人, *Nature*, 341: 544-546 (1989)；PCT公開案第WO 90/05144號)，其包含單一可變域；及(vi)經分離互補決定區(CDR)。此外，儘管Fv片段之兩個域VL及VH經獨立基因編碼，但其可使用重組方法藉由合成性連接子接合，該合成性連接子能夠將其製造成VL與VH區配對以形成一價分子之單一蛋白鏈(被稱為單鏈Fv (scFv)；參見例如Bird等人，*Science*, 242: 423-426 (1988)；及Huston等人，*Proc. Natl. Acad. Sci. USA*, 85: 5879-5883 (1988))。此類單鏈抗體亦意欲涵蓋於術語抗體之「抗原結合部分」及上文給出的等效術語內。亦涵蓋單鏈抗體之其他形式，諸如雙功能抗體。雙功能抗體為二價雙特異性抗體，其中VH及VL域表現於單一多肽鏈上，但使用過短而不允許相同鏈上之兩個域之間進行配對的連接子，從而迫使該等域與另一條鏈之互補域配對且產生兩個抗原結合位點(參見例如Holliger等人, *Proc. Natl. Acad. Sci. USA*, 90: 6444-6448 (1993)。此類抗體結合部分為此項技術中已知的(Kontermann及Dübel編, **Antibody Engineering** (Springer-Verlag, New York, 2001), 第790頁 (ISBN 3-540-41354-5))。另外，單鏈抗體亦包括「線性抗體」，其包含一對串聯Fv區段(VH-CH1-VH-CH1)，該等區段與互補輕鏈多肽一起形成一對抗原結合區(Zapata等人, *Protein Eng.*, 8(10): 1057-1062 (1995)；及美國專利第5,641,870號))。

【0066】 免疫球蛋白恆定(C)域係指重鏈(CH)或輕鏈(CL)恆定域。鼠類及人類IgG重鏈及輕鏈恆定域胺基酸序列為此項技術中已知的。

【0067】 術語「單株抗體」或「mAb」係指自實質上均質抗體之群體獲得的抗體，亦即構成該群體的個別抗體除了可能少量存在的可能天然

存在之突變之外均相同。單株抗體針對單一抗原決定子(抗原決定位)具高度特異性。此外，與通常包括針對不同決定子(抗原決定位)之不同抗體的多株抗體製劑相反，各mAb係針對抗原上之單一決定子。修飾語「單株」不應解釋為需要藉由任何特定方法來產生抗體。

【0068】 術語「人類抗體」包括具有來源於人類生殖系免疫球蛋白序列之可變區及恆定區的抗體。本發明之人類抗體可包括並非由例如CDR且尤其CDR3中之人類生殖系免疫球蛋白序列(例如藉由活體外無規或位點特異性突變誘發或藉由活體內體細胞突變引入之突變)編碼之胺基酸殘基。然而，術語「人類抗體」不包括來源於另一哺乳動物物種(諸如小鼠)之生殖系的CDR序列已經移植至人類構架序列上之抗體。

【0069】 術語「重組人類抗體」包括所有藉由重組手段製備、表現、產生或分離之人類抗體，諸如使用經轉染至宿主細胞中之重組表現載體表現之抗體、自重組組合人類抗體庫分離之抗體Hoogenboom, H.R., *Trends Biotechnol.*, 15: 62-70 (1997)；Azzazy及Highsmith, *Clin. Biochem.*, 35: 425-445 (2002)；Gavilondo及Larrick, *BioTechniques*, 29: 128-145 (2000)；Hoogenboom及Chames, *Immunol. Today*, 21: 371-378 (2000))、自對於人類免疫球蛋白基因為轉殖基因之動物(例如，小鼠)分離的抗體(參見例如Taylor等人, *Nucl. Acids Res.*, 20: 6287-6295 (1992)；Kellermann及Green, *Curr. Opin. Biotechnol.*, 13: 593-597 (2002)；Little等人, *Immunol. Today*, 21: 364-370 (2000))；或藉由任何其他涉及將人類免疫球蛋白基因序列剪接至其他DNA序列之手段製備、表現、產生或分離的抗體。此類重組人類抗體具有來源於人類生殖系免疫球蛋白序列之可變及恆定區。然而，在某些實施例中，此類重組人類抗體可經受活體外突

變誘發(或當使用人類Ig序列之動物轉殖基因時，為活體內體細胞突變誘發)，且因此重組抗體之VH及VL區之胺基酸序列為雖然來源於人類生殖系VH及VL序列且與其相關，但不會活體內天然存在於人類抗體生殖系抗體庫內的序列。

【0070】 術語「嵌合抗體」係指包含來自一個物種之重鏈及輕鏈可變區序列及來自另一物種之恆定區序列的抗體，諸如具有與人類恆定區連接之鼠類重鏈及輕鏈可變區的抗體。

【0071】 術語「CDR移植抗體」係指包含來自一種物種之重鏈及輕鏈可變區序列，但其中VH及/或VL之一或多個CDR區之序列經另一物種之CDR序列置換的抗體，諸如具有人類重鏈及輕鏈可變區但其中一或多個人類CDR已經鼠類CDR序列置換的抗體。

【0072】 術語「人類化抗體」係指包含來自非人類物種(例如小鼠)之重鏈及輕鏈可變區序列但該VH及/或VL序列之至少一部分已變成更「像人類」，亦即，更類似於人類生殖系可變序列的抗體。人類化抗體之一種類型為CDR移植抗體，其中將來自非人類物種(例如小鼠)之CDR序列引入至人類VH及VL構架序列中。人類化抗體為與所關注抗原免疫特異性結合且包含具有實質上人類抗體之胺基酸序列之構架區及恆定區但具有實質上非人類抗體之胺基酸序列之互補決定區(CDR)的抗體或其變體、衍生物、類似物或片段。如本文所用，術語「實質上」在CDR之情形下係指CDR具有與非人類抗體CDR之胺基酸序列具有至少80%、至少85%、至少90%、至少95%、至少98%或至少99%一致的胺基酸序列。人類化抗體包含實質上全部至少一個可變域，且通常兩個可變域(Fab、Fab'、$F(ab')_2$、Fv)，其中全部或實質上全部CDR區對應於非人類免疫球蛋白(亦即供體抗

體)之彼等，且全部或實質上全部構架區為人類免疫球蛋白共有序列之彼等。在一些實施例中，人類化抗體亦包含免疫球蛋白恆定區之至少一部分(Fc)，通常人類免疫球蛋白之至少一部分。在一些實施例中，人類化抗體含有輕鏈以及至少重鏈之可變域兩者。抗體亦可包括重鏈之CH1、鉸鏈、CH2、CH3及CH4區。在一些實施例中，人類化抗體僅含人類化輕鏈。在一些實施例中，人類化抗體僅含有人類化重鏈。在特定實施例中，人類化抗體僅含有輕鏈及/或人類化重鏈之人類化可變域。

【0073】 人類化抗體可選自任何類別之免疫球蛋白，包括IgM、IgG、IgD、IgA及IgE；以及任何同型，其包括(但不限於) IgG1、IgG2、IgG3及IgG4。人類化抗體可包含來自多於一種類別或同型之序列，且可使用此項技術中熟知的技術選擇特定恆定域以使所需效應功能最佳化。

【0074】 人類化抗體之構架區及CDR區不一定精確地對應於親本序列，例如供體抗體CDR或受體架構可藉由取代、插入及/或缺失至少一個胺基酸殘基突變誘發，使得在該位點處之CDR或構架殘基不對應於供體抗體或保守構架。然而，在一例示性實施例中，此類突變不多。通常，人類化抗體殘基之至少80%，較佳至少85%，更佳至少90%且最佳至少95%，將對應於親本FR及CDR序列之彼等殘基。在特定構架位置處恢復供體抗體中該位置處存在之相同胺基酸的回復突變，通常用以保持特定環結構或用以正確地定向CDR序列以與目標抗原接觸。

【0075】 術語「CDR」係指抗體可變域序列內之互補決定區。在重鏈及輕鏈之各可變區中存在三個CDR，稱為CDR-H1、CDR-H2、CDR-H3、CDR-L1、CDR-L2及CDR-L3。如本文所用，術語「CDR組」係指存在於能夠結合抗原之單一可變區中的一組三個CDR。此等CDR之精確

邊界已根據不同系統以不同方式加以定義。由Kabat (Kabat等人, **Sequences of Proteins of Immunological Interest** (National Institutes of Health, Bethesda, Maryland (1987)及(1991))描述之系統，不僅提供適用於抗體之任何可變區之明確的殘基編號系統，且亦提供定義三個CDR之精確殘基邊界。

【0076】 在此項技術中公認之術語「Kabat編號」係指對抗體或其抗原結合部分之重鏈及輕鏈可變區中之較高變(亦即高變)之胺基酸殘基而非其他胺基酸殘基進行編號的系統。參見Kabat等人, *Ann. NY Acad. Sci.*, 190: 382-391 (1971)；及Kabat等人, **Sequences of Proteins of Immunological Interest**, 第五版, U.S. Department of Health and Human Services, NIH公開案第91-3242號 (1991)。

【0077】 在過去二十年間關於可變重鏈及輕鏈區之胺基酸序列之廣泛公共資料庫的成長及分析使得吾人可理解可變區序列內之構架區(FR)與CDR序列之間的典型邊界，且使得熟習此項技術者能夠根據Kabat編號、Chothia編號或其他系統精確判定CDR。參見例如，在Kontermann及Dübel編, **Antibody Engineering** (Springer-Verlag, Berlin, 2001), 第31章, 第432-433頁中之Martin, 「Protein Sequence and Structure Analysis of Antibody Variable Domains」。

【0078】 術語「多價結合蛋白」表示包含兩個或更多個抗原結合位點之結合蛋白。多價結合蛋白較佳經工程改造以具有三個或更多個抗原結合位點，且一般不為天然存在之抗體。術語「雙特異性結合蛋白」係指能夠結合具有不同特異性之兩個目標的結合蛋白。本發明之「串聯Fab免疫球蛋白」(FIT-Ig)結合蛋白包含兩個或更多個抗原結合位點，且通常為四

價結合蛋白。FIT-Ig可為單特異性的，亦即，能夠結合一個抗原；或多特異性的，亦即，能夠結合兩個或更多個抗原。根據本發明之較佳FIT-Ig結合PD-1及LAG-3兩者，且因此為雙特異性的。包含兩條長(重鏈)V-C-V-C-Fc鏈多肽及四條短(輕鏈)V-C鏈多肽之FIT-Ig結合蛋白形成呈現四個Fab抗原結合位點(VH-CH1與VL-CL配對，有時標記為VH-CH1::VL-CL)的六聚體。FIT-Ig之每一半包含重鏈多肽及兩條輕鏈多肽，且三條鏈之VH-CH1與VL-CL元件之互補免疫球蛋白配對產生串聯排列的兩個Fab結構化抗原結合位點。在本發明中，較佳的是，在不使用域間連接子之情況下，將包含Fab元件之免疫球蛋白域直接融合在重鏈多肽中。即，將長(重鏈)多肽鏈之N端V-C元件直接融合在另一V-C元件(其轉而與C端Fc區連接)之N端的C端處。在雙特異性FIT-Ig結合蛋白中，串聯Fab元件將可與不同抗原反應。各Fab結合位點包含重鏈可變域及輕鏈可變域，其中總共六個CDR/抗原結合位點。

【0079】 在PCT公開案WO 2015/103072中提供FIT-Ig分子之設計、表現及特徵之描述。此類FIT-Ig分子之較佳實例包含重鏈及二條不同輕鏈。重鏈包含結構式VL_A-CL-VH_B-CH1-Fc，其中CL直接與VH_B融合，或結構式VH_B-CH1-VL_A-CL-Fc，其中CH1直接與VL_A融合，其中VL_A為來自結合抗原A之親本抗體的可變輕鏈域，VH_B為來自結合抗原B之親本抗體的可變重鏈域，CL為輕鏈恆定域，CH1為重鏈恆定域且Fc為免疫球蛋白Fc區(例如IgG1抗體之重鏈之C端鉸鏈-CH2-CH3部分)。FIT-Ig之兩條輕鏈多肽鏈分別具有式VH_A-CH1及VL_B-CL。在雙特異性FIT-Ig實施例中，抗原A及抗原B為不同抗原或相同抗原之不同抗原決定位。在本發明中，A及B中之一者為PD-1，且另一者為LAG-3。

【0080】 術語「活性」包括諸如以下之特性：特異性結合目標抗原之能力，抗體針對抗原之親和力，中和目標抗原之生物活性之能力，抑制目標抗原與其天然受體之相互作用之能力及其類似者。本發明之較佳抗體及結合蛋白具有抑制PD-1與其配位體PD-L1結合之能力、抑制LAG-3與其配位體MHC II類結合之能力或兩者(在本文所描述之雙特異性結合蛋白之情況下)。

【0081】 如本文所用，術語「k_{on}」(亦稱為「Kon」、「kon」)意欲指結合蛋白(例如抗體)與抗原締合以形成締合複合物，例如抗體/抗原複合物之締合速率常數，如此項技術中已知。如在本文中可互換使用，「k_{on}」亦已知為術語「締合速率常數」或「ka」。此值指示抗體與其目標抗原之結合速率或在抗體與抗原之間形成複合物之速率，如由以下方程式所示：

抗體(「Ab」) + 抗原(「Ag」)→Ab-Ag。

【0082】 如本文所用，術語「k_{off}」(亦稱為「Koff」、「koff」)意欲指結合蛋白(例如抗體)自締合複合物(例如，抗體/抗原複合物)解離之解離速率常數(off rate constant)或「解離速率常數(dissociation rate constant)」，如此項技術中已知。此值指示抗體自其目標抗原之解離速率或Ab-Ag複合物隨時間推移分離為游離抗體及抗原，如由以下方程式所示：

Ab + Ag←Ab-Ag。

【0083】 如本文所用，術語「K_D」(亦稱為「K_d」)意欲指「平衡解離常數」，且係指在滴定量測中在平衡狀態下獲得之值，或藉由將解離速率常數(k_{off})除以締合速率常數(k_{on})獲得之值。締合速率常數(k_{on})、解離速率常數(k_{off})及平衡解離常數(K_D)用於表示抗體對於抗原之結合親和

力。測定締合速率常數及解離速率常數之方法為此項技術中所熟知。使用基於螢光之技術提供高靈敏度及檢查在平衡下生理緩衝液中之樣本的能力。可使用其他實驗方法及儀器，諸如BIAcore® (生物分子相互作用分析)分析法(例如，獲自BIAcore International AB, GE Healthcare company, Uppsala, Sweden之儀器)。使用例如Octet® RED96系統(Pall FortéBio LLC)之生物層干涉法(BLI)為另一親和力分析技術。另外，亦可使用KinExA® (動力學排除分析)分析，其獲自Sapidyne Instruments (Boise, Idaho)。

【0084】 術語「經分離核酸」應意謂藉由人工干預，不與在自然界中發現伴隨其之全部或一部分聚核苷酸結合；與在自然界中不與其連接之聚核苷酸可操作地連接；或在自然界中不作為較大序列之一部分存在的聚核苷酸(例如基因組、cDNA或合成來源，或其某一組合)。

【0085】 如本文所用，術語「載體」意欲指能夠轉運已與其連接之另一核酸的核酸分子。一種載體類型為「質體」，其係指可將額外DNA區段接合至其中之環狀雙股DNA環。另一類型之載體為病毒載體，其中可將額外DNA區段接合至病毒基因組中。某些載體能夠在其所引入之宿主細胞中自主複製(例如具有細菌複製起點之細菌載體及游離型哺乳動物載體)。其他載體(例如非游離型哺乳動物載體)在引入宿主細胞中時可整合至宿主細胞之基因組中，且因此與宿主基因組一起複製。此外，某些載體能夠引導與其可操作地連接之基因之表現。此類載體在本文中被稱作「重組表現載體」(或簡言之，「表現載體」)。一般而言，在重組DNA技術中有用之表現載體通常呈質體形式。在本說明書中，由於質體為載體之最常用形式，故「質體」及「載體」可互換使用。然而，本發明意欲包括提供

等效功能之此類其他形式之表現載體，諸如病毒載體(例如，複製缺陷反轉錄病毒、腺病毒及腺相關病毒)。

【0086】 術語「可操作地連接」係指所描述之組分處於准許其以其預期方式作用的關係中的併接。與編碼序列「可操作地連接」之控制序列以使得編碼序列之表現在與控制序列相容之條件下實現的方式接合。「可操作地連接」之序列包括與所關注基因相鄰之表現控制序列及以反式起作用或在一定距離起作用以控制所關注基因之表現控制序列兩者。如本文所用，術語「表現控制序列」係指實現所接合之編碼序列之表現及加工所需之聚核苷酸序列。表現控制序列包括適當轉錄起始、終止、啟動子及增強子序列；有效RNA加工信號，諸如剪接及聚腺苷酸化信號；使細胞質mRNA穩定之序列；增大轉譯效率之序列(亦即，Kozak共有序列)；增強蛋白質穩定性之序列；及必要時，增強蛋白質分泌之序列。此類控制序列之性質視宿主生物體而不同；在原核生物中，此類控制序列一般包括啟動子、核糖體結合位點及轉錄終止序列；在真核生物中，此類控制序列一般包括啟動子及轉錄終止序列。術語「控制序列」意欲包括其存在對表現及加工而言至關重要之組分，且亦可包括其存在有利之額外組分，例如前導或信號序列及融合搭配物序列。

【0087】 如本文所定義，「轉化」係指外源性DNA藉以進入宿主細胞之任何過程。轉化可在天然或人工條件下使用此項技術中熟知之各種方法來進行。轉化可依賴於將外來核酸序列插入原核或真核宿主細胞中之任何已知方法。方法係基於轉化之宿主細胞選擇，且可包括(但不限於)轉染、病毒感染、電穿孔、脂質體轉染及粒子轟擊。此類「轉化」細胞包括所插入之DNA能夠作為自主複製質體或作為宿主染色體之一部分進行複

製的穩定轉化細胞。其亦包括在有限時間段內短暫表現所插入之DNA或RNA的細胞。

【0088】 術語「重組宿主細胞」(或簡言之「宿主細胞」)意欲指已引入外源性DNA之細胞。在一實施例中，宿主細胞包含編碼抗體之兩個或更多個(例如多個)核酸，諸如美國專利第7,262,028號中所描述之宿主細胞。此類術語意欲不僅指特定個體細胞，且亦指此種細胞之後代。因為某些修飾可能由於突變或環境影響而出現在隨後世代中，所以此類後代實際上無法與親本細胞相同，但仍包括在如本文所用之術語「宿主細胞」的範疇內。在一實施例中，宿主細胞包括選自任一生命界之原核及真核細胞。在另一實施例中，真核細胞包括原生生物、真菌、植物及動物細胞。在另一實施例中，宿主細胞包括(但不限於)原核細胞株大腸桿菌；哺乳動物細胞株CHO、HEK293、COS、NS0、SP2及PER.C6；昆蟲細胞株Sf9；及真菌細胞釀酒酵母。

【0089】 可使用重組DNA、寡核苷酸合成及組織培養及轉化的標準技術(例如電穿孔、脂質體轉染)。可根據製造商之說明書或如通常在此項技術中所實現或如本文所描述進行酶促反應及純化技術。前述技術及程序一般可根據此項技術中熟知及如在本說明書通篇中所引用及論述之各種一般及更特定參考文獻中所描述之習知方法進行。參見例如，Sambrook等人, **Molecular Cloning: A Laboratory Manual**, 第2版 (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989)。

【0090】 如本文所用，術語「促效劑」係指當與所關注分子接觸時，導致分子之某一活性或功能之量值相比與不存在該促效劑之情況下所觀測到之活性或功能之量值相比有所增加的調節劑。如本文所用，術語

「拮抗劑」及「抑制劑」係指當與所關注分子接觸時，導致分子之某一活性或功能之量值與不存在該拮抗劑之情況下所觀測到之活性或功能之量值相比有所減小的調節劑。所關注之特定拮抗劑包括阻斷或降低人類PD-1及人類LAG-3之生物或免疫活性之彼等拮抗劑。

【0091】 如本文所用，術語「有效量」係指足以降低或改善病症或其一或多種症狀之嚴重程度及/或持續時間；預防病症進展；導致病症消退；預防與病症相關之一或多種症狀復發、發展或進展；偵測病症；或增強或改良另一療法(例如預防劑或治療劑)之預防或治療效果的療法之量。

【0092】

抗PD-1及抗LAG-3抗體之產生

根據本發明適用之抗PD-1及抗LAG-3抗體可藉由此項技術中已知之多種技術中之任一者產生。舉例而言，由宿主細胞表現，其中藉由標準技術將編碼重鏈及輕鏈之表現載體轉染至宿主細胞中。術語「轉染」之各種形式意欲涵蓋常用於將外源性DNA引入原核或真核宿主細胞中的各種技術，例如電穿孔、磷酸鈣沈澱、DEAE-聚葡萄糖轉染及其類似技術。儘管有可能在原核或真核宿主細胞中表現本發明抗體，但在真核細胞中表現抗體為較佳的，且在哺乳動物宿主細胞中表現為最佳的，因為此類真核細胞(且尤其哺乳動物細胞)與原核細胞相比更可能組裝且分泌經恰當摺疊且具免疫活性的抗體。

【0093】 用於表現本發明之重組抗體之較佳哺乳動物宿主細胞包括中國倉鼠卵巢(Chinese Hamster Ovary) (CHO細胞) (包括在Urlaub and Chasin, *Proc. Natl. Acad. Sci. USA*, 77: 4216-4220 (1980)中描述之dhfr$^-$ CHO細胞，其與例如在Kaufman及Sharp, *J. Mol. Biol.*, 159: 601-621

(1982)中描述之DHFR可選標記物一起使用)、NS0骨髓瘤細胞、COS細胞及SP2細胞。當將編碼抗體基因之重組表現載體引入至哺乳動物宿主細胞中時，抗體藉由將該等宿主細胞培養足以允許在該等宿主細胞中表現該抗體或更佳地，將該抗體分泌至生長該等宿主細胞之培養基中的時間段來產生。抗體可使用標準蛋白質純化方法而自培養基回收。

【0094】 宿主細胞亦可用於產生功能性抗體片段，諸如Fab片段或scFv分子。應理解，以上程序之變化在本發明之範疇內。舉例而言，可能需要用編碼本發明之抗體之輕鏈及/或重鏈之功能片段的DNA轉染宿主細胞。亦可使用重組DNA技術來移除一些或所有編碼不必與所關注抗原結合的輕鏈及重鏈中之任一者或兩者的DNA。本發明之抗體亦涵蓋自此類截短之DNA分子表現之分子。另外，可藉由標準化學交聯方法使本發明抗體與第二抗體交聯而產生雙功能抗體，其中一條重鏈及一條輕鏈為本發明抗體且另一條重鏈及輕鏈對除所關注抗原以外之抗原具有特異性。

【0095】 在用於重組表現本發明之抗體或其抗原結合部分之例示性系統中，藉由磷酸鈣介導的轉染，將編碼抗體重鏈及抗體輕鏈兩者之重組表現載體引入至dhfr$^-$ CHO細胞中。在重組表現載體內，將抗體重鏈及輕鏈基因各自與CMV增強子/AdMLP啟動子調控元件可操作地連接以驅動高水準基因轉錄。重組表現載體亦攜帶DHFR基因，其允許使用甲胺喋呤選擇/擴增來選擇已經載體轉染之CHO細胞。培養所選擇經轉染宿主細胞以允許表現抗體重鏈及輕鏈，且自培養基回收完整抗體。使用標準分子生物學技術來製備重組表現載體，轉染宿主細胞，選擇轉染體，培養宿主細胞且自培養基回收抗體。又另外，本發明提供一種藉由在適合培養基中培養本發明之經轉染宿主細胞直至產生本發明之重組抗體，來製備本發明之重

組抗PD-1或抗LAG-3抗體的方法。該方法可進一步包含自培養基分離重組抗體。

【0096】

結合PD-1及LAG-3之雙特異性FIT-Ig之產生

使用免疫檢查點抑制劑(諸如靶向PD-1、PD-L1及CTLA-4之抗體)之臨床研究已得到有前景的結果，然而已觀察到，僅一子組患者最初對此等抑制劑起反應，且增加的臨床跡象指示大量比例之初始反應者最終在數月或數年後復發致死性耐藥性疾病。Syn等人, *The Lancet Oncology*, 18(12):e731-e741 (2017)。在耐受腫瘤浸潤淋巴球(TIL)上共表現LAG-3及PD-1兩者，從而促進腫瘤中之免疫抑制；及已提出雙重阻斷LAG-3及PD-1作為在CD8+ T細胞中恢復抗腫瘤功能的手段。Matsuzaki等人, *Proc. Natl. Acad. Sci. USA*, 107(17): 7875-7880 (2010)。因此，可同時阻斷免疫抑制T細胞上之兩個目標之LAG-3/PD-1雙特異性結合蛋白的設計可在此治療領域中提供進展。

【0097】 本發明提供與PD-1及LAG-3兩者結合之串聯Fab免疫球蛋白結合蛋白(FIT-Ig)。此類FIT-Ig分子之例示性實施例包含：(1)重鏈多肽鏈，其包含結構式(i) VL_A-CL-VH_B-CH1-Fc，其中CL直接與VH_B融合，或結構式(ii) VH_B-CH1-VL_A-CL-Fc，其中CH1直接與VL_A融合；(2)式VH_A-CH1之輕鏈多肽鏈；及(3)式VL_B-CL之另一輕鏈多肽鏈，

其中VL為輕鏈可變域，CL為輕鏈恆定域，VH為重鏈可變域，CH1為重鏈恆定域，Fc為免疫球蛋白Fc區，A為PD-1或LAG-3之抗原決定位且B為PD-1或LAG-3之抗原決定位，其限制條件為A與B不同。根據本發明，此類FIT-Ig結合蛋白與PD-1及LAG-3兩者結合。

【0098】 FIT-Ig可包含兩條此類重鏈(1)、兩條此類輕鏈(2)及兩條此類輕鏈(3)，形成呈現四個功能Fab抗原結合位點之六鏈結合蛋白單體。此種FIT-Ig結合蛋白包含兩個一致次單元，其中各次單元包含一條重鏈(1)、一條輕鏈(2)及一條輕鏈(3)，該等鏈一起形成串聯排列的一對Fab結合位點。兩個此類次單元之Fc區之配對產生具有總共四個功能Fab結合單元之本發明之六鏈雙特異性FIT-Ig結合蛋白。

【0099】 可使用重鏈上之肽連接子來分離串聯連接的Fab部分，然而對於根據本發明之雙特異性FIT-Ig，省略此類連接序列為較佳的。而在具有串聯結合位點之多價工程改造免疫球蛋白形式中，在本領域中通常應理解，相鄰結合位點將彼此干擾，除非可撓性連接子用於空間上分開結合位點。然而，已發現，對於本發明之PD-1/LAG-3 FIT-Ig，根據上文給出之鏈式之免疫球蛋白域之排列產生在轉染哺乳動物細胞中良好表現適當組裝且作為結合目標抗原PD-1及LAG-3之雙特異性多價免疫球蛋白樣結合蛋白分泌的多肽鏈。參見實例10及15，見下文。儘管在Fab結合位點之間不存在任何連接子序列，但本發明之PD-1/LAG-3 FIT-Ig保留針對目標抗原之結合親和力，呈現與親本mAb相當的結合親和力。此外，自結合蛋白省略合成連接子序列可避免產生哺乳動物免疫系統可識別之抗原位點，且以此方式，消除連接子降低FIT-Ig之可能免疫原性且導致在循環中類似於天然抗體的半衰期，即FIT-Ig不經由免疫調理及在肝中之捕捉而被快速清除。

【0100】 FIT-Ig中之各可變域(VH或VL)可獲自結合目標抗原中之一者(亦即PD-1或LAG-3)之一或多個「親本」單株抗體。宜使用如本文所揭示之抗PD-1及抗LAG-3單株抗體之可變域序列，來產生FIT-Ig結合蛋白。

較佳地，親本抗體為人類化抗體。

【0101】 本發明之一態樣係關於選擇具有在FIT-Ig分子中所需之至少一或多個特性之親本抗體。在一實施例中，抗體特性係選自由以下組成之群：抗原特異性、對於抗原之親和力、效能、生物功能、抗原決定位識別、穩定性、溶解性、生產效率、免疫原性之缺乏、藥物動力學、生物可用性、組織交叉反應及直系同源抗原結合。PD-1及LAG-3均為細胞表面蛋白質，且與其各別配位體PD-L1 (細胞表面受體)及MHC II類(抗原呈遞細胞上之表面蛋白質)之相互作用引起涉及T細胞抑制及免疫反應的胞內信號傳導。因此，根據本發明之抗LAG-3抗體及PD-1/LAG-3 FIT-Ig結合蛋白抑制PD-1/PD-L1及/或MHC II類/LAG-3相互作用之能力使得其成為免疫細胞活化及免疫效應細胞活性之強效調節劑。

【0102】 根據本發明之抗體、其功能片段及結合蛋白可藉由使用純化抗體及結合蛋白項技術中可用之各種方法及材料中之一或多者來進行純化(以用於預期用途)。此類方法及材料包括(但不限於)：親和層析(例如使用與蛋白A、蛋白G、蛋白質L或抗體、其功能片段或結合蛋白之特異性配位體共軛的樹脂、粒子或膜)、離子交換色譜(例如使用離子交換粒子或膜)、疏水相互作用層析(「HIC」；例如使用疏水性粒子或膜)、超過濾、奈米過濾、透濾、尺寸排阻層析(「SEC」)、低pH處理(以使雜質病毒失活)及其組合，以得到用於預期用途之可接受純度。低pH處理以使雜質病毒失活之非限制性實例，包含在18℃-25℃下，使用0.5 M磷酸降低包含本發明之抗體、其功能片段或結合蛋白之溶液或懸浮液的pH至pH 3.5持續60至70分鐘。

【0103】

本發明之抗體及結合蛋白之用途

鑒於其與人類LAG-3或與人類PD-1及LAG-3兩者結合之能力，本文所描述之抗體、其功能片段及本文所描述之雙特異性多價結合蛋白(諸如FIT-Ig)可用於偵測例如含有表現彼等目標抗原中之一或兩者之細胞的生物樣本中的PD-1或LAG-3或兩者。本發明之抗體、功能片段及結合蛋白可在習知免疫分析，諸如酶聯免疫吸附分析(ELISA)、放射免疫分析(RIA)或組織免疫組織化學中使用。本發明提供一種用於偵測生物樣本中之LAG-3之方法，其包含使生物樣本與本發明之抗體、其抗原結合部分或結合蛋白接觸；及偵測是否與存在之目標抗原結合，從而偵測在該生物樣本中是否存在該目標。抗體、功能片段或結合蛋白可直接地或間接地用可偵測物質標記，以便於偵測結合或未結合的抗體/片段/結合蛋白。適合的可偵測物質包括各種酶、輔基、螢光材料、發光材料及放射性材料。適合的酶之實例包括辣根過氧化酶、鹼性磷酸酶、β-半乳糖苷酶或乙醯膽鹼酯酶。適合的輔基複合物之實例包括抗生蛋白鏈菌素/生物素及抗生素蛋白/生物素；適合的螢光材料之實例包括傘酮、螢光素、異硫氰酸螢光素、若丹明(rhodamine)、二氯三嗪基胺螢光素、丹磺醯氯或藻紅素；發光材料之實例包括流明諾(luminol)；及適合的放射性材料之實例包括^{3}H、^{14}C、^{35}S、^{90}Y、^{99}Tc、^{111}In、^{125}I、^{131}I、^{177}Lu、^{166}Ho或^{153}Sm。

【0104】 本文所描述之抗體、其功能片段及結合蛋白較佳地能夠活體外及活體內中和人類PD-1及/或人類LAG-3活性兩者。因此，本文所描述之抗體、其功能片段及結合蛋白可用於抑制人類PD-1及/或人類LAG-3活性，例如在含有表現PD-1及/或表現LAG-3之細胞之細胞培養物中，在人類個體中，或在具有與本發明之抗體、其功能片段或結合蛋白交叉反應

之PD-1或LAG-3之其他哺乳動物個體中，抑制由PD-1/PD-L1 (或PD-1/PD-L2)相互作用及/或MHC II類/LAG-3相互作用介導的細胞信號傳導。在一個實施例中，本發明提供一種用於恢復活化T細胞之活性(逆轉抑制)之方法，其包含使表現人類PD-1之細胞與本發明之抗PD-1抗體或PD-1結合蛋白接觸，使得PD-1活性受到抑制。在另一實施例中，本發明提供一種用於恢復活化T細胞之活性(逆轉抑制)之方法，其包含使表現人類LAG-3之細胞與本發明之抗LAG-3抗體或LAG-3結合蛋白接觸，使得LAG-3活性受到抑制。

【0105】 在另一實施例中，本發明提供一種用於治療罹患其中PD-1及/或LAG-3活性有害的疾病或病症之個體的方法，此種方法包含向個體投與有效量之本發明之抗體或結合蛋白，使得個體中由PD-1/PD-L1或PD-1/PD-L2結合及/或MHC II類/LAG-3結合介導的活性降低。

【0106】 如本文所用，術語「其中PD-1及/或LAG-3活性有害的病症」意欲包括罹患造成病症之病理生理學或為促進病症惡化之因子之病症之個體疾病及其他病症，其中PD-1與其配位體(PD-L1、PD-L2)中之一或兩者之相互作用或LAG-3與其配位體(MHC II類)之相互作用。因此，其中PD-1及/或LAG-3活性有害的病症為預期抑制PD-1及/或LAG-3活性減輕病症之症狀及/或進展的病症。

【0107】 在另一實施例中，本發明提供用於治療有需要之個體之自體免疫疾病或癌症之方法，其包含向個體投與本文所描述之能夠結合LAG-3、PD-1或LAG-3與PD-1兩者之抗體、其功能片段或結合蛋白，且其中該自體免疫疾病或癌症為對免疫療法有反應之疾病。在另一實施例中，使用本發明之方法來治療與免疫療法不相關之自體免疫疾病或癌症。

在另一實施例中，使用本發明之方法來治療癌症，即難治性或復發性惡性疾病。在另一實施例中，在抑制腫瘤細胞之生長或存活之方法中使用本發明之LAG-3抗體、其功能片段或LAG-3/PD-1雙特異性結合蛋白。

【0108】 在另一實施例中，本發明提供一種治療個體之癌症之方法，其包含向個體投與本文所描述之抗LAG-3抗體、其功能片段或本文所描述之LAG-3/PD-1雙特異性結合蛋白，例如串聯Fab免疫球蛋白(FIT-Ig)結合蛋白的步驟，其中癌症係選自由以下組成之群中的任一者：黑素瘤(例如轉移性惡性黑素瘤)、腎癌(例如透明細胞癌)、前列腺癌(例如激素抗性前列腺腺癌)、胰臟腺癌、乳癌、結腸癌、肺癌(例如非小細胞肺癌)、食道癌、頭頸部鱗狀細胞癌、肝癌、卵巢癌、宮頸癌、甲狀腺癌、神經膠母細胞瘤、神經膠瘤、白血病、淋巴瘤、原發性骨癌(例如骨肉瘤、尤文氏肉瘤(Ewing sarcoma)、惡性纖維組織細胞瘤及軟骨肉瘤)、轉移癌及其他贅生性惡性疾病。

【0109】 本發明亦提供醫藥組合物，其包含本發明之抗體或其抗原結合部分、或雙特異性多價結合蛋白(亦即主要活性成分)及醫藥學上可接受之載劑。包含本發明蛋白質之醫藥組合物用於(但不限於)診斷、偵測或監視病症；治療、處理或改善病症或其一或多種症狀；及/或研究。在一具體實施例中，組合物包含一或多種本發明之抗體或結合蛋白。在另一實施例中，醫藥組合物包含一或多種本發明之抗體或結合蛋白及一或多種除本發明之抗體或結合蛋白以外之預防劑或治療劑，以用於治療其中PD-1及/或LAG-3活性有害的病症。在一實施例中，預防劑或治療劑已知適用於或已經用於或正用於預防、治療、管理或改善病症或其一或多種症狀。根據此等實施例，組合物可進一步包含載劑、稀釋劑或賦形劑。賦形劑一

般為除主要活性成分以外(亦即除本發明之抗體、其功能部分或結合蛋白以外)，為組合物提供所需特徵之任何化合物或化合物組合。

【0110】 可將本發明之抗體(包括其功能片段)及結合蛋白併入適合於向個體投與之醫藥組合物中。通常，醫藥組合物包含本發明之抗體或結合蛋白及醫藥學上可接受之載劑。如本文所用，「醫藥學上可接受之載劑」包括生理學上相容之任何及所有溶劑、分散介質、包衣、抗細菌劑及抗真菌劑、等張劑及吸收延遲劑以及其類似者。醫藥學上可接受之載劑之實例包括水、鹽水、磷酸鹽緩衝鹽水、右旋糖、甘油、乙醇及其類似者，以及其組合。在許多情況下，組合物中將較佳包括等張劑，例如糖、多元醇(諸如甘露醇或山梨糖醇)或氯化鈉。醫藥學上可接受之載劑可進一步包含少量輔助物質，諸如潤濕劑或乳化劑、防腐劑，或緩衝劑，其提高組合物中存在之抗體或結合蛋白之存放期或效果。

【0111】 將本發明之醫藥組合物調配成與其預期投與途徑相容。投與途徑之實例包括(但不限於)非經腸(例如靜脈內、皮內、皮下、肌肉內)、經口、鼻內(例如吸入)、經皮(例如局部)、腫瘤內、經黏膜及直腸投與。在一具體實施例中，組合物係根據常規程序調配為適合於向人類靜脈內、皮下、肌肉內、經口、鼻內或局部投與之醫藥組合物。通常，用於靜脈內投與之組合物為於無菌等張水性緩衝液中之溶液。必要時，組合物亦可包括增溶劑及諸如利多卡因(lidocaine) (昔羅卡因(xylocaine)、利諾卡因(lignocaine))之局部麻醉劑以減輕注射位點之疼痛。

【0112】 本發明之方法可包含藉由注射(例如藉由快速注射或連續輸注)投與經調配用於非經腸投與之組合物。注射用調配物可以添加有防腐劑之單位劑型(例如，於安瓿或多劑量容器中)呈現。組合物可採用諸如於

油性或水性媒劑中之懸浮液、溶液或乳液之形式，且可含有諸如懸浮劑、穩定劑及/或分散劑之調配劑。可替代地，主要活性成分可呈在使用之前用適合的媒劑(例如，無菌無熱原質水)復原之粉末形式。

【0113】 本發明之方法可另外包含投與調配為儲槽式製劑之組合物。此類長效調配物可藉由(例如，皮下或肌肉內)植入或藉由肌肉內注射來投與。因此，舉例而言，組合物可用適合的聚合或疏水性材料(例如呈於可接受之油中的乳液形式)或離子交換樹脂調配，或調配成微溶性衍生物(例如微溶性鹽)。

【0114】 本發明之抗體、其功能片段或結合蛋白亦可與適用於治療多種疾病之一或多種額外治療劑一起投與。本文所描述之抗體、其功能片段及結合蛋白可單獨使用或與額外藥劑(例如治療劑)組合使用，該額外藥劑由熟習此項技術者出於其預期目的進行選擇。舉例而言，該額外藥劑可為此項技術中公認適用於治療藉由本發明之抗體或結合蛋白所治療之疾病或病狀之治療劑。額外藥劑亦可為賦予治療組合物有益屬性之藥劑，例如影響組合物黏度之藥劑。

【0115】 現已詳細描述了本發明，參考以下實例將更清楚地理解本發明，該等實例僅出於說明之目的包括在內且不意欲限制本發明。

【0116】

實例

【0117】

實例1：抗人類PD-1單株抗體之產生

如下產生抗人類PD-1單株抗體：

【0118】

實例1.1：用人類PD-1抗原進行免疫接種

在第1天，將50 μg與弗氏完全佐劑(Complete Freund's adjuvant)混合之重組純化人類PD-1胞外域(ECD)多肽，腹膜內注射至五隻6-8週齡Balb/C小鼠及五隻SJL小鼠中。在第16及26天，將25 μg與不完全弗氏佐劑混合之重組純化人類PD-1 ECD免疫原，腹膜內注射至相同小鼠中。在融合3-4天之前，給予具有25 μg免疫原之最終加強注射。

【0119】

實例1.2：融合瘤之產生

根據Kohler及Milstein, *Nature*, 256: 495-497 (1975)中所描述之確立方法，將自實例1.1中描述之免疫小鼠獲得之脾細胞與SP2/0-Ag-14細胞，以5:1之比率融合，產生融合瘤。將融合產物，以1 × 10^5個脾細胞/孔之密度，塗鋪在96孔盤之含有次黃嘌呤-胺基喋呤-胸苷(HAT)之選擇培養基中。在融合七至十天後，觀測到肉眼可見的融合瘤群落。

【0120】

實例1.3：藉由ELISA及FACS進行PD-1結合活性之評定

藉由酶聯免疫吸附分析(ELISA)，如下分析PD-1特異性抗體之存在：

【0121】 首先，藉由Synbio技術(Suzhou, China)，定製抗人類PD-1、抗食蟹獼猴PD-1及抗鼠類PD-1之合成目標。各目標由與人類IgG Fc區融合之人類、食蟹獼猴或鼠類PD-1蛋白之胞外域(ECD)之多肽區段組成。將編碼各ECD-Fc融合蛋白之合成基因次選殖至pCP表現載體(Chempartner, Shanghai, China)中，且將表現質體短暫轉染至1-3公升培養基中之HEK 293E細胞中且在CO_2振盪器中培養七天。用於各融合之

ECD序列闡述於下表1中。各融合蛋白之PD-1 ECD部分為加底線的。

表1：PD-1 ECD-Fc融合蛋白目標之胺基酸序列

SEQ ID NO.	PD-1來源	胺基酸序列 12345678901234567890123456789012345678901234567890
1	人類	LDSPDRPWNPPTFSPALLVVTEGDNATFTCSFSNTSESFVL NWYRMSPSNQTDKLAAFPEDRSQPGQDCRFRVTQLPNGRDF HMSVVRARRNDSGTYLCGAISLAPKAQIKESLRAELRVTER RAEVPTAHPSPSPRPAGQFQIEGRMDPKSCDKTHTCPPCPA PELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPGK
2	食蟹獼猴	LESPDRPWNAPTFSPALLLVTEGDNATFTCSFSNASESFVL NWYRMSPSNQTDKLAAFPEDRSQPGQDCRFRVTRLPNGRDF HMSVVRARRNDSGTYLCGAISLAPKAQIKESLRAELRVTER RAEVPTAHPSPSPRPAGQFQIEGRMDPKSCDKTHTCPPCPA PELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPGK
3	小鼠	LEVPNGPWRSLTFYPAWLTVSEGANATFTCSLSNWSEDLML NWNRLSPSNQTEKQAAFCNGLSQPVQDARFQIIQLPNRHDF HMNILDTRRNDSGIYLCGAISLHPKAKIEESPGAELVVTER ILETSTRYPSPSPKPEGRFQIEGRMDPKSCDKTHTCPPCPA PELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPGK

【0122】 藉由在4000 × g下離心30分鐘來收穫含有重組ECD/Fc融合物之HEK 293E轉染體之上清液，隨後使用MabSelect SuRe™親和力樹脂(GE Healthcare)進行蛋白A純化。將融合產物相對於磷酸鹽緩衝鹽水(PBS) pH 7.4進行透析，且儲存在-80℃下。

【0123】 在4℃下，將ELISA盤與50 μl以1 μg/ml稀釋於PBS緩衝液pH 7.4中之上文所描述之合成人類PD-1 ECD/Fc融合蛋白目標一起培育隔夜。在洗滌緩衝液(含有0.05% Tween 20之PBS)中洗滌盤四次，且在37℃

下用200 μl/孔阻斷緩衝液(含1% BSA之含有0.05% Tween 20的PBS)阻斷1小時。在移除阻斷緩衝液之後，以100 μl/孔，向各孔添加融合瘤上清液(或稍後稀釋的純化mAb)，且在37℃下培育1小時。孔用洗滌緩衝液洗滌四次，且以1:5000稀釋小鼠抗人類PD-1抗體特徵之抗小鼠HRP (Sigma)，並以100 μl/孔向各孔中添加。在37℃下培育培養盤1小時，且在洗滌緩衝液中洗滌四次。每孔添加100 μl四甲基聯苯胺(TMB)發色溶液。在顯色之後，用1N HCl終止反應，且在SpectraMax® M5e讀板儀(Molecular Devices；San Jose，California，US)上量測在450 nm下之吸光度。

【0124】

實例1.4：表現PD-1之細胞株之製備及FACS分析

藉由用具有編碼人類PD-1或食蟹獼猴PD-1之插入基因之pLvx慢病毒質體載體(Clontech)轉染CHO-K1細胞(獲自ATCC)，來產生過度表現人類PD-1或食蟹獼猴PD-1的穩定細胞株。藉由限制稀釋法分離單一純系。對於表現量，藉由FACS分析，使用以重組方式自已知抗體序列(Chempartner)產生之抗PD-1抗體篩選純系，且選擇具有最高PD-1表現之純系用於FACS結合分析及功能分析，如下文所描述。

【0125】 針對細胞表面目標之結合分析：藉由FACS分析來測定純化抗體與細胞膜人類PD-1或食蟹獼猴PD-1結合的能力。將穩定地表現人類PD-1 (CHO-K1-hPD-1細胞)或食蟹獼猴PD-1 (CHO-K1-cynoPD-1)之CHO-K1細胞再懸浮於含有2% FBS之PBS (FACS緩衝液)中，且以2×10^4個細胞/孔接種至96孔圓底培養盤(Corning；目錄號3799)中。向各孔添加產生抗PD-1抗體之融合瘤之上清液，且用AlexaFluor® 488驢抗小鼠IgG (H+L)高度交叉吸附二級抗體(Invitrogen；目錄號A-21202)偵測，且隨後

在流式細胞儀上讀取分析培養盤。使用CHO-K1/cynoPD-1細胞測定抗體與食蟹獼猴PD-1之交叉反應性來對表現人類PD-1之目標陽性信號傳導之產融合瘤上清液進行進一步表徵。

【0126】

實例1.5：受體阻斷分析(RBA)

使用固定的人類PD-1 ECD/Fc作為目標，及以與以上實例1.3中描述之PD-1 ECD/Fc結合蛋白相同的方式製備之PD-L1/Fc與PD-L2/Fc融合蛋白，測試展示PD-1特異活性之上清液之阻斷PD-1與其配位體PD-L1及PD-L2結合的能力。為了測定含抗體上清液之相對效能，評價其抑制人類PD-1配位體(PD-L1或PD-L2)與人類PD-1蛋白結合之能力。ELISA盤用100 μl含50 ng/ml之huPD-1/Fc (亦即移植至人類Fc區之N端上之PD-1之胞外域，作為均二聚體回收)之PBS塗覆，且在4℃下培育隔夜。在洗滌緩衝液(含有0.05% Tween 20之PBS)中洗滌盤四次，且在37℃下用200 μl/孔阻斷緩衝液(含1% BSA之含有0.05% Tween 20的PBS)阻斷1小時。在移除阻斷緩衝液之後，向各孔添加與含50 μl生物素標記的人類PD-L1/Fc (1.0 mg/ml最終濃度)之阻斷緩衝液或含50 μl生物素標記的人類PD-L2/Fc (最終濃度50 μg/ml)之阻斷緩衝液混合的融合瘤上清液(50 μl)，隨後在37℃下培育1小時。藉由添加抗生蛋白鏈菌素-HRP (Sigma，目錄號S2468) (100微升/孔之抗生蛋白鏈菌素-HRP，以1:5000稀釋)及在37℃下培育40分鐘來發展信號，且在洗滌緩衝液中洗滌四次。向每孔添加100 μl TMB溶液。在顯色之後，用1 N HCl終止反應，且量測在450 nm下之吸光度。

【0127】

實例1.6：抗PD-1單株抗體之表現及純化

在FreeStyle™ 293表現培養基(Gibco/Life Technologies)中，於CO_2振盪器中，在37℃下培養產生鼠類單株抗體之融合瘤細胞5至7天。經由在4000 × g下離心30分鐘移除所有細胞及細胞碎片來收集條件培養基，隨後在純化之前經由0.22 μm膜過濾。根據製造商之指南，施加鼠類抗體且與MabSelect™ SuRe (GE Healthcare) 蛋白A樹脂管柱結合，用PBS洗滌，用含有20 mM檸檬酸鹽、150 mM NaCl pH 3.5之緩衝液溶離。溶離材料緊接著用1 M Tris pH 8.0中和，且相對於PBS進行透析。一步純化抗體通常具有高於90%純度，如由SEC-HPLC所偵測。藉由量測在280 nm下之吸光度，或藉由NanoDrop™ microvolume分光光度計(Thermo Scientific)，來測定蛋白質濃度。以等分試樣形式將純化抗體儲存於-80℃冰箱中。

【0128】

實例2：純化抗PD-1抗體之結合活性

【0129】

實例2.1：藉由ELISA進行表徵

以與以上實例1.3中所描述相同的方式進行結合ELISA。各純化抗體進行10倍連續稀釋且重複。在阻斷具有含固定的PD-1 ECD/Fc融合蛋白目標之孔之96孔分析培養盤之後，向分析培養盤之各孔添加具有稀釋濃度之純化抗體樣本。連接HRP之抗小鼠IgG抗體(A0168，Sigma)及TMB試劑用於偵測及發展ELISA信號，該等信號在SpectraMax® M5e讀板儀上在450 nm波長下讀取。使用GraphPad軟體擬合曲線，且計算EC50。類似地，亦如實例1.5中所描述進行受體阻斷分析(RBA)，其中測定滴定純化抗體及最高阻斷百分比及IC50值。

【0130】

實例2.2：藉由FACS進行表徵

以2 × 10^4個細胞/孔，將上文所描述之CHO-K1/huPD-1或CHO-K1/cynoPD-1細胞饋入至96孔分析圓底分析培養盤(目錄號3799；Corning)中，且用純化抗PD-1抗體染色。用AlexaFluor®驢抗小鼠IgG(H+L)高度交叉吸附的二級抗體(目錄號A21202；Invitrogen)偵測PD-1抗體，且使用流式細胞儀監測細胞螢光。由GraphPad軟體處理資料，且計算EC50值。

【0131】 此等結合特徵分析之結果顯示於下表2中。

表2：純化抗PD-1抗體之結合活性

	ELISA	**FACS**		**受體阻斷分析(RBA)**			
mAb標識符	塗覆huPD-1/Fc	CHO-K1/huPD-1	CHO-K1/cynoPD-1	配位體1 (huPD-L1)		配位體2 (huPD-L2)	
	EC50 (nM)	EC50 (nM)	EC50 (nM)	最高抑制 (%)	IC50 (nM)	最高抑制 (%)	IC50 (nM)
mAb701	0.10	3.0	3.8	87.1	5.32	94.1	2.67
mAb703	0.05	0.5	0.7	96.0	3.00	95.7	2.02
mAb707	0.10	27.4	4.3	87.7	13.94	23.1	9.91
mAb709	0.01	0.2	0.2	91.6	0.80	93.7	0.52
mAb711	0.03	18.6	3.0	89.3	11.56	27.4	6.77
mAb713	0.08	1.1	0.9	94.4	2.95	93.5	2.52
mAb714	0.05	1.6	0.8	92.3	2.95	93.1	2.24
mAb715	0.04	1.1	0.9	86.9	2.91	88.0	2.17
mAb716	0.02	0.7	0.7	95.8	1.56	96.9	1.05
mAb718	0.02	3.2	4.2	96.6	4.19	96.6	1.91
mAb719	0.02	1.7	2.1	96.5	3.39	95.2	1.85
人類IgG1(對照)	63.95			0.0	NA	9.9	NA

【0132】

實例2.3：藉由表面電漿子共振(SPR)進行親和力量測

藉由表面電漿子共振，使用Biacore T200儀(GE Healthcare)，使用

標準程序，來量測純化抗體之結合動力學。簡言之，將山羊抗小鼠IgG Fc多株抗體(Genway)直接固定在生物感測器晶片中，且以5 μl/min之流速，將抗體樣本注射在反應基質上。用30 μl/min之連續流速，分別測定締合速率常數及解離速率常數k_{on} ($M^{-1}s^{-1}$)及k_{off} (s^{-1})。藉由在人類PD-1/Fc蛋白之五個不同濃度下進行動力學結合量測，推導出速率常數。隨後使用式$K_D = k_{off}/k_{on}$，根據動力學速率常數計算抗體與相關目標蛋白質之間的反應的平衡解離常數K_D (M)。量測十一種鼠類抗PD-1抗體之親和力，如下表3中所闡述。

表3：11種抗PD-1單株抗體之親和力量測

mAb標識符	k_{on} (1/Ms)	k_{off} (1/s)	K_D (M)
mAb701	7.52×10^4	5.12×10^{-4}	6.81×10^{-9}
mAb703	3.47×10^5	8.50×10^{-4}	2.45×10^{-9}
mAb707	5.26×10^4	3.10×10^{-4}	5.89×10^{-9}
mAb709	1.11×10^5	1.04×10^{-4}	9.39×10^{-9}
mAb711	4.80×10^4	2.52×10^{-4}	5.24×10^{-9}
mAb713	1.45×10^5	2.85×10^{-4}	1.96×10^{-9}
mAb714	9.94×10^4	2.10×10^{-4}	2.11×10^{-9}
mAb715	1.58×10^5	2.37×10^{-4}	1.50×10^{-9}
mAb716	1.26×10^5	1.40×10^{-4}	1.11×10^{-9}
mAb718	5.84×10^4	2.83×10^{-4}	4.84×10^{-9}
mAb719	7.15×10^4	2.15×10^{-4}	3.00×10^{-9}

【0133】

實例3：抗PD-1抗體之功能活動

使用來自一個供體之單核球源性樹突狀細胞及來自另一供體之同種異體CD4+ T細胞，進行混合淋巴球反應(MLR)分析。自健康供體採集全血樣本，且使用Ficoll-Pague梯度離心自全血分離出PBMC。在第1天，分離來自一個供體之PBMC，且用無血清RPMI 1640，以1×10^6個細胞/毫升進行稀釋。以3毫升/孔，將稀釋的PBMC接種至6孔組織培養盤中，且培育3小時。移除上清液，且洗掉未附著細胞。用含250 U/ml IL-4及500 U/ml GM-CSF之含有10% FBS的RPMI 1640，使附著單核球極化成樹突

狀細胞。在第4天，培養基用含有IL-4及GM-CSF之新鮮培養基置換。在第7天，採集不成熟樹突狀細胞，且用含1 μg/ml細菌脂多醣(LPS)(Sigma)之具有10% FBS的RPMI 1640處理額外24小時以使其成熟。在第8天，藉由負選擇，自來自另一供體之PBMC分離CD4+ T細胞，且調節至2 × 10^6個細胞/毫升的最終濃度。在37℃下，成熟樹突狀細胞用絲裂黴素C處理1.5小時，隨後樹突狀細胞用PBS洗滌且調節至1 × 10^6個細胞/毫升的最終濃度。以100微升/孔將CD4+ T細胞(應答細胞)添加至96孔盤中，且用在稀釋濃度下之測試抗體預處理30分鐘。以100微升/孔，將成熟樹突狀細胞(刺激細胞)添加至各孔中。各孔之最終體積為200 μl。在37℃下培育混合淋巴球。在72小時之後量測IL-2產量(參見圖1A及圖1B)；在120小時量測IFN-γ(參見圖2A及圖2B)。

【0134】

實例4：抗PD-1 mAb之選殖及序列分析

用TRIzol試劑(目錄號15596；Invitrogen)，自> 5 × 10^6個細胞分離各融合瘤純系之總RNA。藉由SuperScript™ III第一股合成超混合液(目錄號18080；Invitrogen)合成cDNA，且用作小鼠Ig-引子組(目錄號69831-3；Novagen)之PCR模板。藉由用SYBR™安全DNA凝膠染色(Invitrogen)之1.2%瓊脂糖凝膠電泳，分析PCR產物。根據製造商之說明書，具有正確大小之DNA片段用NucleoSpin®凝膠及PCR Clean-up (目錄號740609；Macherey-Nagel GmbH)純化，且獨立地將其次選殖至pMD18-T載體(Sino Biological Inc.)中。選擇來自各轉化之十五個群落，且藉由DNA定序分析插入片段之序列。若對於VH及VL，存在至少8個匹配共有序列，則確認序列。藉由序列同源性比對分析鼠類抗PD-1 mAb可變區之

蛋白質序列，且列於表4中。基於Kabat編號鑑別互補決定區(CDR)，且在下表4中以加底線形式呈現。

表4：8種抗PD-1鼠類單株抗體之胺基酸序列

抗體	域	SEQ ID NO.	胺基酸序列 12345678901234567890123456789012345678901234567890
mAb701	VH	4	EVLLVESGGGLVKPGGSLKLSCAASGFTFSSYMMSWIRQTP ERRLEWVASMSGGGRDTYYPDSVKGRFTISRDNAKNTLYLQ MSSLRSEDTALYYCARRGTYAMDYWGQGTSVTVSS
	VL	5	DIQMTQSPASQSASLGESVTITCLASQTIGTWLTWYQQKPG KSPQLLIYAATSLADGVPSRFSGSGSGTKFSFKISSLQAED FVSYYCQQLYSTPWTFGGGTKLEIK
mAb703	VH	6	DVQLQESGPGLVKPSQSLSLTCSVTGYSITTGYYWNWIRQF PGNKLEWMGYMSYDGNNNYNPSLKNRISITRDTSKNQFLLR LNSVTTEDTATYFCARDRGTTILGGTMDYWGQGTSVTVS
	VL	7	SIVMTQTPKFLFVSAGDRVTIACKASQSVSNDVAWYQQKPG QSPKLLIYYAFYRYTGVPDRFTGSGYGTDFTFTISTVQAED LAVYFCQQDYSSPWTFGGGTKLEIK
mAb709	VH	8	EVKLVESGGGLVKPGGSLKLSCAASGFTFSFYTMSWVRQTP EKRLEWVATISGGGRDTYYPDSVKGRFTISRDNAKNTLYLH MSSLRSEDTALYYCAGQGGNYLFAYWGQGTLVTVSA
	VL	9	DIVMTQSHKFMSTSVGDSVTITCKASQDVNTVVAWYQQKPG QSLKVLISWASTRHTGVPARFTGSGSGTDYTLTISSVQAED LALYYCQQHYTTPYTFGGGTQLEIK
mAb713	VH	10	EVKLVESGGGLVKPGGSLELSCAASGFTSSDYGMHWVRQAP EKGLEWVAYISSGSYTIYYADTVKGRFTISRDNAKNTLFLQ MTSLRSEDTAMYYCAKRGGSSHVNVMDYWGQGTSVTVSS
	VL	11	DIQMTQSSSYLSVSLGGRVTITCKASDHINNWLAWYQQKPG NAPRLLISGATSLETGVPSRFSGSGSGKDYTLSITSLQTED VATYYCQQYWSPPYTFGGGTKLEIK
mAb714	VH	12	EVHLQQSGPELVKPGASVKIFCKASGYTFTDNNVEWVKQSH GKSLEWIGDINPNNGDTLYSQYFKDKATLTVDKSSTTAYME LRSLTSEDTGLYYCARGKSDQFDYWGQGTTLTVSS
	VL	13	DIQMTQSPASQSASLGESVTITCLASQTIGTWLAWYQQKPG KSPQLLIYAATSLADGVPSRFSGSGSGTKFSFKISSLQGED FVSYYCQQLYSSPWTFGGGTKLEIK
mAb715	VH	14	EVMLVESGGGLLKPGGSLKLSCAASGFTFSSYAMSWVRQTP EKRLEWVATISGGGRDTYYPDSVKGRFTISRDNAKNTLYLQ MTSLRSEDTAFYYCAGQGGTYLFASWGQGTLVTVSA
	VL	15	DIVMTQSHKFMSTSVGDSVTITCKASQDVNTAVAWYQQKPG QPPKVLIYWASTRHTGVPDRFTGSGSGTDYTLTISSVQAED LALYYCQQHYTTPYTFGGGTKLEIK
mAb718	VH	16	QVQLQQSGAELVRPGASVTLSCKASGYTFTDYEMHWAKQTP VHGLEWIGVIEPESGGTVYNQKFKGKAKLTADKSSRTAYME LRSLTSEDSAVYYCTREGFNSDHYFDYWGQGTTLTVSS
	VL	17	DVLMTQTPLSLPVSLGDQASISCRSSQNIVHSNGNTYLEWY LQKPGQSPKLLIYKVFNRFSGVPDRFSGSGSGTDFTLKISR VEAEDLGVYYCFQGSHVPYTFGGGTKLEIK
mAb719	VH	18	EVKLVESGGGLVKPGGSLKLSCTASGFSFSSHLMSWVRQTP EKRLEWVAAISGGGADTYYPDSVKGRFTISRDNAKNTLYLQ MRSLRSEDTALYYCTRQILAFDSWGQGTTLTVSS

	VL	19	DIQMNQSPSSLSVSLGDTITITCHASQNIYVWLNWYQQKPG NIPKLLIYKASNLHTGVPSRFSGGGSGTGFTLTISSLQPED IATYYCQQGQSYPWTFGGGTKLEIK

【0135】

實例5：鼠類抗PD-1抗體之人類化

基於人類PD-1結合活性，食蟹獼猴PD-1交叉反應類似於人類，RBA分析中之幾乎100%阻斷活性、MLR中之功能活性及如藉由Biacore所量測之至少奈莫耳級親和力，選擇四種抗PD-1抗體mAb709、mAb713、mAb703及mAb719以用於人類化。

【0136】

實例5.1：鼠類抗體mAb709之人類化

mAb709可變區基因用於產生人類化抗體。在此過程之第一步驟中，將mAb709之VH及VL之胺基酸序列與人類Ig V-基因序列之可用資料庫進行比較，以尋找總體最佳匹配的人類生殖系Ig V-基因序列。另外，將VH或VL之構架4區段與J-區資料庫進行比較，以尋找分別與鼠類VH及VL區具有最高同源性之人類構架。對於輕鏈，最接近的人類V-基因匹配為O12基因；且對於重鏈，最接近的人類匹配為VH3-7基因。隨後，設計人類化可變域序列，其中將mAb709輕鏈之CDR-L1、CDR-L2及CDR-L3移植至O12基因之構架序列上，其中JK4構架4序列在CDR-L3之後；且將mAb709重鏈之CDR-H1、CDR-H2及CDR-H3移植至VH3-7之構架序列上，其中JH1構架4序列在CDR-H3之後。隨後產生mAb709之3維Fv模型，以判定是否存在其中小鼠胺基酸對於支持環結構或VH/VL界面而言關鍵的任何構架位置。人類化序列中之此等殘基應在相同位置處回復突變成小鼠殘基以保留親和力/活性。在輕鏈之情況下，在位置71處Phe回復突變成Tyr (F71Y，Kabat編號)、在位置49處Tyr回復突變成Ser (Y49S，

Kabat編號)、在位置3處Gln回復突變成Val (Q3V，Kabat編號)、在位置46處Leu回復突變成Val (L46V，Kabat編號)、在位置63處Ser回復突變成Thr (S63T，Kabat編號)、在位置43處Ala回復突變成Ser (A43S，Kabat編號)及在位置44處Pro回復突變成Leu (P44L，Kabat編號)，鑑別為所需回復突變。在重鏈之情況下，在位置98處Arg突變成Gly (R94G，Kabat編號)及在位置44處Gly突變成Arg (G44R，Kabat編號)，鑑別為所需回復突變。構築含有此等回復突變中之一或多者之經突變可變域。參見下表5。(回復突變的構架胺基酸殘基由雙下劃線指示；來自初始親本抗體之鼠類CDR為加底線的。)

表5：mAb709 w/回復突變成鼠類殘基之人類化VH/VL設計

人類化mAb709 VH或VL標識符	SEQ ID NO.	胺基酸序列 12345678901234567890123456789012345678901234567890
mAb709 VH.1	20	EVQLVESGGGLVQPGGSLRLSCAASGFTFSFYTMSWVRQA PGKGLEWVATISGGGRDTYYPDSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARQGGNYLFAYWGQGTLVTVSS
mAb709 VH.1A	21	EVQLVESGGGLVQPGGSLRLSCAASGFTFSFYTMSWVRQA PGKGLEWVATISGGGRDTYYPDSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCAGQGGNYLFAYWGQGTLVTVSS
mAb709 VH.1B	22	EVQLVESGGGLVQPGGSLRLSCAASGFTFSFYTMSWVRQA PGKRLEWVATISGGGRDTYYPDSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCAGQGGNYLFAYWGQGTLVTVSS
mAb709 VK.1A	23	DIQMTQSPSSLSASVGDRVTITCKASQDVNTVVAWYQQKP GKAPKLLIYWASTRHTGVPSRFSGSGSGTDYTLTISSLQP EDFATYYCQQHYTTPYTFGGGTKVEIK
mAb709 VK.1B	24	DIQMTQSPSSLSASVGDRVTITCKASQDVNTVVAWYQQKP GKAPKLLISWASTRHTGVPSRFSGSGSGTDYTLTISSLQP EDFATYYCQQHYTTPYTFGGGTKVEIK
mAb709 VK.1C	25	DIVMTQSPSSLSASVGDRVTITCKASQDVNTVVAWYQQKP GKAPKVLISWASTRHTGVPSRFSGSGSGTDYTLTISSLQP EDFATYYCQQHYTTPYTFGGGTKVEIK
mAb709 VK.1D	26	DIVMTQSPSSLSASVGDRVTITCKASQDVNTVVAWYQQKP GKAPKVLISWASTRHTGVPSRFTGSGSGTDYTLTISSLQP EDFATYYCQQHYTTPYTFGGGTKVEIK
mAb709 VK.1E	27	DIVMTQSPSSLSASVGDRVTITCKASQDVNTVVAWYQQKP GKSLKVLISWASTRHTGVPSRFTGSGSGTDYTLTISSLQP EDFATYYCQQHYTTPYTFGGGTKVEIK

【0137】 以合成方式產生人類化VH及VK基因，且隨後分別選殖至

含有人類IgG1及人類κ恆定域之載體中。(參見下表6。)

表6：用於抗體人類化之人類恆定區序列

恆定區	SEQ ID NO.	胺基酸序列 12345678901234567890123456789012345678901234567890
人類恆定區Igγ1突變	28	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGG PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
人類恆定區κ	29	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGEC

【0138】 人類化VH及人類化VK鏈之配對產生15種人類化抗體，稱為HumAb709-1至HumAb709-15 (表7)。亦產生具有親本小鼠VH/VL及人類恆定區序列之嵌合抗體(mAb709c)作為親和力比較之陽性對照。表現所有重組mAb且進行純化。

表7：抗PD-1人類化mAb709抗體之生產清單

抗體標識符	重鏈中之VH區	輕鏈κ鏈中之VL區
HumAb709-1	mAb709 VH.1	mAb709 VK.1A
HumAb709-2	mAb709 VH.1A	mAb709 VK.1A
HumAb709-3	mAb709 VH.1B	mAb709 VK.1A
HumAb709-4	mAb709 VH.1	mAb709 VK.1B
HumAb709-5	mAb709 VH.1A	mAb709 VK.1B
HumAb709-6	mAb709 VH.1B	mAb709 VK.1B
HumAb709-7	mAb709 VH.1	mAb709 VK.1C
HumAb709-8	mAb709 VH.1A	mAb709 VK.1C
HumAb709-9	mAb709 VH.1B	mAb709 VK.1C
HumAb709-10	mAb709 VH.1	mAb709 VK.1D
HumAb709-11	mAb709 VH.1A	mAb709 VK.1D
HumAb709-12	mAb709 VH.1B	mAb709 VK.1D
HumAb709-13	mAb709 VH.1	mAb709 VK.1E
HumAb709-14	mAb709 VH.1A	mAb709 VK.1E
HumAb709-15	mAb709 VH.1B	mAb709 VK.1E
HumAb709c	SEQ ID NO:8	SEQ ID NO:9

【0139】 藉由結合ELISA及基於細胞之RBA對所有15種人類化抗體及嵌合抗體(mAb709c)進行表徵。對於基於細胞之RBA，向預阻斷的96孔

圓底培養盤中添加2 × 10^5個細胞/孔之CHO-K1-huPD1細胞，且在洗滌之後，向各孔中添加具有在0.064 nM至200 nM範圍內之稀釋濃度的50 µl抗體。接下來，添加50 µl 60 µg/ml生物素標記的PD-L1/Fc或生物素標記的PD-L2/Fc蛋白。在平緩混合且在4℃下培育之後，洗滌細胞且用Alexa Fluor™ 488抗生蛋白鏈菌素溶液(1:1000，ThermoFisher Scientific；目錄號S32354)進行染色。藉由FACS讀出信號，且藉由GraphPad軟體擬合曲線。計算之IC50值顯示於下表8中。藉由表面電漿子共振量測，使用Biacore T200儀，進一步分析具有正(低) IC50值(亦即針對至少一種PD-1配位體低於約1.0 nM)之抗體的結合親和力。簡言之，將山羊抗人類IgG Fc多株抗體直接固定在生物感測器晶片中，且以5 µl/min之流速，將抗PD-1人類化抗體或嵌合抗體樣本注射在反應基質上。藉由在30 µl/min之連續流速下，在人類PD-1-His蛋白之五個不同濃度下進行動力學結合量測，來分別測定締合速率常數及解離速率常數k_{on} ($M^{-1}s^{-1}$)及k_{off} (s^{-1})。使用式$K_D = k_{off}/k_{on}$，根據動力學速率常數計算抗體與相關目標蛋白質之間的反應的平衡解離常數K_D (M)。mAb709人類化抗PD-1衍生物中之五者之親和力顯示於表8中。HumAb709-8具有極少回復突變，同時最大程度維持嵌合mAb709c上之親本可變域之親和力。

表8：人類化mAb709抗PD-1抗體之RBA值及結合親和力

人類化抗體ID	PD-L1 RBA IC50 (nM)	PD-L2 RBA IC50 (nM)	k_{on} (1/Ms)	k_{off} (1/s)	K_D (M)
HumAb709-1	1.02	1.64	1.95×10^5	2.145×10^{-3}	1.10×10^{-8}
HumAb709-2	0.47	0.99	8.03×10^4	5.5×10^{-5}	6.84×10^{-10}
HumAb709-3	1.25	1.64			
HumAb709-4	0.78	1.68			
HumAb709-5	0.67	0.97			
HumAb709-6	1.23	1.26			
HumAb709-7	0.40	0.84	1.41×10^5	3.36×10^{-4}	2.36×10^{-9}
HumAb709-8	0.44	1.00	1.27×10^5	4.69×10^{-5}	3.68×10^{-10}
HumAb709-9	1.04	1.76			

HumAb709-10	0.29	0.80	1.46×10^{5}	2.97×10^{-4}	2.04×10^{-9}
HumAb709-11	0.55	0.92			
HumAb709-12	0.45	1.35			
HumAb709-13	0.50	0.78			
HumAb709-14	0.51	0.92			
HumAb709-15	0.90	1.21			
mAb709c	0.62	0.56	1.21×10^{5}	6.88×10^{-5}	5.67×10^{-10}

【0140】

實例5.2：鼠類抗體mAb713之人類化

抗PD-1 mAb713之可變區基因用於產生人類化抗體。將mAb713之VH及VK之胺基酸序列與人類Ig V-基因序列之可用資料庫進行比較，以尋找總體最佳匹配的人類生殖系Ig V-基因序列。另外，將VH或VL之構架4區段與J-區資料庫進行比較，以尋找分別與鼠類VH及VL區具有最高同源性之構架。對於輕鏈，最接近的人類V-基因匹配為O18基因；且對於重鏈，最接近的人類匹配為VH3-48基因。隨後，設計人類化可變域序列，其中將mAb713輕鏈之CDR-L1、CDR-L2及CDR-L3移植至O18基因之構架序列上，其中JK4構架4序列在CDR-L3之後；且將mAb713重鏈之CDR-H1、CDR-H2及CDR-H3移植至VH3-48之構架序列上，其中JH6構架4序列在CDR-H3之後。隨後產生mAb709之3維Fv模型，以判定是否存在其中小鼠胺基酸對於支持環結構或VH/VL界面而言關鍵的任何構架位置。人類化序列中之此等殘基應在相同位置處回復突變成小鼠殘基以保留親和力/活性。在輕鏈之情況下，在位置71處Phe回復突變成Tyr (F71Y，Kabat編號)、在位置49處Tyr回復突變成Ser (Y49S，Kabat編號)及在位置69處Thr回復突變成Lys (T69K，Kabat編號)，鑑別為所需回復突變。在重鏈之情況下，在位置98處Arg突變成Lys (R94K，Kabat編號)、在位置29處Phe回復突變成Ser (F29S，Kabat編號)及在位置49處Ser回復突變成Ala (S49A，Kabat編號)，鑑別為所需回復突變。構築含有此等回復突變中之

一或多者之經突變可變域。參見下表9。(回復突變的構架胺基酸殘基由雙下劃線指示；來自初始親本抗體之鼠類CDR為加底線的。)

表9：mAb713 VH及VL之可變域序列變體

mAb713 VH/VL變體	SEQ ID NO.	胺基酸序列 1234567890123456789012345678901234567890
mAb713 VH.1	30	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYGMHWVRQA PGKGLEWVSYISSGSYTIYYADTVKGRFTISRDNAKNSLY LQMNSLRDEDTAVYYCARRGGSSHVNVMDYWGQGTTVTVS S
mAb713 VH.1A	31	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYGMHWVRQA PGKGLEWVSYISSGSYTIYYADTVKGRFTISRDNAKNSLY LQMNSLRDEDTAVYYCAKRGGSSHVNVMDYWGQGTTVTVS S
mAb713 VH.1B	32	EVQLVESGGGLVQPGGSLRLSCAASGFTSSDYGMHWVRQA PGKGLEWVSYISSGSYTIYYADTVKGRFTISRDNAKNSLY LQMNSLRDEDTAVYYCAKRGGSSHVNVMDYWGQGTTVTVS S
mAb713 VH.1C	33	EVQLVESGGGLVQPGGSLRLSCAASGFTSSDYGMHWVRQA PGKGLEWVAYISSGSYTIYYADTVKGRFTISRDNAKNSLY LQMNSLRDEDTAVYYCAKRGGSSHVNVMDYWGQGTTVTVS S
mAb713 VK.1	34	DIQMTQSPSSLSASVGDRVTITCKASDHINNWLAWYQQKP GKAPKLLIYGATSLETGVPSRFSGSGSGTDFTFTISSLQP EDIATYYCQQYWSPPYTFGGGTKVEIK
mAb713 VK.1A	35	DIQMTQSPSSLSASVGDRVTITCKASDHINNWLAWYQQKP GKAPKLLIYGATSLETGVPSRFSGSGSGTDYTFTISSLQP EDIATYYCQQYWSPPYTFGGGTKVEIK
mAb713 VK.1B	36	DIQMTQSPSSLSASVGDRVTITCKASDHINNWLAWYQQKP GKAPKLLISGATSLETGVPSRFSGSGSGTDYTFTISSLQP EDIATYYCQQYWSPPYTFGGGTKVEIK
mAb713 VK.1C	37	DIQMTQSPSSLSASVGDRVTITCKASDHINNWLAWYQQKP GKAPKLLISGATSLETGVPSRFSGSGSGKDYTFTISSLQP EDIATYYCQQYWSPPYTFGGGTKVEIK

【0141】以合成方式產生人類化VH及VK基因，且隨後獨立地選殖至含有人類IgG1及人類κ恆定域之載體中(參見表6，見上文)。人類VH變體與人類VK變體之配對產生16種人類化抗體，稱為HumAb713-1至HumAb713-16 (表10)。亦產生具有親本小鼠VH/VL及人類恆定序列之嵌合抗體(mAb713c)作為親和力比較之陽性對照。

表10：人類化mAb713抗PD-1抗體之生產清單

抗體標識符	重鏈中之VH區	輕鏈κ鏈中之VL區
HumAb713-1	mAb713 VH.1	mAb713 VK.1
HumAb713-2	mAb713 VH.1A	mAb713 VK.1

HumAb713-3	mAb713 VH.1B	mAb713 VK.1
HumAb713-4	mAb713 VH.1C	mAb713 VK.1
HumAb713-5	mAb713 VH.1	mAb713 VK.1A
HumAb713-6	mAb713 VH.1A	mAb713 VK.1A
HumAb713-7	mAb713 VH.1B	mAb713 VK.1A
HumAb713-8	mAb713 VH.1C	mAb713 VK.1A
HumAb713-9	mAb713 VH.1	mAb713 VK.1B
HumAb713-10	mAb713 VH.1A	mAb713 VK.1B
HumAb713-11	mAb713 VH.1B	mAb713 VK.1B
HumAb713-12	mAb713 VH.1C	mAb713 VK.1B
HumAb713-13	mAb713 VH.1	mAb713 VK.1C
HumAb713-14	mAb713 VH.1A	mAb713 VK.1C
HumAb713-15	mAb713 VH.1B	mAb713 VK.1C
HumAb713-16	mAb713 VH.1C	mAb713 VK.1C
mAb713c	SEQ ID NO:10	SEQ ID NO:11

【0142】藉由結合ELISA、基於細胞之RBA及Biacore親和力測試，對所有16種人類化抗體及嵌合抗體(mAb713c)進行表徵。結果概述於表11中。

表11：人類化mAb713抗PD-1抗體之RBA值及結合親和力

人類化抗體ID	PD-L1 RBA IC50 (nM)	PD-L2 RBA IC50 (nM)	k_{on} (1/Ms)	k_{off} (1/s)	K_D (M)
HumAb713-1	0.50	1.20	9.010×10^{4}	1.003×10^{-3}	1.113×10^{-8}
HumAb713-2	1.71	3.13			
HumAb713-3	0.77	1.24	8.447×10^{4}	2.082×10^{-4}	2.465×10^{-9}
HumAb713-4	1.06	2.24			
HumAb713-5	0.91	2.95			
HumAb713-6	1.04	1.46			
HumAb713-7	0.76	1.40	1.237×10^{5}	3.500×10^{-4}	2.829×10^{-9}
HumAb713-8	1.05	1.91			
HumAb713-9	1.20	2.00			
HumAb713-10	0.80	1.23			
HumAb713-11	0.51	0.97	1.591×10^{5}	3.776×10^{-4}	2.373×10^{-9}
HumAb713-12	0.94	1.59			
HumAb713-13	0.70	2.13			
HumAb713-14	0.91	1.45			
HumAb713-15	0.88	1.65			
HumAb713-16	0.65	1.63			
mAb713c	0.91	2.20	2.182×10^{5}	2.839×10^{-4}	1.301×10^{-9}

【0143】HumAb713-7具有極少的回復突變，維持嵌合抗體mAb713c之親本可變域之親和力特徵。在如實例3中所描述之MLR分析中驗證mAb713人類化抗體之功能活性。如圖5中所見，在MLR中，

HumAb713-7呈現與嵌合抗體mAb713c相當的活性，與其保留的結合特性一致。

【0144】

實例5.3：鼠類抗體mAb703之人類化

按照與實例5.1及5.2中之程序相同的程序，選擇鼠類抗PD-1抗體mAb703且進行人類化。構築人類化可變域(一些含有一或多個回復突變)，且胺基酸序列闡述於下表12中。(回復突變的構架胺基酸殘基由雙下劃線指示；來自初始親本抗體之鼠類CDR為加底線的。)

表12：mAb703 VH及VL之可變域序列變體

mAb703 VH/VL變體	SEQ ID NO.	胺基酸序列 12345678901234567890123456789012345678901234567890
mAb703 VH.1A	38	EVQLQESGPGLVKPSETLSLTCAVSGYSISTGYYWNWIRQ PPGKGLEWIGYMSYDGNNNYNPSLKNRVTISRDTSKNQFS LKLSSVTAADTAVYYCARDRGTTILGGTMDYWGQGTTVTV SS
mAb703 VH.1B	39	EVQLQESGPGLVKPSETLSLTCAVSGYSISTGYYWNWIRQ PPGKGLEWIGYMSYDGNNNYNPSLKNRITISRDTSKNQFS LKLSSVTAADTAVYYCARDRGTTILGGTMDYWGQGTTVTV SS
mAb703 VH.1C	40	EVQLQESGPGLVKPSETLSLTCAVSGYSISTGYYWNWIRQ PPGKGLEWMGYMSYDGNNNYNPSLKNRITISRDTSKNQFS LKLSSVTAADTAVYYCARDRGTTILGGTMDYWGQGTTVTV SS
mAb703 VH.1D	41	EVQLQESGPGLVKPSETLSLTCAVSGYSITTGYYWNWIRQ PPGKGLEWMGYMSYDGNNNYNPSLKNRITISRDTSKNQFS LKLSSVTAADTAVYYCARDRGTTILGGTMDYWGQGTTVTV SS
mAb703 VH.1E	42	EVQLQESGPGLVKPSETLSLTCAVSGYSITTGYYWNWIRQ PPGKKLEWMGYMSYDGNNNYNPSLKNRITISRDTSKNQFS LKLSSVTAADTAVYFCARDRGTTILGGTMDYWGQGTTVTV SS
mAb703 VK.1	43	DIQMTQSPSSLSASVGDRVTITCKASQSVSNDVAWYQQKP GKAPKLLIYYAFYRYTGVPSRFSGSGSGTDFTLTISSLQP EDFATYYCQQDYSSPWTFGGGTKVEIK
mAb703 VK.1A	44	DIQMTQSPSSLSASVGDRVTITCKASQSVSNDVAWYQQKP GKAPKLLIYYAFYRYTGVPSRFSGSGYGTDFTLTISSLQP EDFATYYCQQDYSSPWTFGGGTKVEIK
mAb703 VK.1B	45	DIQMTQSPSSLSASVGDRVTITCKASQSVSNDVAWYQQKP GKAPKLLIYYAFYRYTGVPDRFSGSGYGTDFTLTISSLQP EDFATYYCQQDYSSPWTFGGGTKVEIK
mAb703 VK.1C	46	DIQMTQSPSSLSASVGDRVTITCKASQSVSNDVAWYQQKP GKSPKLLIYYAFYRYTGVPDRFSGSGYGTDFTLTISSLQP

		EDFATYFCQQDYSSPWTFGGGTKVEIK
mAb703 VK.1D	47	SIVMTQSPSSLSASVGDRVTITCKASQSVSNDVAWYQQKP GKSPKLLIYYAFYRYTGVPDRFTGSGYGTDFTLTISSLQP EDFATYFCQQDYSSPWTFGGGTKVEIK

【0145】 以合成方式產生人類化VH及VK基因，且隨後獨立地選殖至含有人類IgG1及人類κ恆定域之載體中(參見表6，見上文)。人類VH變體與人類VK變體之配對產生25種人類化抗體，稱為HumAb703-1至HumAb703-25 (表13)。亦產生具有親本小鼠VH/VL及人類恆定序列之嵌合抗體作為親和力比較之陽性對照。

表13：人類化mAb703抗PD-1抗體之生產清單

抗體標識符	重鏈中之VH區	輕鏈κ鏈中之VL區
HumAb703-1	mAb703 VH.1A	mAb703 VK.1
HumAb703-2	mAb703 VH.1B	mAb703 VK.1
HumAb703-3	mAb703 VH.1C	mAb703 VK.1
HumAb703-4	mAb703 VH.1D	mAb703 VK.1
HumAb703-5	mAb703 VH.1E	mAb703 VK.1
HumAb703-6	mAb703 VH.1A	mAb703 VK.1A
HumAb703-7	mAb703 VH.1B	mAb703 VK.1A
HumAb703-8	mAb703 VH.1C	mAb703 VK.1A
HumAb703-9	mAb703 VH.1D	mAb703 VK.1A
HumAb703-10	mAb703 VH.1E	mAb703 VK.1A
HumAb703-11	mAb703 VH.1A	mAb703 VK.1B
HumAb703-12	mAb703 VH.1B	mAb703 VK.1B
HumAb703-13	mAb703 VH.1C	mAb703 VK.1B
HumAb703-14	mAb703 VH.1D	mAb703 VK.1B
HumAb703-15	mAb703 VH.1E	mAb703 VK.1B
HumAb703-16	mAb703 VH.1A	mAb703 VK.1C
HumAb703-17	mAb703 VH.1B	mAb703 VK.1C
HumAb703-18	mAb703 VH.1C	mAb703 VK.1C
HumAb703-19	mAb703 VH.1D	mAb703 VK.1C
HumAb703-20	mAb703 VH.1E	mAb703 VK.1C
HumAb703-21	mAb703 VH.1A	mAb703 VK.1D
HumAb703-22	mAb703 VH.1B	mAb703 VK.1D
HumAb703-23	mAb703 VH.1C	mAb703 VK.1D
HumAb703-24	mAb703 VH.1D	mAb703 VK.1D
HumAb703-25	mAb703 VH.1E	mAb703 VK.1D
mAb703c	SEQ ID NO:6	SEQ ID NO:7

【0146】 藉由結合ELISA及Biacore親和力測試，對所有25種人類化抗體及嵌合抗體(mAb703c)進行表徵。陽性結合劑之親和力結果概述於表14中。

表14：所選擇人類化mAb703抗PD-1抗體之結合親和力

人類化抗體ID	k_{on} (1/Ms)	k_{off} (1/s)	K_D (M)
HumAb703-11	1.874×10^{5}	1.757×10^{-3}	9.374×10^{-9}
HumAb703-12	1.770×10^{5}	1.594×10^{-3}	9.003×10^{-9}
HumAb703-13	1.454×10^{5}	1.537×10^{-3}	1.057×10^{-8}
HumAb703-18	6.572×10^{4}	1.242×10^{-3}	1.890×10^{-8}
HumAb703-22	2.294×10^{5}	1.593×10^{-3}	6.942×10^{-9}
mAb703c	3.594×10^{5}	9.664×10^{-4}	2.684×10^{-9}

【0147】在如實例3中所描述進行之MLR分析中驗證人類化mAb703抗體之功能活性，如圖2A及圖3中所示。

【0148】

實例5.4：鼠類抗體mAb719之人類化

按照與實例5.1及5.2中之程序相同的程序，選擇鼠類抗PD-1抗體mAb719且進行人類化。構築人類化可變域(一些含有一或多個回復突變)，且胺基酸序列闡述於下表15中。(回復突變的構架胺基酸殘基由雙下劃線指示；來自初始親本抗體之鼠類CDR為加底線的。)另外，製備CDR-H2中之Asp→Ala取代及CDR-H3中之Ser→Ala取代，以避免重組抗體常見之可能的Asp異構化。(參見表15中之mAb719 VH.1E及mAb719 VH.1F序列。)

表15：mAb719 VH及VL之可變域序列變體

mAb719 VH/VL變體	SEQ ID NO.	胺基酸序列 12345678901234567890123456789012345678901234567890
mAb719 VH.1	48	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSHLMSWVRQA PGKGLEWVSAISGGGADTYYPDSVKGRFTISRDNSKNTLY LQMNSLRAEDTAVYYCAKQILAFDS-WGQGTTVTVSS
mAb719 VH.1A	49	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSHLMSWVRQA PGKGLEWVSAISGGGADTYYPDSVKGRFTISRDNSKNTLY LQMNSLRAEDTAVYYCTRQILAFDS-WGQGTTVTVSS
mAb719 VH.1B	50	EVQLLESGGGLVQPGGSLRLSCAASGFSFSSHLMSWVRQA PGKGLEWVSAISGGGADTYYPDSVKGRFTISRDNSKNTLY LQMNSLRAEDTAVYYCTRQILAFDS-WGQGTTVTVSS
mAb719 VH.1C	51	EVQLLESGGGLVQPGGSLRLSCAASGFSFSSHLMSWVRQA PGKGLEWVAAISGGGADTYYPDSVKGRFTISRDNSKNTLY LQMNSLRAEDTAVYYCTRQILAFDS-WGQGTTVTVSS
mAb719 VH.1D	52	EVQLLESGGGLVQPGGSLRLSCAASGFSFSSHLMSWVRQA PGKRLEWVAAISGGGADTYYPDSVKGRFTISRDNSKNTLY LQMNSLRAEDTAVYYCTRQILAFDS-WGQGTTVTVSS

mAb719 VH.1E	53	EVQLLESGGGLVQPGGSLRLSCAASGFSFSSHLMSWVRQA PGKGLEWVAAISGGGADTYYPASVKGRFTISRDNSKNTLY LQMNSLRAEDTAVYYCTRQILAFDA-WGQGTTVTVSS
mAb719 VH.1F	54	EVQLLESGGGLVQPGGSLRLSCAASGFSFSSHLMSWVRQA PGKRLEWVAAISGGGADTYYPASVKGRFTISRDNSKNTLY LQMNSLRAEDTAVYYCTRQILAFDA-WGQGTTVTVSS
mAb719 VK.1	55	DIQMTQSPSSLSASVGDRVTITCHASQNIYVWLNWYQQKP GKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTFTISSLQP EDIATYYCQQGQSYPWTFGGGTKVEIK
mAb719 VK.1A	56	DIQMNQSPSSLSASVGDRVTITCHASQNIYVWLNWYQQKP GKAPKLLIYKASNLHTGVPSRFSGSGSGTDFTFTISSLQP EDIATYYCQQGQSYPWTFGGGTKVEIK
mAb719 VK.1B	57	DIQMNQSPSSLSASVGDRVTITCHASQNIYVWLNWYQQKP GKIPKLLIYKASNLHTGVPSRFSGSGSGTDFTFTISSLQP EDIATYYCQQGQSYPWTFGGGTKVEIK

【0149】以合成方式產生人類化VH及VK基因，且隨後獨立地選殖至含有人類IgG1及人類κ恆定域之載體中(參見表6，見上文)。人類VH變體與人類VK變體之配對產生21種人類化抗體，稱為HumAb719-1至HumAb719-21 (表16)。亦產生具有親本小鼠VH/VL及人類恆定序列之嵌合抗體作為親和力比較之陽性對照。表現所有重組mAb且進行純化。

表16：人類化mAb719抗PD-1抗體之生產清單

抗體標識符	重鏈中之VH區	輕鏈κ鏈中之VL區
HumAb719-1	mAb719 VH.1	mAb719 VK.1
HumAb719-2	mAb719 VH.1A	mAb719 VK.1
HumAb719-3	mAb719 VH.1B	mAb719 VK.1
HumAb719-4	mAb719 VH.1C	mAb719 VK.1
HumAb719-5	mAb719 VH.1D	mAb719 VK.1
HumAb719-6	mAb719 VH.1E	mAb719 VK.1
HumAb719-7	mAb719 VH.1F	mAb719 VK.1
HumAb719-8	mAb719 VH.1	mAb719 VK.1A
HumAb719-9	mAb719 VH.1A	mAb719 VK.1A
HumAb719-10	mAb719 VH.1B	mAb719 VK.1A
HumAb719-11	mAb719 VH.1C	mAb719 VK.1A
HumAb719-12	mAb719 VH.1D	mAb719 VK.1A
HumAb719-13	mAb719 VH.1E	mAb719 VK.1A
HumAb719-14	mAb719 VH.1F	mAb719 VK.1A
HumAb719-15	mAb719 VH.1	mAb719 VK.1B
HumAb719-16	mAb719 VH.1A	mAb719 VK.1B
HumAb719-17	mAb719 VH.1B	mAb719 VK.1B
HumAb719-18	mAb719 VH.1C	mAb719 VK.1B
HumAb719-19	mAb719 VH.1D	mAb719 VK.1B
HumAb719-20	mAb719 VH.1E	mAb719 VK.1B
HumAb719-21	mAb719 VH.1F	mAb719 VK.1B
mAb719c	SEQ ID NO:18	SEQ ID NO:19

【0150】 藉由結合ELISA及親和力測定，使用Octet® RED96生物層干涉法系統(Pall FortéBio LLC)，使用具有固定的人類PD-1/Fc作為抗體目標之生物感測器，對所有21種人類化抗體及嵌合抗體(mAb719c)進行表徵。藉由在抗體之五個不同濃度下進行動力學結合量測，推導出速率常數。由於二價結合目標，親和力顯示高於先前Biacore測試。陽性結合劑之親和力結果概述於表17中。

表17：所選擇人類化mAb719抗PD-1抗體之結合親和力

人類化抗體ID	k_{on} (1/Ms)	k_{off} (1/s)	K_D (M)
HumAb719-8	1.066×10^{5}	4.905×10^{-5}	4.602×10^{-10}
HumAb719-11	5.944×10^{4}	2.270×10^{-4}	3.819×10^{-9}
HumAb719-12	6.882×10^{4}	5.805×10^{-5}	8.435×10^{-10}
HumAb719-21	1.042×10^{5}	6.256×10^{-5}	6.005×10^{-10}
mAb719c	9.735×10^{4}	$<1.00 \times 10^{-5}$	$<1.027 \times 10^{-10}$

【0151】 在MLR分析中驗證人類化mAb719抗體之功能活性，如圖2B及圖3中所示。

【0152】

實例6：前導抗PD-1抗體之藥物動力學特性

在雄性Sprague - Dawley (SD)大鼠中評定HumAb709-8及HumAb713-7之藥物動力學特性。以5 mg/kg之單一靜脈內劑量，向雄性SD大鼠投與抗體。經28天時段，在不同時間點採集血清樣本，其中在0、5、15及30分鐘；1、2、4、8及24小時；及2、4、7、10、14、21及28天，經由尾部靜脈連續出血進行取樣，且藉由一般ELISA進行分析。簡言之，在4℃下，ELISA盤用125奈克/孔之山羊抗人類IgG Fc抗體(Rockland，目錄號：609-101-017)塗覆隔夜，用1X PBS/1% BSA/0.05% Tween-20/0.05% ProClin™ 300阻斷。所有血清樣本首先在阻斷緩衝液中稀釋20倍。在5%合併大鼠血清中進行額外稀釋，且在37℃下在培養盤上

培育60分鐘。用共軛的抗人類IgG (Fab片段)過氧化酶(Sigma；目錄號A0293)進行偵測，且藉助於標準曲線，使用四參數對數擬合，測定濃度。藉由非分室模型，使用WinNonlin軟體(Pharsight Corporation，Mountain View，Calif.)，來測定藥物動力學參數之值。如此等結果(表18)所表明，HumAb09-8及HumAb13-7之特性為穩定的。

表18：HumAb709-8及HumAb713-7之藥物動力學特性

PK參數	CL	Vss	β $t_{1/2}$	AUC	MRT
抗體	mL/天/kg	mL/kg	天	天*μg/mL	天
HumAb709-8	8.6	129.6	10.9	594.2	15.4
HumAb713-7	6.4	114.4	12.7	789.3	18.1

【0153】

實例7：抗LAG-3單株抗體之產生

藉由融合瘤融合產生抗LAG-3單株抗體(mAb)。

【0154】

實例7.1：免疫接種、融合瘤融合及選殖。

以與上文關於抗PD-1抗體產生(實例1)所描述相同的方式進行Balb/C小鼠之免疫接種，不同之處在於使用人類LAG-3 D1-D2/鼠類Fc均二聚體作為免疫原。以2-3週間隔，對免疫動物進行增強免疫接種2-4次。在最終增強免疫接種三天之後，分離來自免疫小鼠之脾細胞，且使用標準技術，將其與鼠類骨髓瘤細胞株SP2/0融合。

【0155】

實例7.2：抗LAG-3抗體之鑑別及特徵

藉由Synbio技術(Suzhou, China)，定製抗人類LAG-3及抗食蟹獼猴LAG-3之合成目標。各目標由與人類IgG Fc區融合之人類或食蟹獼猴LAG-3蛋白之胞外域之多肽區段組成。將編碼各LAG-3 ECD/Fc融合蛋白

之合成基因次選殖至pCP表現載體(Chempartner, Shanghai, China)中，且將表現質體短暫轉染至1-3公升培養基中之HEK 293E細胞中且在CO_2振盪器中培養七天。用於各融合之ECD序列闡述於下表19中。各融合蛋白之LAG-3 ECD部分為加底線的。

表19：LAG-3 ECD/Fc融合蛋白目標之胺基酸序列

SEQ ID NO.	LAG-3來源	胺基酸序列 12345678901234567890123456789012345678901234567890
58	人類	LQPGAEVPVVWAQEGAPAQLPCSPTIPLQDLSLLRRAGVTW QHQPDSGPPAAAPGHPLAPGPHPAAPSSWGPRPRRYTVLSV GPGGLRSGRLPLQPRVQLDERGRQRGDFSLWLRPARRADAG EYRAAVHLRDRALSCRLRLRLGQASMTASPPGSLRASDWVI LNCSFSRPDRPASVHWFRNRGQGRVPVRESPHHHLAESFLF LPQVSPMDSGPWGCILTYRDGFNVSIMYNLTVLGLEPPTPL TVYAGAGSRVGLPCRLPAGVGTRSFLTAKWTPPGGGPDLLV TGDNGDFTLRLEDVSQAQAGTYTCHIHLQEQQLNATVTLAI ITVTPKSFGSPGSLGKLLCEVTPVSGQERFVWSSLDTPSQR SFSGPWLEAQEAQLLSQPWQCQLYQGERLLGAAVYFTELSS PGAQRSGRAPGALPAGHLIEGRMDPKSCDKTHTCPPCPAPE LLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK
59	食蟹獼猴	PQPGAEISVVWAQEGAPAQLPCSPTIPLQDLSLLRRAGVTW QHQPDSGPPAXAPGHPPVPGHRPAAPYSWGPRPRRYTVLSV GPGGLRSGRLPLQPRVQLDERGRQRGDFSLWLRPARRADAG EYRATVHLRDRALSCRLRLRVGQASMTASPPGSLRTSDWVI LNCSFSRPDRPASVHWFRSRGQGRVPVQGSPHHHLAESFLF LPHVGPMDSGLWGCILTYRDGFNVSIMYNLTVLGLEPATPL TVYAGAGSRVELPCRLPPAVGTQSFLTAKWAPPGGGPDLLV AGDNGDFTLRLEDVSQAQAGTYICHIRLQGQQLNATVTLAI ITVTPKSFGSPGSLGKLLCEVTPASGQEHFVWSPLNTPSQR SFSGPWLEAQEAQLLSQPWQCQLHQGERLLGAAVYFTELSS PGAQRSGRAPGALRAGHLIEGRMDPKSCDKTHTCPPCPAPE LLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK

【0156】藉由ELISA對融合瘤純系之上清液進行初步篩選。簡言

之，將50微升/孔之含1 μg/ml人類LAG-3 ECD/Fc之$NaHCO_3$直接塗覆在96孔盤之各孔中隔夜。培養盤用1X PBST，300微升/孔洗滌3次。在用含1% BSA之PBST以250微升/孔阻斷且在室溫下培育1小時之後，以50微升/孔添加融合瘤上清液，且在37℃下培育1小時。在洗滌之後，以100微升/孔添加連接HRP的山羊抗小鼠IgG Fc二級抗體(目錄號A0168，Sigma)，且在室溫下培育培養盤1小時。以100微升/孔，TMB試劑(InnoReagents)用於偵測及發展ELISA信號15分鐘，且反應用1N HCl終止。培養盤用讀板儀(SpectraMax® M5e，Molecular Devices，USA)在450 nm波長下讀取。藉由FACS分析，使用類似於上文實例1.4之方法，進一步驗證ELISA陽性抗體產生者純系，不同之處在於使用表現人類LAG-3或食蟹獼猴LAG-3之穩定HEK 293F細胞株。選擇產生LAG-3結合活性之融合瘤，且在受體阻斷分析(RBA)中對其進一步表徵。

【0157】

實例7.3：受體阻斷分析(RBA)

測試展示LAG-3特異活性之上清液之阻斷LAG-3受體與MHC II類結合的能力。Raji人類B細胞淋巴母細胞表現高水準之MCH II類，且用作上文所描述之LAG-3 ECD/Fc蛋白的結合目標。簡言之，收穫Raji細胞且將其再懸浮於FACS緩衝液中並塗鋪在96孔盤(2×10^5個細胞/孔)中。將抗LAG-3融合瘤上清液與可溶性LAG-3 ECD/Fc混合，且以100微升/孔之最終體積向各孔添加該混合物。在向細胞添加混合物之後，在室溫下培育培養盤30分鐘。在用PBS洗滌兩次之後，將細胞與抗人類IgG Alexa Fluor® 488二級抗體一起在4℃下培育1小時，用PBS洗滌兩次，隨後在流式細胞儀上量測螢光。

【0158】

實例7.4：抗LAG-3單株抗體之表現及純化

在FreeStyle™ 293表現培養基(Gibco/Life Technologies)中，於CO_2振盪器中，在37℃下培養產生鼠類單株抗體之融合瘤細胞5至7天。經由在4000 × g下離心30分鐘移除所有細胞及細胞碎片來收集條件培養基，隨後在純化之前經由0.22 μm膜過濾。根據製造商之指南，施加鼠類抗體且與MabSelect™ SuRe (GE Healthcare) 蛋白A樹脂管柱結合，用PBS洗滌，用含有20 mM檸檬酸鹽、150 mM NaCl pH 3.5之緩衝液溶離。溶離材料緊接著用1 M Tris pH 8.0中和，且相對於PBS進行透析。一步純化抗體通常具有高於90%純度，如由SEC-HPLC所偵測。藉由量測在280 nm下之吸光度，或藉由NanoDrop™ microvolume分光光度計(Thermo Scientific)，來測定蛋白質濃度。以等分試樣形式將純化抗體儲存於-80℃冰箱中。

【0159】

實例7.5：純化抗LAG-3抗體之結合活性

【0160】

藉由ELISA進行表徵

以與以上實例7.2中所描述相同的方式進行結合ELISA。將各純化抗體進行10倍連續稀釋。在阻斷具有含固定的LAG-3 ECD/Fc融合蛋白目標之孔之96孔分析培養盤之後，向分析培養盤之各孔添加具有稀釋濃度之純化抗體樣本。連接HRP之抗小鼠IgG抗體(A0168，Sigma)及TMB試劑用於偵測及發展ELISA信號，該等信號在SpectraMax® M5e讀板儀上在450 nm波長下讀取。使用GraphPad軟體擬合曲線，且計算EC50值。類似地，

亦如實例7.3中所描述進行RBA，其中測定滴定純化抗體及最大抑制百分比及IC50值。

【0161】

藉由FACS進行表徵

使用類似於上文實例1.4之方法進行FACS分析，不同之處在於使用表現人類LAG-3或食蟹獼猴LAG-3之穩定HEK 293F細胞株。以2 × 10^4個細胞/孔，將LAG-3表現細胞饋入至96孔分析圓底分析培養盤(目錄號3799；Corning)中，且用純化抗LAG-3抗體進行染色。用AlexaFluor®驢抗小鼠IgG (H+L)高度交叉吸附的二級抗體(目錄號A21202；Invitrogen)偵測LAG-3抗體，且使用流式細胞儀監測細胞螢光。由GraphPad軟體處理資料，且計算EC50值。

【0162】 此等結合特徵分析之結果顯示於下表20中。

表20：純化鼠類抗LAG-3抗體之結合活性

mAb標識符	與人類LAG-3結合			與食蟹獼猴LAG-3結合		
	ELISA	**FACS**		**ELISA**	**FACS**	
	EC50 (nM)	EC50 (nM)	Max-MFI	EC50 (nM)	EC50 (nM)	Max-MFI
mAb742	0.22	2.8	102.9	0.32	56.4	48.5
mAb743	0.26	30.4	115.7	0.26	111.5	36.9
mAb744	0.19	9.5	135.0	0.21	67.0	37.8
mAb745	0.27	32.2	54.8	0.30	224.3	26.0
mAb746	0.31	1.3	120.8	0.21	4.1	66.2
mAb747	0.25	1.1	104.4	0.34	3.1	65.2
mAb748	0.24	13.4	73.1	0.25	79.6	31.9
mAb749	0.55	3.3	123.6	0.33	14.3	67.4
mAb750	0.25	24.1	88.7	0.32	113.6	36.7
mAb751	0.22	26.2	88.9	0.27	79.3	33.1
mAb757	0.23	25.3	91.8	0.30	77.2	35.1
mAb758	0.87	9.8	64.8	3.18	15.0	17.3
mAb759	0.43	3.0	60.2	0.53	6.3	18.6
mAb760	N/A	N/A	12.3	N/A	N/A	4.9
mAb761	0.1.18	17.8	105.2	1.24	34.6	39.5
人類IgG1 (對照)	0.13	0.9	190.6	78.23	63.7	28.1

【0163】 在此表中，「N/A」表示未量測到結合活性。

【0164】

實例7.6：藉由RBA及抗原依賴性活化分析進行表徵

亦在RBA中以與實例7.3中所描述相同的方式測試純化抗LAG-3抗體。亦在抗原特異性T細胞活化分析中如下測試抗體：藉由ChemPartner (Shanghai，CN)定製產生表現huLAG-3之鼠類T融合瘤細胞株。來自相同小鼠細胞株之小鼠脾細胞用作效應細胞。表現huLAG-3受體蛋白之融合瘤能夠與MHC II類陽性小鼠脾細胞結合，經由II類之接合具有抑制作用。該分析測試抗LAG-3抗體介導之抑制作用之反轉，如藉由IL-2之產量增加所量測。自6-8週齡雌性C57BL/6小鼠收穫小鼠脾細胞，且根據製造商之說明書，使用紅血球裂解緩衝液(Sigma-Aldrich；R7757)裂解紅血球。接下來，將50 μl T融合瘤-huLAG-3細胞(2 × 10^6個細胞/毫升)接種在96孔培養盤之各孔中，且隨後以50微升/孔添加一系列含抗LAG-3單株抗體之溶液且在37℃下培育30 min。將小鼠脾細胞(4 × 10^6個細胞/毫升)與抗原(20 μg/ml)混合，且在37℃下培育30 min。將混合物(100微升/孔)添加至已經接種有T融合瘤-huLAG-3細胞及抗LAG-3 mAb之各孔中。培養抗體、T融合瘤-huLAG-3細胞、小鼠脾細胞及抗原之混合物3天。在72小時之後，抽取100 μl細胞培養物上清液且稀釋成適當濃度，以用於根據製造商之方案，使用R&D Systems ELISA套組執行小鼠IL-2定量ELISA。使用ELISA-Endpoint-TMB & HRP方案，在SpectraMax M5讀板儀(Molecular Devices)上讀取ELISA培養盤。RBA及抗原依賴性活化分析結果顯示於表21中。

表21：鼠類抗LAG-3抗體之特徵

	FACS RBA		抗原依賴性活化	
	Raji 1 μg/ml HuLAG-3 ECD/Fc		小鼠IL-2	
mAb標識符	IC50 (nM)	最大抑制(%)	EC50 (nM)	最大IL-2 (pg/ml)
mAb742	3.84	96.5	++	732.8
mAb743	11.66	96.6	++	583.2
mAb744	10.77	96.5	++	612.3
mAb745	12.38	95.0	+	357.1
mAb746	2.92	96.2	1.28	653.5
mAb747	2.84	96.3	1.27	729.2
mAb748	4.80	96.1	++	539.2
mAb749	4.73	93.9	+++	513.0
mAb750	7.15	96.6	+++	552.5
mAb751	6.59	96.0	++	447.0
mAb757	7.80	96.8	++	570.9
mAb758	N/A	7.9	-	182.9
mAb759	86.46	34.2		
mAb760	N/A	3.4		
mAb761	17.98	96.0		
人類IgG1 (對照)	2.30	94.7	0.71	785.7

【0165】

實例7.7：藉由Biacore進行結合親和力測定

對於在ELISA及FACS分析中具有高結合親和力以及強效功能活性之抗體，基於使用Biacore表面電漿子共振進行之實時結合反應之結合動力學常數量測來判定結合親和力。簡言之，使用Biacore T200系統，利用抗體捕捉方法，進行抗體對於抗原之結合分析。根據製造商之說明書，將抗小鼠IgG Fc抗體固定在CM5感測器晶片上。注射測試抗LAG-3鼠類單株抗體，且由固定的抗小鼠IgG Fc捕捉。隨後，獨立地注射連續濃度之LAG-3抗原，且記錄各抗原分析物濃度之結合概況。分析溫度為25℃，且締合時間及解離時間分別為180秒及1200秒。使用Biacore T200評價軟體1.0，根據1:1結合模型，擬合Biacore資料，以計算締合(k_{on})速率常數及解離(k_{off})速率常數，且根據此等計算，判定平衡解離常數(K_D)。四種所選擇抗LAG-3抗體之親和力(K_D)顯示於下表22中。

表22：所選擇抗LAG-3抗體之結合親和力

抗體標識符	針對LAG-3抗原之親和力(K_D)
mAb746	3.774×10^{-8} M
mAb747	5.201×10^{-8} M
mAb749	1.893×10^{-7} M
mAb750	7.506×10^{-8} M

【0166】

實例7.8：在PBMC分析中，抗LAG-3抗體功能之比較

為了進一步驗證人類PBMC中之抗LAG-3抗體功能，使用超級抗原金黃色葡萄球菌(*Staphylococcus aureus*)腸毒素B (SEB)進行細菌毒素刺激分析。SEB為用於藉由刺激人類T細胞而活化免疫系統(此轉而引起過度產生若干細胞介素)之已知超級抗原。自來自健康人類供體之血液樣本分離PBMC。以2×10^5個細胞/孔，將PBMC接種至96孔分析培養盤中，隨後將各種抗LAG-3測試抗體添加至培養盤中且在37℃下與PBMC一起培育30 min。添加SEB溶液至10 ng/ml之最終濃度。隨後培育培養盤96小時。在此培育結束時，採集100 μl細胞培養物上清液，且使用ELISA IL-2偵測套組(R&D Systems；目錄號DY202)來量測IL-2產量。結果顯示於圖6中。

【0167】

實例8：鼠類抗LAG-3抗體可變區之定序

為了擴增重鏈及輕鏈可變區，用TRIzol® RNA分離試劑(Invitrogen；目錄號15596)，自> 5×10^6個細胞分離所選擇融合瘤純系之總RNA。藉由SuperScript™ III第一股合成超混合液(Invitrogen；目錄號18080)合成cDNA，且用作小鼠Ig-引子組(Novagen；目錄號69831-3)之PCR模板。藉由用SYBR™安全DNA凝膠染色(Invitrogen)之1.2%瓊脂糖凝膠電泳，分析PCR產物。根據製造商之說明書，用NucleoSpin®凝膠及

PCR Clean-up (Macherey-Nagel GmbH；目錄號740609)純化正確大小之DNA片段，且獨立地將其次選殖至pMD18-T選殖載體中。選擇來自各轉化之十五個群落，且藉由DNA定序分析插入片段之序列。若對於VH及VL，存在至少8個匹配共有序列，則確認序列。藉由序列同源性比對分析之七種鼠類mAb之可變區序列列於表23中。基於Kabat編號，鑑別互補決定區(CDR)。

表23：7種鼠類抗LAG-3抗體之VH/VL胺基酸序列

α-LAG-3 mAb ID	域	SEQ ID NO.	胺基酸序列 12345678901234567890123456789012345678901234567890
mAb746	VH	60	EVQLQQSGAELVRPGASVKLSCTASDFNIKDDYMHWVKQRP EQGLDWIGWIVPENGNTEYASKFQGKATITADTSSNTAYLQ LSSLTSEDTAVYYCTVYGDYWGQGTTLTVSS
	VL	61	DIQMTQSPSSLSASLGERVSLNCRASQEISGYLSWLQQKSD GTIKRLIYAASTLDSGVPKRFSGSRSGSDYSLTISSLESED FADYYCLQYASYPLTFGAGTKLELK
mAb747	VH	60	EVQLQQSGAELVRPGASVKLSCTASDFNIKDDYMHWVKQRP EQGLDWIGWIVPENGNTEYASKFQGKATITADTSSNTAYLQ LSSLTSEDTAVYYCTVYGDYWGQGTTLTVSS
	VL	62	DIQMTQSPSSLSASLGERVSLNCRASQEISGYLSWLQQKPD GTIKRLIYAASTLDSGVPKRFSGSRSGSDYSLTISSLESED FAAYYCLQYASYPLTFGAGTKLELK
mAb742	VH	63	QGQLQQSGAELVRPGASVTLSCKASGYTFNDYEMHWVKQTP VHGLEWIGAIDPETGGTAYNQKFKGKAILTADKSSSTAYME LRSLTSEDSAVYYCIRWGSTVFPYWGQGTLVTVS
	VL	64	DGVLTQTPLSLPVNIGDQASISCKSTKSLLNSDGFTYLDWY LQKPGQSPQLLIYLVSNRFSGVPDRFSGSGSGTDFTLKISR VEAEDLGVYYCFQSNYLPWTFGGGTKLEIK
mAb744	VH	65	QVQLQQSGAELVRPGTSVTLSCKASGYTFTDYEMHWMKQTP VHGLEWIGAIDPATGGTAYNQKFKGKAILTADKSSSTAYMD FRSLTSEDSAVYYCIRWGTTVFPYWGQGTLVTVS
	VL	66	DVVLTQTPLSLPVNIGDQASISCKSTKSLLNSDGFTYLDWY LQKPGQSPQLLIYLVSNRFSGVPDRFSGSGSGTDFTLKISR VEAEDLGVYYCFQSNYLPWTFGGGTKLEIK
mAb748	VH	67	EVQMQQSGAELVRPGASVKLSCTVSGFNIKDDYMHWVKQRP EQGLEWIGWIDPENGDTEYASKFQGKATITADTSSNTAYLQ LNSLTSEDTAVYYCTYFDYWGQGTTLTVSS
	VL	68	DVVMTQTPLTLSVTIGQPASISCKSSQSLLDSDGKTYLNWL LQRPGQSPKRLIYLVSKLDSGVPDRFTGSGSGTDFTLKISR VEAEDLGVYYCWQGSHFPQTFGGGTKLEIK
mAb749	VH	69	EVQLQQSGAELVRPGASVKVSCTASDFNIKDDYVHWVKQRP EQGLEWIGWIDPENGDTEYASKFQGKATITADTSSNTAYLQ LSSLTSEDTAVYFCSTWDAEENYWGQGTTLSVSS
	VL	70	DIVLTQAAPSVPVTPGESVSISCRSSKSLLHSNGNTYLYWF LQRPGQSPQVLIYRMSNLASGVPVRFSGSGSGTAFTLRISR VEAEDVGVYYCMQHLEYPFTFGSGTKLEIK
mAb750	VH	71	EVQLQQSGAELVRPGASVKLSCTPSGLNIKDDYIHWVKQRP

			EQGLEWIGWIDPENGDTEYASKFQGKATITADTSSNTAYLQ LSSLTSEDSAVYYCCTADYRNWYWGQGTTLTVSS
	VL	68	DVVMTQTPLTLSVTIGQPASISCKSSQSLLDSDGKTYLNWL LQRPGQSPKRLIYLVSKLDSGVPDRFTGSGSGTDFTLKISR VEAEDLGVYYCWQGSHFPQTFGGGTKLEIK

【0168】

實例9：鼠類抗LAG-3抗體mAb747之人類化

基於抗原結合活性、食蟹獼猴LAG-3蛋白交叉反應、功能活性及親和力，選擇mAb747用於人類化。

【0169】

實例9.1：mAb747之人類化

抗LAG-3 mAb747可變區基因用於產生人類化mAb。在此過程之第一步驟中，將mAb747之VH及VK之胺基酸序列(SEQ ID NO:60及SEQ ID NO:62)與人類Ig V-基因序列之可用資料庫進行比較，以尋找總體最佳匹配的人類生殖系Ig V-基因序列。另外，將VH或VL之構架4序列與J-區資料庫進行比較，以尋找與鼠類VH及VL區分別具有最高同源性之人類構架。對於輕鏈，最接近的人類V-基因匹配為A1基因；且對於重鏈，最接近的人類匹配為VH1-f基因。隨後，設計人類化可變域序列，其中將mAb747輕鏈之CDR-L1、CDR-L2及CDR-L3移植至A1基因之構架序列上，其中JK4構架4序列在CDR-L3之後；且將mAb747重鏈之CDR-H1、CDR-H2及CDR-H3序列移植至VH1-f之構架序列上，其中JH1構架4序列在CDR-H3之後。隨後產生mAb747之3維Fv模型，以測定是否存在其中小鼠胺基酸對於支持環結構或VH/VL界面而言關鍵的任何構架位置。人類化序列中之此類殘基應在相同位置處回復突變成小鼠殘基以保留親和力/活性。指示針對mAb747 VH及VL之若干所需回復突變，且構築三種替代性VH及VL設計，如下表24中所示。(回復突變的構架胺基酸殘基由雙下

劃線指示；來自初始親本抗體之鼠類CDR為加底線的。)

表24：mAb747-回復突變成鼠類殘基之人類化VH/VL設計

人類化VH/VL標識符	SEQ ID NO.	胺基酸序列 12345678901234567890123456789012345678901234567890
mAb747 VH.2A	72	EVQLVQSGAEVKKPGASVKVSCKASDFNIKDDYMHWVRQAP GQGLEWIGWIVPENGNTEYASKFQGRVTITADTSINTAYME LSRLRSDDTAVYYCTVYGDY----WGQGTTVTVSS
mAb747 VH.2B	73	EVQLVQSGAEVKKPGASVKVSCKASDFNIKDDYMHWVRQAP GQGLEWIGWIVPENGNTEYASKFQGKATITADTSINTAYME LSRLRSDDTAVYYCTVYGDY----WGQGTTVTVSS
mAb747 VH.1G	74	EVQLVQSGAEVKKPGATVKISCKASDFNIKDDYMHWVQQAP GKGLEWIGWIVPENGNTEYASKFQGRVTITADTSTNTAYME LSSLRSEDTAVYYCTVYGDY----WGQGTTVTVSS
mAb747 VK.1E	75	DIQMTQSPSSLSASVGDRVTINCRASQEISGYLSWLQQKPG KTIKRLIYAASTLDSGVPSRFSGSRSGSDYTLTISSLQPED FATYYCLQYASYPLTFGGGTKVEIK
mAb747 VK.2A	76	DIQMTQSPSSLSASVGDRVTINCRASQEISGYLSWLQQKPE KTIKRLIYAASTLDSGVPSRFSGSRSGSDYTLTISSLQPED FATYYCLQYASYPLTFGGGTKVEIK
mAb747 VK.2B	77	DIQMTQSPSSLSASVGDRVTINCRASQEISGYLSWLQQKPE GTIKRLIYAASTLDSGVPSRFSGSRSGSDYTLTISSLQPED FATYYCLQYASYPLTFGGGTKVEIK

【0170】以合成方式產生人類化VH及VK基因，且隨後分別選殖至含有人類IgG1及人類κ恆定域之載體中。人類VH與人類VK之配對產生9種人類化抗LAG-3抗體，稱為HumAb747-34至-42 (表25)。亦產生具有親本小鼠VH/VL及人類恆定序列之嵌合抗體(mAb747c)作為親和力比較之陽性對照。

表25：人類化mAb747抗LAG-3抗體之生產清單

抗體標識符	重鏈中之VH區	輕鏈κ鏈中之VL區
HumAb747-34	mAb747 VH.1G	mAb747 VK.1E
HumAb747-35	mAb747 VH.1G	mAb747 VK.2A
HumAb747-36	mAb747 VH.1G	mAb747 VK.2B
HumAb747-37	mAb747 VH.2A	mAb747 VK.1E
HumAb747-38	mAb747 VH.2A	mAb747 VK.2A
HumAb747-39	mAb747 VH.2A	mAb747 VK.2B
HumAb747-40	mAb747 VH.2B	mAb747 VK.1E
HumAb747-41	mAb747 VH.2B	mAb747 VK.2A
HumAb747-42	mAb747 VH.2B	mAb747 VK.2B

【0171】根據解離速率常數(k_{off})，對所有9種人類化抗體(表25)及具有親本鼠類VH與VL域之嵌合抗體(mAb747c)進行排名。簡言之，藉由

Octet® RED96生物層干涉法(Pall FortéBio LLC)，對抗體進行親和力及結合動力學表徵。在100 nM濃度下，抗體經抗HIgG Fc捕捉(AHC)生物感測器(Pall)捕捉30秒。隨後，將感測器浸漬至操作緩衝液(1X pH7.2 PBS，0.05% Tween 20，0.1% BSA)中60秒，以檢查基線。藉由將感測器浸漬至單一濃度之重組人類LAG-3-his蛋白(Novoprotein)中，來量測結合。在將感測器浸漬至操作緩衝液中1200秒之後，解離。使用FortéBio資料分析軟體(Pall)，將締合曲線及解離曲線擬合於1:1朗繆爾結合模型。結果顯示於表26中。

表26：人類化抗LAG-3抗體之解離速率排名

抗體	解離速率(k_{off}) (1/s)
mAb747c	3.77×10^{-4}
HumAb747-42	8.30×10^{-4}
HumAb747-39	1.14×10^{-3}

【0172】 HumAb747-42顯示其解離速率常數僅比具有親本可變域之嵌合對照的高2.2倍。

【0173】

實例10：PD-1/LAG-3串聯Fab免疫球蛋白(FIT-Ig)之產生

構築識別人類PD-1及人類LAG-3兩者之雙特異性串聯Fab免疫球蛋白結合蛋白。

【0174】 對於以下表中所描述之各FIT-Ig構築體，顯示在三組分多肽鏈中之每一者之表現載體中使用的信號序列。在以下所描述之FIT-Ig蛋白之產生中使用MDMRVPAQLLGLLLLWFPGSRC (SEQ ID NO:79)或MEFGLSWLFLVAILKGVQC (SEQ ID NO:84)，但許多替代性信號肽將為熟習此項技術者已知的且亦可進行使用。應理解，此類信號序列將在表現宿主細胞分泌多肽期間裂解，且因此信號序列不為最終FIT-Ig結合蛋白

之一部分。

【0175】

實例10.1：FIT107-1-2a

使用來自親本抗體mAb709 (鼠類抗PD-1，參見表4，見上文)及mAb746 (鼠類抗LAG-3，參見表23，見上文)之免疫球蛋白域之編碼序列，構築PD-1/LAG-3 FIT-Ig，稱為FIT107-1-2a。FIT-Ig FIT107-1-2a為包含三組分多肽鏈之六聚體：

多肽鏈1號具有域式：mAb709之VL-CL直接與mAb746之VH-CH1融合，該VH-CH1直接與突變人類恆定IgG1 (參見表6，見上文)之鉸鏈-CH2-CH3融合；

多肽鏈2號具有域式：mAb709之VH-CH1；及

多肽鏈3號具有域式：mAb746之輕鏈(VL-CL)。

【0176】 三條所表現FIT107-1-2a多肽鏈之胺基酸序列顯示於下表27中。

表27：FIT107-1-2a組分鏈之胺基酸序列

多肽	SEQ ID NO:	胺基酸序列 12345678901234567890123456789012345678901234567890
FIT107-1-2a FIT-Ig多肽鏈1號	78	MDMRVPAQLLGLLLLWFPGSRC**DIVMTQSHKFMSTSVGDS** **VTITCKASQDVNTVVAWYQQKPGQSLKVLISWASTRHTGV** **PARFTGSGSGTDYTLTISSVQAEDLALYYCQQHYTTPYTF** **GGGTQLEIK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC**EVQL** **QQSGAELVRPGASVKLSCTASDFNIKDDYMHWVKQRPEQG** **LDWIGWIVPENGNTEYASKFQGKATITADTSSNTAYLQLS** **SLTSEDTAVYYCTVYGDYWGQGTTLTVSS**ASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
mAb之VL-CL 鼠類mAb709 (VL為加底線的)	80	DIVMTQSHKFMSTSVGDSVTITCKASQDVNTVVAWYQQKP GQSLKVLISWASTRHTGVPARFTGSGSGTDYTLTISSVQA EDLALYYCQQHYTTPYTFGGGTQLEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
mAb之VH-CH1 鼠類mAb746 (VH為加底線的)	81	EVQLQQSGAELVRPGASVKLSCTASDFNIKDDYMHWVKQR PEQGLDWIGWIVPENGNTEYASKFQGKATITADTSSNTAY LQLSSLTSEDTAVYYCTVYGDYWGQGTTLTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSC
人類IgG1之鉸鏈- CH2-CH3	82	DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK
FIT107-1-2a FIT-Ig多肽鏈2號	83	MEFGLSWLFLVAILKGVQC**EVKLVESGGGLVKPGGSLKLS CAASGFTFSFYTMSWVRQTPEKRLEWVATISGGGRDTYYP DSVKGRFTISRDNAKNTLYLHMSSLRSEDTALYYCAGQGG NYLFAYWGQGTLVTVSA**ASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
信號序列	84	MEFGLSWLFLVAILKGVQC
鼠類mAb709之 VH-CH1 (VH為加底線的)	85	EVKLVESGGGLVKPGGSLKLSCAASGFTFSFYTMSWVRQT PEKRLEWVATISGGGRDTYYPDSVKGRFTISRDNAKNTLY LHMSSLRSEDTALYYCAGQGGNYLFAYWGQGTLVTVSAAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKKVEPKSC
FIT107-1-2a FIT-Ig多肽鏈3號	86	MDMRVPAQLLGLLLLWFPGSRC**DIQMTQSPSSLSASLGER VSLNCRASQEISGYLSWLQQKSDGTIKRLIYAASTLDSGV PKRFSGSRSGSDYSLTISSLESEDFADYYCLQYASYPLTF GAGTKLELK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
鼠類mAb746之 VL-CL (VL為加底線的)	87	DIQMTQSPSSLSASLGERVSLNCRASQEISGYLSWLQQKS DGTIKRLIYAASTLDSGVPKRFSGSRSGSDYSLTISSLES EDFADYYCLQYASYPLTFGAGTKLELKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC

【0177】

實例10.2：FIT107-1-2b

構築識別人類PD-1及人類LAG-3兩者之另一雙特異性串聯Fab免疫

球蛋白結合蛋白。此PD-1/LAG-3 FIT-Ig稱為FIT107-1-2b。FIT107-1-2b結合蛋白之構築使用來自親本鼠類抗體mAb709及mAb746之免疫球蛋白域之編碼序列，但在此FIT-Ig構築體中，LAG-3結合域係在N端(外部)位置，且PD-1結合域係在內部位置LAG-3結合區之VL-CL域的融合C端。FIT-Ig FIT107-1-2b為包含三組分多肽鏈之六聚體：

多肽鏈1號具有域式：mAb746之VL-CL直接與mAb709之VH-CH1融合，該VH-CH1直接與突變人類恆定IgG1 (參見表6，見上文)之鉸鏈-CH2-CH3融合；

多肽鏈2號具有域式：mAb746之VH-CH1；及

多肽鏈3號具有域式：mAb709之輕鏈(VL-CL)。

【0178】 三條所表現FIT107-1-2b多肽鏈之胺基酸序列顯示於下表28中：

表28：FIT107-1-2b組分鏈之胺基酸序列

多肽	SEQ ID NO:	胺基酸序列 1234567890123456789012345678901234567890
FIT107-1-2b FIT-Ig多肽鏈1號	88	MDMRVPAQLLGLLLLWFPGSRC**DIQMTQSPSSLSASLGER VSLNCRASQEISGYLSWLQQKSDGTIKRLIYAASTLDSGV PKRFSGSRSGSDYSLTISSLESEDFADYYCLQYASYPLTF GAGTKLELK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC**EVKL VESGGGLVKPGGSLKLSCAASGFTFSFYTMSWVRQTPEKR LEWVATISGGGRDTYYPDSVKGRFTISRDNAKNTLYLHMS SLRSEDTALYYCAGQGGNYLFAYWGQGTLVTVSA**ASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
鼠類mAb746之VL-CL	89	DIQMTQSPSSLSASLGERVSLNCRASQEISGYLSWLQQKS DGTIKRLIYAASTLDSGVPKRFSGSRSGSDYSLTISSLES EDFADYYCLQYASYPLTFGAGTKLELKRTVAAPSVFIFPP

(VL為加底線的)		SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
鼠類mAb709之 VH-CH1 (VH為加底線的)	90	EVKLVESGGGLVKPGGSLKLSCAASGFTFSFYTMSWVRQT PEKRLEWVATISGGGRDTYYPDSVKGRFTISRDNAKNTLY LHMSSLRSEDTALYYCAGQGGNYLFAYWGQGTLVTVSAAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKKVEPKSC
人類IgG1之鉸鏈-CH2-CH3	82	DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK
FIT107-1-2b FIT-Ig多肽鏈2號	91	MEFGLSWLFLVAILKGVQC**EVQLQQSGAELVRPGASVKLS CTASDFNIKDDYMHWVKQRPEQGLDWIGWIVPENGNTEYA SKFQGKATITADTSSNTAYLQLSSLTSEDTAVYYCTVYGD YWGQGTTLTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
信號序列	84	MEFGLSWLFLVAILKGVQC
鼠類mAb746之 VH-CH1 (VH為加底線的)	92	EVQLQQSGAELVRPGASVKLSCTASDFNIKDDYMHWVKQR PEQGLDWIGWIVPENGNTEYASKFQGKATITADTSSNTAY LQLSSLTSEDTAVYYCTVYGDYWGQGTTLTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSC
FIT107-1-2b FIT-Ig多肽鏈3號	93	MDMRVPAQLLGLLLLWFPGSRC**DIVMTQSHKFMSTSVGDS VTITCKASQDVNTVVAWYQQKPGQSLKVLISWASTRHTGV PARFTGSGSGTDYTLTISSVQAEDLALYYCQQHYTTPYTF GGGTQLEIK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
鼠類mAb709之 VL-CL (VL為加底線的)	94	DIVMTQSHKFMSTSVGDSVTITCKASQDVNTVVAWYQQKP GQSLKVLISWASTRHTGVPARFTGSGSGTDYTLTISSVQA EDLALYYCQQHYTTPYTFGGGTQLEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC

【0179】

實例10.3：FIT107-1-5a

使用來自親本人類化抗體HumAb709-8 (抗PD-1，SEQ ID NO:21及SEQ ID NO:25)及HumAb747-42 (SEQ ID NO:73及SEQ ID NO:77)之免疫球蛋白域之編碼序列，構築PD-1/LAG-3 FIT-Ig，稱為FIT107-1-5a。

FIT-Ig FIT107-1-5a為包含三組分多肽鏈之六聚體：

多肽鏈1號具有域式：HumAb709-8之VL-CL直接與HumAb747-42之VH-CH1融合，該VH-CH1直接與突變人類恆定IgG1 (參見表6，見上文)之鉸鏈-CH2-CH3融合；

多肽鏈2號具有域式：HumAb709-8之VH-CH1；及

多肽鏈3號具有域式：HumAb747-42之輕鏈(VL-CL)。

【0180】 三條所表現FIT107-1-5a多肽鏈之胺基酸序列顯示於下表29中：

表29：FIT107-1-5a組分鏈之胺基酸序列

多肽	SEQ ID NO:	胺基酸序列 12345678901234567890123456789012345678901234567890
FIT107-1-5a FIT-Ig多肽鏈1號	95	MDMRVPAQLLGLLLLWFPGSRC**DIVMTQSPSSLSASVGDR VTITCKASQDVNTVVAWYQQKPGKAPKVLISWASTRHTGV PSRFSGSGSGTDYTLTISSLQPEDFATYYCQQHYTTPYTF GGGTKVEIK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC**EVQL VQSGAEVKKPGASVKVSCKASDFNIKDDYMHWVRQAPGQG LEWIGWIVPENGNTEYASKFQGKATITADTSINTAYMELS RLRSDDTAVYYCTVYGDYWGQGTTVTVSS**ASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
mAb HumAb709-8之VL-CL (VL為加底線的)	96	DIVMTQSPSSLSASVGDRVTITCKASQDVNTVVAWYQQKP GKAPKVLISWASTRHTGVPSRFSGSGSGTDYTLTISSLQP EDFATYYCQQHYTTPYTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
mAb HumAb747-42之VH-CH1 (VH為加底線的)	97	EVQLVQSGAEVKKPGASVKVSCKASDFNIKDDYMHWVRQA PGQGLEWIGWIVPENGNTEYASKFQGKATITADTSINTAY MELSRLRSDDTAVYYCTVYGDYWGQGTTVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSC
人類IgG1之鉸鏈-	82	DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVT

CH2-CH3		CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK
FIT107-1-5a FIT-Ig多肽鏈2號	98	MEFGLSWLFLVAILKGVQC**EVQLVESGGGLVQPGGSLRLS CAASGFTFSFYTMSWVRQAPGKGLEWVATISGGGRDTYYP DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAGQGG NYLFAYWGQGTLVTVSS**ASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
信號序列	84	MEFGLSWLFLVAILKGVQC
HumAb709-8之 VH-CH1 (VH為加底線的)	99	EVQLVESGGGLVQPGGSLRLSCAASGFTFSFYTMSWVRQA PGKGLEWVATISGGGRDTYYPDSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCAGQGGNYLFAYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKKVEPKSC
FIT107-1-5a FIT-Ig多肽鏈3號	100	MDMRVPAQLLGLLLLWFPGSRC**DIQMTQSPSSLSASVGDR VTINCRASQEISGYLSWLQQKPEGTIKRLIYAASTLDSGV PSRFSGSRSGSDYTLTISSLQPEDFATYYCLQYASYPLTF GGGTKVEIK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
HumAb747-42之 VL-CL (VL為加底線的)	101	DIQMTQSPSSLSASVGDRVTINCRASQEISGYLSWLQQKP EGTIKRLIYAASTLDSGVPSRFSGSRSGSDYTLTISSLQP EDFATYYCLQYASYPLTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC

【0181】

實例10.4：FIT107-1-5b

構築識別人類PD-1及人類LAG-3兩者之另一雙特異性串聯Fab免疫球蛋白結合蛋白。此PD-1/LAG-3 FIT-Ig稱為FIT107-1-5b。FIT107-1-5b結合蛋白之構築使用來自親本人類化抗體HumAb709-8及HumAb747-42之免疫球蛋白域之編碼序列，但在此FIT-Ig構築體中，LAG-3結合域係在N端(外部)位置，且PD-1結合域係在內部位置，N端LAG-3結合區之VL-CL域的融合C端。FIT-Ig FIT107-1-5b為包含三組分多肽鏈之六聚體：

多肽鏈1號具有域式：HumAb747-42之VL-CL直接與HumAb709-8之

VH-CH1融合，該VH-CH1直接與突變人類恆定IgG1 (參見表6，見上文)之鉸鏈-CH2-CH3融合；

多肽鏈2號具有域式：mAb747-42之VH-CH1；及

多肽鏈3號具有域式：HumAb709-8之輕鏈(VL-CL)。

【0182】 三條所表現FIT107-1-5b多肽鏈之胺基酸序列顯示於下表30中：

表30：FIT107-1-5b組分鏈之胺基酸序列

多肽	SEQ ID NO:	胺基酸序列 12345678901234567890123456789012345678901234567890
FIT107-1-5b FIT-Ig多肽鏈1號	102	MDMRVPAQLLGLLLLWFPGSRC**DIQMTQSPSSLSASVGDR** **VTINCRASQEISGYLSWLQQKPEGTIKRLIYAASTLDSGV** **PSRFSGSRSGSDYTLTISSLQPEDFATYYCLQYASYPLTF** **GGGTKVEIK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC**EVQL** **VESGGGLVQPGGSLRLSCAASGFTFSFYTMSWVRQAPGKG** **LEWVATISGGGRDTYYPDSVKGRFTISRDNAKNSLYLQMN** **SLRAEDTAVYYCAGQGGNYLFAYWGQGTLVTVSS**ASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
HumAb747-42之 VL-CL (VL為加底線的)	103	DIQMTQSPSSLSASVGDRVTINCRASQEISGYLSWLQQKP EGTIKRLIYAASTLDSGVPSRFSGSRSGSDYTLTISSLQP EDFATYYCLQYASYPLTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
HumAb709-8之 VH-CH1 (VH為加底線的)	104	EVQLVESGGGLVQPGGSLRLSCAASGFTFSFYTMSWVRQA PGKGLEWVATISGGGRDTYYPDSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCAGQGGNYLFAYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKKVEPKSC
人類IgG1之鉸鏈- CH2-CH3	82	DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG

		NVFSCSVMHEALHNHYTQKSLSLSPGK
FIT107-1-5b FIT-Ig多肽鏈2號	105	MEFGLSWLFLVAILKGVQC**EVQLVQSGAEVKKPGASVKVS CKASDFNIKDDYMHWVRQAPGQGLEWIGWIVPENGNTEYA SKFQGKATITADTSINTAYMELSRLRSDDTAVYYCTVYGD YWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
信號序列	84	MEFGLSWLFLVAILKGVQC
HumAb747-42之 VH-CH1 (VH為加底線的)	106	EVQLVQSGAEVKKPGASVKVSCKASDFNIKDDYMHWVRQA PGQGLEWIGWIVPENGNTEYASKFQGKATITADTSINTAY MELSRLRSDDTAVYYCTVYGDYWGQGTTVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSC
FIT107-1-5b FIT-Ig多肽鏈3號	107	MDMRVPAQLLGLLLLWFPGSRC**DIVMTQSPSSLSASVGDR VTITCKASQDVNTVVAWYQQKPGKAPKVLISWASTRHTGV PSRFSGSGSGTDYTLTISSLQPEDFATYYCQQHYTTPYTF GGGTKVEIK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
mAb HuMAb709-8 之VL-CL (VL為加底線的)	108	DIVMTQSPSSLSASVGDRVTITCKASQDVNTVVAWYQQKP GKAPKVLISWASTRHTGVPSRFSGSGSGTDYTLTISSLQP EDFATYYCQQHYTTPYTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC

【0183】

實例10.5：FIT-Ig之表現及純化

四種PD-1/LAG-3 FIT-Ig構築體FIT107-1-2a、FIT107-1-2b、FIT107-1-5a及FIT107-1-5b為一種類型之雙特異性多價結合蛋白，被稱為一般在WO 2015/103072及WO 2017/136820中描述的串聯Fab免疫球蛋白(或FIT-Ig)。藉由在經所有三條鏈之表現載體轉染之哺乳動物宿主細胞中共表現三組分多肽鏈，產生結合蛋白。結合蛋白之設計需要長多肽鏈(鏈1號)，以與短多肽鏈(鏈2號及3號)兩者配對，形成功能串聯Fab部分，且亦設計長鏈以經由Fc區(鉸鏈-CH2-CH3)進行二聚合，使得形成呈現四個完整Fab結合位點的六鏈結合蛋白。在結合蛋白FIT107-1-2a及FIT107-1-5a中，N端或「外部」Fab結合位點結合PD-1，且相鄰「內部」Fab結合位

點結合LAG-3。藉由視具體情況而定可分別將VL-CL_{mAb709}或VL-$CL_{HumAb709-8}$直接融合在其VH-$CH1_{mAb746}$或VH-$CH1_{HumAb747-42}$之N端的C端，FIT107-1-2a及FIT107-1-5a之外部Fab片段(抗PD-1)，僅經由長鏈(鏈1號)，與內部Fab片段(抗LAG-3)接合，而不使用連接免疫球蛋白域的連接子。類似地，藉由視具體情況而定可分別將VL-CL_{mAb746}或VL-$CL_{mAb747-42}$直接融合在其VH-$CH1_{mAb709}$或VH-$CH1_{mAb709-8}$之N端的C端，FIT107-1-2b及FIT107-1-5b之外部Fab片段(抗LAG-3)，僅經由長鏈(鏈1號)，與內部Fab片段(抗PD-1)接合，而不使用連接免疫球蛋白域的連接子。

【0184】使用聚乙烯亞胺(PEI)作為轉染劑，在人胎腎293E細胞中短暫共表現編碼各FIT-Ig (FIT107-1-2a、FIT107-1-2b、FIT107-1-5a及FIT107-1-5b)之多肽鏈1號、2號及3號的表現載體。簡言之，將FreeStyle™ 293表現培養基中之DNA與PEI混合，其中DNA與PEI之最終濃度比率為1:2，在室溫下培育15-20分鐘，且隨後以60 μg DNA/120 ml培養物，將其添加至HEK293E細胞(1.0-1.2 × 10^6個/毫升，細胞生存力>95%)。在振盪器中培養6-24小時之後，在以125 rpm/min振盪之情況下，在37℃、8% CO_2下，以5%之最終濃度，向經轉染細胞中添加蛋白腖。在第6-第7天，藉由離心及過濾收穫上清液，且根據製造商之說明書，使用蛋白A層析(Pierce，Rockford，IL)來純化FIT-Ig蛋白。

【0185】對於表現FIT107-1-2a、FIT107-1-2b、FIT107-1-5a及FIT107-1-5b，使用1:3:3之鏈1號:鏈2號:鏈3號莫耳比，轉染編碼鏈1號、2號及3號之表現的DNA。此係設計用於使得待表現之短鏈2號及3號相對於長鏈(鏈1號)更呈比例，此轉而將降低長鏈(鏈1號)上不與對應輕鏈配對，

且因此將不能形成功能Fab片段的VL-CL及VH-CH1區段的存在。藉由蛋白A層析，來純化FIT-Ig蛋白表現產物。藉由尺寸排阻層析(SEC)，來分析純化FIT-Ig之組成及純度。將含純化FIT-Ig之PBS施加在TSKgel SuperSW3000, 300 × 4.6 mm管柱(TOSOH)上。使用在280 nm及214 nm下之UV偵測，HPLC儀器Model U3000 (DIONEX)用於進行SEC。參見下表31。

表31：PD-1/LAG-3 FIT-Ig結合蛋白之表現及SEC分析

FIT-Ig蛋白	DNA莫耳比：鏈1號:2號:3號	表現量 (mg/L)	藉由SEC之峰單體部分 %
FIT107-1-2a	1:3:3	5.40	>90%
FIT107-1-2b	1:3:3	5.04	>80%
FIT107-1-5a	1:3:3	7.95	>80%
FIT107-1-5b	1:3:3	8.52	>80%

【0186】 FIT107-1-2b、-5a及-5b之較低單體部分含量指示一些可能聚集。

【0187】

實例11：FIT-Ig針對目標抗原之結合親和力

藉由Biacore SPR量測，來測定FIT-Ig與PD-1及LAG-3目標結合之動力學。FIT107-1-2a及FIT107-1-2b針對目標抗原PDL-1及LAG-3兩者之結合親和力顯示於下表32中。

表32：FIT107-1-2a及FIT107-1-2b之結合親和力

固定在感測器晶片上之目標	分析物	分析物特異性	k_{on} (1/Ms)	k_{off} (1/s)	K_D (M)
HuPD-1 ECD/Fc 及 HuLAG-3 ECD/Fc	FIT107-1-2a	外部：PD-1 內部：LAG-3	6.97×10^{4}	1.17×10^{-5}	1.68×10^{-10}
	FIT107-1-2b	外部：LAG-3 內部：PD-1	1.68×10^{5}	8.76×10^{-5}	5.23×10^{-10}
	mAb709c	PD-1	2.88×10^{5}	9.72×10^{-6}	3.37×10^{-11}
	mAb746c	LAG-3	9.51×10^{3}	1.54×10^{-4}	1.62×10^{-8}
	mAb709c + mAb746c	PD-1及LAG-3	2.82×10^{5}	2.08×10^{-5}	7.35×10^{-11}
HuPD-1 ECD/Fc	mAb709c	PD-1	2.52×10^{5}	8.82×10^{-6}	3.50×10^{-11}

HuLAG-3 ECD/Fc	mAb746c	LAG-3	5.58×10^{3}	1.81×10^{-4}	3.25×10^{-8}

【0188】

實例12：FIT-Ig特異性及功能測定

在PBMC活化分析中，使用葡萄球菌(Staphylococcal)腸毒素B(SEB)作為超級抗原(參見實例7.8)，測試FIT107-1-2a結合蛋白之抗PD1與抗LAG-3雙特異性及生物活性。簡言之，自健康供體分離PBMC，隨後以50微升/孔，2×10^{5}個細胞/孔，將其接種至96孔盤中。將測試結合蛋白(亦即FIT107-1-2a，市售抗PD-1及抗LAG-3單株抗體之組合，或單株抗PD-1抗體)添加至培養盤中，且在37℃下，與PBMC一起培育30 min。添加SEB溶液至10 ng/ml之最終濃度。培育培養盤96小時，隨後採集100 µl細胞培養物上清液，且使用ELISA IL-2偵測套組(R&D Systems；目錄號DY202)來量測IL-2產量。結果顯示於圖7中。與抗PD-1抗體單獨或抗LAG-3與抗PD-1抗體之混合物相比，FIT107-1-2a雙特異性FIT-Ig蛋白能夠增強T細胞活化，如由IL-2產量所指出。

【0189】另外，以與實例3中所描述的相似之方式進行混合淋巴球反應(MLR)分析，以進一步驗證FIT107-1-2a之抗PD-1及抗LAG-3功能。混合淋巴球反應為當混合在一起時發生在兩個同種異體淋巴球群體之間的離體細胞免疫反應。回應於兩個細胞群體(其被稱為應答細胞及刺激細胞)之間的主要組織相容抗原(MHC I類及II類)差異，同種異體淋巴球經歷母細胞轉化、DNA合成及細胞增殖。在用於測試FIT107-1-2a之MLR中，在第1天，自健康供體純化PBMC，且分離CD14+單核球。將單核球接種至6孔盤中，且在RPMI 1640培養基加10% FBS中，用35 ng/ml IL-4 (R&D Systems)及50 ng/ml GM-CSF (R&D Systems)處理。在4天之後，更換培養基。在第7天，採集分化為不成熟樹突狀細胞之單核球，且在成熟化培

養基中用20 ng/ml TNF-α (R&D Systems)、50 μg/ml聚I:C (Sigma)、35 ng/ml IL-4及50 ng/ml GM-CSF另外處理兩天。對於MLR共培養分析，不含血清之X-VIVO™ 15培養基用於避免抗體效力中之血清干擾。對96孔U形底培養盤以1 × 10^5個細胞/孔接種同種異體CD4+ T細胞(應答細胞)，且用測試結合蛋白(亦即FIT107-1-2a，市售抗PD-1與抗LAG-3單株抗體之組合，或單株抗PD-1抗體)預處理30 min。隨後，以1 × 10^4個細胞/孔，將成熟樹突狀細胞(刺激細胞)接種至各孔中，且與應答細胞一起共培養五天，此時採集100 μl上清液且藉由ELISA來量測IFN-γ產量。結果顯示於圖8中。與抗PD-1與抗LAG-3抗體之組合或抗PD-1抗體單獨之16.84 nM的EC50值相比，FIT-Ig雙特異性結合蛋白顯示0.5084 nM的EC50。因此，在MLR中，在比單一抗體或抗體組合低30倍之濃度下，FIT-Ig結合蛋白增強IFN-γ (γ干擾素)產量。

【0190】

實例13：mAb747之新批次人類化

抗LAG-3 mAb747可變區基因用於產生其他抗LAG-3人類化mAb。在此過程之第一步驟中，將mAb747之VH及VK之胺基酸序列(SEQ ID NO:60及SEQ ID NO:62)與人類Ig V-基因序列之可用資料庫進行比較，以尋找最佳匹配的人類生殖系Ig V-基因序列。另外，將VH或VL之構架4 (FW4)序列與J-區資料庫進行比較，以尋找與鼠類VH及VL區分別具有最高同源性之人類構架。對於輕鏈，最佳的人類V-基因匹配為A30基因；且對於重鏈，最佳的人類匹配為VH1-69-2基因。隨後，設計人類化可變域序列，其中將mAb747輕鏈之CDR-L1、CDR-L2及CDR-L3移植至A30基因之構架序列上，其中JK4構架4序列在CDR-L3之後；且將mAb747重鏈之CDR-H1、CDR-H2及CDR-H3序列移植至VH1-69-2之構架序列上，其

中JH6構架4序列在CDR-H3之後。隨後產生mAb747之3維Fv模型，以測定是否存在其中小鼠胺基酸對於支持環結構或VH/VL界面而言關鍵的任何構架位置。人類化序列中之此類殘基應在相同位置處回復突變成小鼠殘基以保留親和力/活性。指示針對mAb747 VH及VL之若干所需回復突變，且構築三種替代性VH及VL設計，如下表33中所示。(回復突變的構架胺基酸殘基由雙下劃線指示；CDR根據Kabat編號系統加底線，不同之處在於VH CDR1用ABM編號系統進行定義。)

表33：mAb747-回復突變成鼠類殘基之人類化VH/VL設計

人類化VH/VL標識符	SEQ ID NO.	胺基酸序列 12345678901234567890123456789012345678901234567890
huEpi001-VHv1	109	EVQLVQSGAEVKKPGATVKISCKVSDFNIKDDYMHWVQQAP GKGLEWIGWIVPENGNTEYASKFQGRVTITADTSTDTAYLE LSSLRSEDTAVYYCTVYGDYWGQGTTVTVSS
huEpi001-VHv2	110	EVQLVQSGAEVKKPGATVKLSCKASDFNIKDDYMHWVQQAP GKGLEWIGWIVPENGNTEYASKFQGRVTITADTSTDTAYLE LSSLRSEDTAVYYCTVYGDYWGQGTTVTVSS
huEpi001-VHv3	111	EVQLVQSGAEVKKPGATVKLSCTASDFNIKDDYMHWVQQAP GKGLEWIGWIVPENGNTEYASKFQGRVTITADTSTDTAYLE LSSLRSEDTAVYYCTVYGDYWGQGTTVTVSS
huEpi001-VHv4	112	EVQLVQSGAEVKKPGATVKLSCTASDFNIKDDYMHWVKQAP GKGLEWIGWIVPENGNTEYASKFQGRATITADTSTNTAYLE LSSLRSEDTAVYYCTVYGDYWGQGTTVTVSS
huEpi001-VHv5	113	EVQLVQSGAEVKKPGATVKLSCTASDFNIKDDYMHWVKQRP EQGLEWIGWIVPENGNTEYASKFQGRATITADTSTNTAYLE LSSLRSEDTAVYYCTVYGDYWGQGTTVTVSS
huEpi001-VHv6	114	EVQLVQSGAEVKKPGATVKLSCTASDFNIKDDYMHWVKQRP EQGLDWIGWIVPENGNTEYASKFQGKATITADTSTNTAYLE LSSLRSEDTAVYYCTVYGDYWGQGTTVTVSS
huEpi001 VLv1	115	DIQMTQSPSSLSASVGDRVTITCRASQEISGYLSWLQQKPG KAIKSLIYAASTLDSGVPSRFSGSRSGTDFTLTISSLQPED FATYYCLQYASYPLTFGQGTKLEIK
huEpi001 VLv2	116	DIQMTQSPSSLSASVGDRVTITCRASQEISGYLSWLQQKPG KAIKRLIYAASTLDSGVPSRFSGSRSGTDFTLTISSLQPED FATYYCLQYASYPLTFGQGTKLEIK
huEpi001 VLv3	117	DIQMTQSPSSLSASVGDRVTITCRASQEISGYLSWLQQKPG GAIKRLIYAASTLDSGVPSRFSGSRSGSDYTLTISSLQPED FADYYCLQYASYPLTFGQGTKLELK
huEpi001 VLv4	118	DIQMTQSPSSLSASVGDRVTITCRASQEISGYLSWLQQKPG GAIKRLIYAASTLDSGVPSRFSGSRSGSDYTLTISSLEPED FADYYCLQYASYPLTFGQGTKLELK

【0191】 以合成方式產生人類化VH及VK基因，且隨後分別選殖至

含有人類IgG1及人類κ恆定域之載體中。人類VH與人類VK之配對產生9種人類化抗LAG-3抗體，稱為HumAb747-43至HumAb747-60 (表34)。亦使用具有上文所描述之親本小鼠VH/VL及人類恆定序列之嵌合抗體(mAb747c)作為親和力比較之陽性對照。

表34：人類化mAb747抗LAG-3抗體之生產清單

抗體標識符	重鏈中之VH區	輕鏈κ鏈中之VL區
HumAb747-43	huEpi001-VHv1	huEpi001 VLv1
HumAb747-44	huEpi001-VHv2	huEpi001 VLv1
HumAb747-45	huEpi001-VHv3	huEpi001 VLv1
HumAb747-46	huEpi001-VHv4	huEpi001 VLv1
HumAb747-47	huEpi001-VHv1	huEpi001 VLv2
HumAb747-48	huEpi001-VHv2	huEpi001 VLv2
HumAb747-49	huEpi001-VHv3	huEpi001 VLv2
HumAb747-50	huEpi001-VHv4	huEpi001 VLv2
HumAb747-51	huEpi001-VHv1	huEpi001 VLv3
HumAb747-52	huEpi001-VHv2	huEpi001 VLv3
HumAb747-53	huEpi001-VHv3	huEpi001 VLv3
HumAb747-54	huEpi001-VHv4	huEpi001 VLv3
HumAb747-55	huEpi001-VHv1	huEpi001 VLv4
HumAb747-56	huEpi001-VHv2	huEpi001 VLv4
HumAb747-57	huEpi001-VHv3	huEpi001 VLv4
HumAb747-58	huEpi001-VHv4	huEpi001 VLv4
HumAb747-59	huEpi001-VHv5	huEpi001 VLv3
HumAb747-60	huEpi001-VHv6	huEpi001 VLv3

【0192】 根據解離速率常數(k_{off})，對所有18種人類化抗體(表34)及具有親本鼠類VH與VL域之嵌合抗體(mAb747c)進行排名。簡言之，藉由Octet® RED96生物層干涉法(Pall FortéBio LLC)，對抗體進行親和力及結合動力學表徵。在100 nM濃度下，抗體經抗HIgG Fc捕捉(AHC)生物感測器(Pall)捕捉30秒。隨後，將感測器浸漬至操作緩衝液(1X pH7.2 PBS，0.05% Tween 20，0.1% BSA)中60秒，以檢查基線。藉由將感測器浸漬至單一濃度之重組人類LAG-3-his蛋白(Novoprotein)中，來量測結合。在將感測器浸漬至操作緩衝液中1200秒之後，解離。使用FortéBio資料分析軟體(Pall)，將締合曲線及解離曲線擬合於1:1朗繆爾結合模型。結

果顯示於表35中。在各測試組中，抗體之解離率能夠與mAb747c進行比較。藉由抗體之解離速率與其組之mAb747c之解離速率之比，計算解離速率比率，且全部一起進行比較。比率愈低，抗體之親和力愈高。

表35：人類化抗LAG-3抗體之解離速率排名

測試組	抗體	解離速率(k_{off}) (1/s)	與mAb747c之解離速率的解離速率比
1	HumAb747-43	9.25×10^{-3}	682%
	HumAb747-44	1.10×10^{-2}	809%
	HumAb747-45	1.08×10^{-2}	797%
	HumAb747-46	1.09×10^{-2}	801%
	HumAb747-47	1.44×10^{-2}	1062%
	HumAb747-48	8.03×10^{-3}	592%
	mAb747c	1.36×10^{-3}	100%
2	HumAb747-49	7.73×10^{-3}	575%
	HumAb747-50	7.19×10^{-3}	534%
	HumAb747-51	1.19×10^{-2}	888%
	HumAb747-52	4.36×10^{-3}	324%
	HumAb747-53	4.30×10^{-3}	319%
	HumAb747-54	4.23×10^{-3}	314%
	mAb747c	1.35×10^{-3}	100%
3	HumAb747-55	1.19×10^{-2}	972%
	HumAb747-56	4.31×10^{-3}	352%
	HumAb747-57	4.11×10^{-3}	335%
	HumAb747-58	4.05×10^{-3}	331%
	mAb747c	1.23×10^{-3}	100%
4	HumAb747-59	1.20×10^{-3}	226%
	HumAb747-60	8.10×10^{-4}	153%
	mAb747c	5.30×10^{-4}	100%

【0193】 HumAb747-60顯示其解離速率常數僅比具有親本可變域之嵌合對照高的1.5倍。

【0194】 為了進一步驗證人類PBMC中之抗LAG-3抗體功能，以上文實例7.8中描述之方式，使用超級抗原金黃色葡萄球菌腸毒素B (SEB)進行細菌毒素刺激分析。使用PerkinElmer IL-2偵測套組(PerkinElmer；目錄號TRF1221M)，來量測IL-2產量。藉由阻斷LAG-3信號路徑，HumAb747-60能夠增強SEB刺激的PBMC之IL-2分泌。結果顯示於圖9中。因此，證實HumAb747-60起作用，且選擇其用於進一步工程改造。

【0195】

實例14：HumAb747-60之親和力成熟

【0196】

實例14.1：親和力成熟文庫構築及篩選

儘管HumAb747-60顯示其解離速率常數僅比嵌合對照mAb747c之解離速率常數高1.5倍，但PBMC-SEB分析結果指示，HumAb747-60具有略微較弱的功能活性。為了進一步提高親和力，藉由基於HumAb747-39 (參見表24、25)之親和力成熟，對CDR殘基(ABM編號系統)進行最佳化。設計且構築兩個噬菌體庫。一個設計成突變CDR-L1、CDR-L3及CDR-H3 (ABM編號)，其中之每一者具有一個隨機突變殘基。另一個設計成突變CDR-L2、CDR-H1及CDR-H2 (ABM編號)，其中之每一者具有一個隨機突變殘基。

【0197】 使用報導於*Journal of Immunological Methods*, 201:35-55 (1997)中之方法，構築噬菌體呈現文庫。簡言之，用引入突變之簡併引子擴增VH-CH1及VL-CL，且隨後依序將其選殖至噬菌質體載體之兩個多選殖位點(MCS)中。隨後，將噬菌質體載體電轉化至TG1 (目錄號60502-1，Lucigen)中，分別產生顯示高序列多樣性之大致1.2×10^8個純系的文庫。用M13K07輔助噬菌體(目錄號N0315S)，以大致1:20比率(細胞:噬菌體)，修復文庫。用重組人類LAG-3蛋白進行噬菌體呈現文庫選擇，隨後進行洗滌步驟。亦在噬菌質體載體中構築HumAb747-39之Fab片段作為陽性對照。使用所選擇噬菌體來感染宿主細胞。藉由ELISA篩選來自單一純系之Fab上清液之結合能力。簡言之，藉由在30℃下與1 mM IPTG一起培養隔夜，來製備單一純系之Fab上清液。將含2 μg/ml人類LAG-3蛋白之100

μL磷酸鹽緩衝鹽水(PBS)直接塗覆在96孔盤之各孔中。連接HRP的抗c-myc抗體(目錄號Ab1261，Abcam)及TMB試劑用於偵測及發展ELISA信號，該等信號藉由讀板儀(SpectraMax® Plus 384吸光度讀板儀，Molecular Devices)在450 nm波長下讀出。

【0198】挑取篩選ELISA中之陽性純系用於定序。考慮到篩選ELISA中之序列冗餘及信號強度，選擇以下7個純系用於進一步評價。VH/VL序列顯示於表36中。(藉由親和力成熟鑑別之經突變胺基酸殘基由雙下劃線指示；CDR根據Kabat編號系統加底線。)

表36：具有親和力成熟突變之7種抗體之VH/VL胺基酸序列

親和力成熟純系	域	SEQ ID NO.	蛋白序列 12345678901234567890123456789012345678901234567890
B2-53	VH	119	EVQLVQSGAEVKKPGASVKVSCKASGFNIKDDYMHWVR QAPGQGLEWIGWIVPENGNTVYASKFQGRVTITADTSI NTAYMELSRLRSDDTAVYYCTVYGDYWGQGTTVTVSS
	VL	120	DIQMTQSPSSLSASVGDRVTINCRASQEISGYLSWLQQ KPEGTIKRLIYAASALDSGVPSRFSGSRSGSDYTLTIS SLQPEDFATYYCLQYASYPLTFGGGTKVEIK
B3-21	VH	121	EVQLVQSGAEVKKPGASVKVSCKASDFNIKDDYMHWVR QAPGQGLEWIGWIVPENGNTEYASKFQGRVTITADTSI NTAYMELSRLRSDDTAVYYCTVYGDVWGQGTTVTVSS
	VL	122	DIQMTQSPSSLSASVGDRVTINCRAMQEISGYLSWLQQ KPEGTIKRLIYAASTLDSGVPSRFSGSRSGSDYTLTIS SLQPEDFATYYCLQYAYYPLTFGGGTKVEIK
B3-43	VH	123	EVQLVQSGAEVKKPGASVKVSCKASGFNIKDDYMHWVC QAPGQGLEWIGWIVPENGNTEYASKFQGRVTITADTSI NTAYMELSRLRSDDTAVYYCTVYGDYWGQGTTVTVSS
	VL	124	DIQMTQSPSSLSASVGDRVTINCRASQEISGYLSWLQQ KPEGTIKRLIYAASHLDSGVPSRFSGSRSGSDYTLTIS SLQPEDFATYYCLQYASYPLTFGGGTKVEIK
B3-46	VH	125	EVQLVQSGAEVKKPGASVKVSCKASGFNIKDDYMHWVR QAPGQGLEWIGWIVPENGLTEYASKFQGRVTITADTSI NTAYMELSRLRSDDTAVYYCTVYGDYWGQGTTVTVSS
	VL	126	DIQMTQSPSSLSASVGDRVTINCRASQEISGYLSWLQQ KPEGTIKRLIYATSTLDSGVPSRFSGSRSGSDYTLTIS SLQPEDFATYYCLQYASYPLTFGGGTKVEIK
B3-48	VH	127	EVQLVQSGAEVKKPGASVKVSCKASDFSIKDDYMHWVR QAPGQGLEWIGWIVPENGKTEYASKFQGRVTITADTSI NTAYMELSRLRSDDTAVYYCTVYGDYWGQGTTVTVSS
	VL	128	DIQMTQSPSSLSASVGDRVTINCRASQEISGYLSWLQQ KPEGTIKRLIYAAMTLDSGVPSRFSGSRSGSDYTLTIS SLQPEDFATYYCLQYASYPLTFGGGTKVEIK

B3-69	VH	129	EVQLVQSGAEVKKPGASVKVSCKASGFNIKDDYMHWVR QAPGQGLEWIGWIVPENGNTHYASKFQGRVTITADTSI NTAYMELSRLRSDDTAVYYCTVYGDYWGQGTTVTVSS
	VL	130	DIQMTQSPSSLSASVGDRVTINCRASQEISGYLSWLQQ KPEGTIKRLIYEASTLDSGVPSRFSGSRSGSDYTLTIS SLQPEDFATYYCLQYASYPLTFGGGTKVEIK
D1-70	VH	131	EVQLVQSGAEVKKPGASVKVSCKASGFNIKDDYMHWVR QAPGQGLEWIGWIVPRNGNTMYASKFQGRVTITADTSI NTAYMELSRLRSDDTAVYYCTVYGDYWGQGTTVTVSS
	VL	132	DIQMTQSPSSLSASVGDRVTINCRASQEISGYLSWLQQ KPEGTIKRLIYAASTLDLGVPSRFSGSRSGSDYTLTIS SLQPEDFATYYCLQYASYPLTFGGGTKVEIK

【0199】

實例14.2：陽性純系之IgG轉化及特徵

將七個Fab純系轉化成全IgG蛋白。簡言之，以合成方式產生VH及VL基因，且隨後分別選殖至含有人類IgG1及人類κ恆定域之編碼序列之載體中。獨立地將重鏈及同源輕鏈質體共轉染至HEK 293E細胞中。在轉染細胞培養物大致六天之後，收穫上清液且經受蛋白A親和層析。藉由Octet® RED96生物層干涉法(參見實例9.1，見上文)，對純化抗體之親和力進行排名。結果顯示於表37中。

表37：在親和力成熟之後，抗LAG-3抗體之解離速率排名

測試組	全長抗體	解離速率(k_{off}) (1/s)	與mAb747c之解離速率的解離速率比
1	B3-21-IgG	1.98×10^{-3}	132%
	B3-43-IgG	5.88×10^{-3}	392%
	B3-46-IgG	2.48×10^{-3}	165%
	B3-48-IgG	2.85×10^{-3}	190%
	B3-69-IgG	3.59×10^{-3}	239%
	B2-53-IgG	1.80×10^{-3}	120%
	mAb747c	1.50×10^{-3}	100%
2	D1-70-IgG	2.60×10^{-3}	160%
	HumAb747-42	4.28×10^{-3}	263%
	HumAb747-39	3.91×10^{-3}	240%
	mAb747c	1.63×10^{-3}	100%

【0200】 相較於HumAb747-39，D1-70-IgG及B2-53-IgG顯示解離速率常數具有極少增加，反映大部分親和力在突變之後增加。因此，將D1-70-IgG及B2-53-IgG中之突變引入至HumAb747-60 (其為在人類化之

後的最佳候選者)之序列中。

【0201】

實例14.3：其他工程改造抗體之產生及特徵

藉由親和力成熟過程鑑別之D1-70中之突變為VH域中之D26G、E53R及E58M，以及VL域中之S56L(殘基位置如藉由Kabat編號系統所測定)。藉由親和力成熟過程鑑別之B2-53中之突變為VH域中之D26G及E58V，以及VL域中之T53A (殘基位置如藉由Kabat編號所測定)。將此等突變單獨地或組合地併入HumAb747-60之VH/VL序列中。

【0202】 在HumAb747-60之CDR-H2中存在NG圖案，其可由於去胺基作用反應而在製造期間產生異源性，因此亦評價NG突變成NA之突變。經計算VH域中之G55A突變不干擾HumAb747-60之活性同時破壞NG圖案。包括上文所論述之突變之抗體變體之胺基酸序列顯示於表38中。(CDR根據Kabat編號加底線。)

表38：針對HumAb747-60之工程改造VH/VL設計

工程改造VH/VL標識符	SEQ ID NO.	胺基酸序列 12345678901234567890123456789012345678901234567890
huEpi001-VHv6(G55A)	133	EVQLVQSGAEVKKPGATVKLSCTASDFNIKDDYMHWVKQRP EQGLDWIGWIVPENANTEYASKFQGKATITADTSTNTAYLE LSSLRSEDTAVYYCTVYGDYWGQGTTVTVSS
huEpi001-VHv6.1	134	EVQLVQSGAEVKKPGATVKLSCTASGFNIKDDYMHWVKQRP EQGLDWIGWIVPRNGNTMYASKFQGKATITADTSTNTAYLE LSSLRSEDTAVYYCTVYGDYWGQGTTVTVSS
huEpi001-VHv6.2	135	EVQLVQSGAEVKKPGATVKLSCTASGFNIKDDYMHWVKQRP EQGLDWIGWIVPENGNTVYASKFQGKATITADTSTNTAYLE LSSLRSEDTAVYYCTVYGDYWGQGTTVTVSS
huEpi001-VHv6.3	136	EVQLVQSGAEVKKPGATVKLSCTASGFNIKDDYMHWVKQRP EQGLDWIGWIVPRNGNTVYASKFQGKATITADTSTNTAYLE LSSLRSEDTAVYYCTVYGDYWGQGTTVTVSS
huEpi001-VLv3.4	137	DIQMTQSPSSLSASVGDRVTITCRASQEISGYLSWLQQKPG GAIKRLIYAASTLDLGVPSRFSGSRSGSDYTLTISSLQPED FADYYCLQYASYPLTFGQGTKLELK
huEpi001-VLv3.5	138	DIQMTQSPSSLSASVGDRVTITCRASQEISGYLSWLQQKPG GAIKRLIYAASALDSGVPSRFSGSRSGSDYTLTISSLQPED FADYYCLQYASYPLTFGQGTKLELK
huEpi001-VLv3.6	139	DIQMTQSPSSLSASVGDRVTITCRASQEISGYLSWLQQKPG GAIKRLIYAASALDLGVPSRFSGSRSGSDYTLTISSLQPED FADYYCLQYASYPLTFGQGTKLELK

【0203】 以合成方式產生工程改造VH及VK基因，且隨後分別選殖至含有人類IgG1及人類κ恆定域之載體中。人類VH與人類VK之配對產生13種工程改造抗LAG-3抗體，稱為HumAb747V-61至HumAb747V-73 (表39)。亦使用具有親本小鼠VH/VL及人類恆定序列之嵌合抗體(mAb747c)作為親和力比較之陽性對照。

表39：工程改造抗LAG-3抗體之生產清單

抗體標識符	重鏈中之VH區	輕鏈κ鏈中之VL區
HumAb747V-61	huEpi001-VHv6(G55A)	huEpi001 VLv3
HumAb747V-62	huEpi001-VHv6.1	huEpi001 VLv3.4
HumAb747V-63	huEpi001-VHv6.1	huEpi001 VLv3.5
HumAb747V-64	huEpi001-VHv6.1	huEpi001 VLv3.6
HumAb747V-65	huEpi001-VHv6.1	huEpi001 VLv3
HumAb747V-66	huEpi001-VHv6.2	huEpi001 VLv3.4
HumAb747V-67	huEpi001-VHv6.2	huEpi001 VLv3.5
HumAb747V-68	huEpi001-VHv6.2	huEpi001 VLv3.6
HumAb747V-69	huEpi001-VHv6.2	huEpi001 VLv3
HumAb747V-70	huEpi001-VHv6.3	huEpi001 VLv3.4
HumAb747V-71	huEpi001-VHv6.3	huEpi001 VLv3.5
HumAb747V-72	huEpi001-VHv6.3	huEpi001 VLv3.6
HumAb747V-73	huEpi001-VHv6.3	huEpi001 VLv3

【0204】 根據解離速率常數(k_{off})，以與上文實例9.1中所描述的相同方式，對所有13種人類化抗體(表39)及具有親本鼠類VH及VL域之嵌合抗LAG-3抗體mAb747c進行排名。結果顯示於表40中。在各測試組中，抗體之解離率能夠與mAb747c進行比較。藉由抗體之解離速率與其組之mAb747c之解離速率之比，計算解離速率比率，且全部一起進行比較。比率愈低，抗體之親和力愈高。

表40：在其他工程改造之情況下，抗LAG-3抗體之解離速率排名

測試組	全長抗體	Off-rate (k_{off}) (1/s)	與mAb747c之解離速率的解離速率比
1	HumAb747V-61	6.86×10^{-4}	112%
	HumAb747V-62	4.80×10^{-4}	78%
	HumAb747V-63	5.22×10^{-4}	85%
	HumAb747V-64	4.50×10^{-4}	73%
	HumAb747V-65	2.92×10^{-4}	47%
	HumAb747V-66	5.84×10^{-4}	95%
	mAb747c	6.15×10^{-4}	100%

2	HumAb747V-67	3.19×10^{-4}	47%
	HumAb747V-68	2.95×10^{-4}	44%
	HumAb747V-69	3.57×10^{-4}	53%
	HumAb747V-70	2.73×10^{-4}	40%
	HumAb747V-71	2.92×10^{-4}	43%
	HumAb747V-72	2.47×10^{-4}	37%
	mAb747c	6.76×10^{-4}	100%
3	HumAb747V-73	3.21×10^{-4}	51%
	mAb747c	6.31×10^{-4}	100%

【0205】 基於HumAb747-60，與mAb747c之解離速率相比，具有在親和力成熟之後採用之CDR突變之大部分抗體顯示解離速率提高，從而預測親和力提高。HumAb747V-61具有與mAb747c類似的解離速率，此指示，VH G55A胺基酸取代並不干擾親和力。在基於細胞之功能分析中，進一步評價解離速率比率低於其測試組中之mAb747c之解離速率比的60%的抗體。

【0206】 在PBMC活化分析中，使用葡萄球菌腸毒素B (SEB)作為超級抗原，測試抗LAG-3活性。簡言之，以2×10^5個細胞/孔，將PBMC接種至96孔盤中。將測試蛋白質(抗LAG-3單株抗體)添加至培養盤中，且在37℃下與PBMC一起培育30 min。添加SEB溶液至10 ng/ml之最終濃度。培育培養盤96小時，隨後採集100 μl細胞培養物上清液，且使用PerkinElmer IL-2偵測套組(PerkinElmer；目錄號TRF1221M)來量測IL-2產量。結果顯示於圖10中。結果顯示，工程改造抗體變體可藉由阻斷LAG-3介導的信號傳導，而增強來自SEB刺激的PBMC的IL-2產量。

【0207】 基於PBMC-SEB分析結果，HumAb747V-67、HumAb747V-72及HumAb747V-73表明優良的LAG-3阻斷活性；因此，使用此等三種抗體來產生靶向LAG-3以及PD-1的FIT-Ig結合蛋白。

【0208】

實例15：使用新穎抗LAG-3抗體序列，產生PD-1/LAG-3 FIT-Ig

按照上文實例10中描述之程序，如上文所描述產生之抗LAG-3抗體HumAb747V-67、HumAb747V-72及HumAb747V-73，以及兩種抗PD-1抗體HumAb709-8 (參見表5及7，見上文)及HumAb713-7 (參見表9及10，見上文)，用於產生FIT-Ig結合蛋白。抗LAG-3 Fab部分之所有VH域之序列設計包括G55A突變。

【0209】

實例15.1：PD-1/LAG-3 FIT-Ig結合蛋白FIT107-1-6a-1之產生

使用來自親本抗體mAb709-8 (人類化抗PD-1，參見表5及6，見上文)及HumAb747V-67 (人類化抗LAG-3，參見表38及39，見上文)之免疫球蛋白域之編碼序列，構築PD-1/LAG-3 FIT-Ig，稱為FIT107-1-6a-1。FIT-Ig FIT107-1-6a-1為包含三組分多肽鏈之六聚體：

多肽鏈1號具有域式：HumAb709-8之VL-CL直接與HumAb747V-67之VH-CH1融合，該VH-CH1直接與突變人類恆定IgG1 (參見表6，見上文)之鉸鏈-CH2-CH3融合；

多肽鏈2號具有域式：HumAb709-8之VH-CH1；及

多肽鏈3號具有域式：HumAb747V-676之輕鏈(VL-CL)。

【0210】 三條所表現FIT107-1-6a-1多肽鏈之胺基酸序列顯示於下表41中。

表41：FIT107-1-6a-1組分鏈之胺基酸序列

多肽	SEQ ID NO:	胺基酸序列 1234567890123456789012345678901234567890
FIT107-1-6a-1 FIT-Ig多肽鏈1號	140	MDMRVPAQLLGLLLLWFPGSRC**DIVMTQSPSSLSASVGDR** **VTITCKASQDVNTVVAWYQQKPGKAPKVLISWASTRHTGV** **PSRFSGSGSGTDYTLTISSLQPEDFATYYCQQHYTTPYTF** **GGGTKVEIK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC**EVQL** **VQSGAEVKKPGATVKLSCTASGFNIKDDYMHWVKQRPEQG** **LDWIGWIVPENANTVYASKFQGKATITADTSTNTAYLELS**

		SLRSEDTAVYYCTVYGDYWGQGTTVTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
mAb HumAb709-8之VL-CL (VL為加底線的)	141	DIVMTQSPSSLSASVGDRVTITCKASQDVNTVVAWYQQKP GKAPKVLISWASTRHTGVPSRFSGSGSGTDYTLTISSLQP EDFATYYCQQHYTTPYTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
mAb HumAb747V-67之VH-CH1 (VH為加底線的)	142	EVQLVQSGAEVKKPGATVKLSCTASGFNIKDDYMHWVKQR PEQGLDWIGWIVPENANTVYASKFQGKATITADTSTNTAY LELSSLRSEDTAVYYCTVYGDYWGQGTTVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSC
人類IgG1之鉸鏈-CH2-CH3	82	DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK
FIT107-1-6a-1 FIT-Ig多肽鏈2號	143	MEFGLSWLFLVAILKGVQC**EVQLVESGGGLVQPGGSLRLS CAASGFTFSFYTMSWVRQAPGKGLEWVATISGGGRDTYY PDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAGQG GNYLFAYWGQGTLVTVSS**ASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS C
信號序列	84	MEFGLSWLFLVAILKGVQC
HumAb709-8之VH-CH1 (VH為加底線的)	144	EVQLVESGGGLVQPGGSLRLSCAASGFTFSFYTMSWVRQA PGKGLEWVATISGGGRDTYYPDSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCAGQGGNYLFAYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKKVEPKSC
FIT107-1-6a-1 FIT-Ig多肽鏈3號	145	MDMRVPAQLLGLLLLWFPGSRC**DIQMTQSPSSLSASVGDR VTITCRASQEISGYLSWLQQKPGGAIKRLIYAASALDSGV PSRFSGSRSGSDYTLTISSLQPEDFADYYCLQYASYPLTF GQGTKLELK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
HumAb747V-67之VL-CL (VL為加底線的)	146	DIQMTQSPSSLSASVGDRVTITCRASQEISGYLSWLQQKP GGAIKRLIYAASALDSGVPSRFSGSRSGSDYTLTISSLQP EDFADYYCLQYASYPLTFGQGTKLELKRTVAAPSVFIFPP

		SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC

【0211】

實例15.2：PD-1/LAG-3 FIT-Ig結合蛋白FIT107-1-6b-1之產生

構築識別人類PD-1及人類LAG-3兩者之另一雙特異性串聯Fab免疫球蛋白結合蛋白。此PD-1/LAG-3 FIT-Ig稱為FIT107-1-6b-1。FIT107-1-6b-1結合蛋白之構築使用來自親本抗體HumAb747V-67 (抗LAG-3)及HumAb709-8 (抗PD-1)之免疫球蛋白域的編碼序列。此FIT-Ig構築體呈現在N端(外部)位置的LAG-3結合域及在LAG-3結合區之VL-CL域之融合C端之內部位置的PD-1結合域。FIT-Ig FIT107-1-6b-1為包含三組分多肽鏈之六聚體：

多肽鏈1號具有域式：HumAb747V-67之VL-CL直接與HumAb709-8之VH-CH1融合，該VH-CH1直接與突變人類恆定IgG1 (參見表6，見上文)之鉸鏈-CH2-CH3融合；

多肽鏈2號具有域式：HumAb747V-67之VH-CH1；及

多肽鏈3號具有域式：HumAb709-8之輕鏈(VL-CL)。

【0212】 三條所表現FIT107-1-6b-1多肽鏈之胺基酸序列顯示於下表42中：

表42：FIT107-1-6b-1組分鏈之胺基酸序列

多肽	SEQ ID NO:	胺基酸序列 12345678901234567890123456789012345678901234567890
FIT107-1-6b-1 FIT-Ig多肽鏈1號	147	MDMRVPAQLLGLLLLWFPGSRC**DIQMTQSPSSLSASVGDR** **VTITCRASQEISGYLSWLQQKPGGAIKRLIYAASALDSGV** **PSRFSGSRSGSDYTLTISSLQPEDFADYYCLQYASYPLTF** **GQGTKLELK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC**EVQL** **VESGGGLVQPGGSLRLSCAASGFTFSFYTMSWVRQAPGKG** **LEWVATISGGGRDTYYPDSVKGRFTISRDNAKNSLYLQMN** **SLRAEDTAVYYCAGQGGNYLFAYWGQGTLVTVSS**ASTKGP

		SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
mAb HumAb747V-67之VL-CL (VL為加底線的)	148	DIQMTQSPSSLSASVGDRVTITCRASQEISGYLSWLQQKP GGAIKRLIYAASALDSGVPSRFSGSRSGSDYTLTISSLQP EDFADYYCLQYASYPLTFGQGTKLELKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
mAb HumAb709-8之VH-CH1 (VH為加底線的)	149	EVQLVESGGGLVQPGGSLRLSCAASGFTFSFYTMSWVRQA PGKGLEWVATISGGGRDTYYPDSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCAGQGGNYLFAYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKKVEPKSC
人類IgG1之鉸鏈-CH2-CH3	82	DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK
FIT107-1-6b-1 FIT-Ig多肽鏈2號	150	MEFGLSWLFLVAILKGVQC**EVQLVQSGAEVKKPGATVKLS CTASGFNIKDDYMHWVKQRPEQGLDWIGWIVPENANTVY ASKFQGKATITADTSTNTAYLELSSLRSEDTAVYYCTVYG DYWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
信號序列	84	MEFGLSWLFLVAILKGVQC
HumAb747V-67之VH-CH1 (VH為加底線的)	151	EVQLVQSGAEVKKPGATVKLSCTASGFNIKDDYMHWVKQR PEQGLDWIGWIVPENANTVYASKFQGKATITADTSTNTAY LELSSLRSEDTAVYYCTVYGDYWGQGTTVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSC
FIT107-1-6b-1 FIT-Ig多肽鏈3號	152	MDMRVPAQLLGLLLLWFPGSRC**DIVMTQSPSSLSASVGDR VTITCKASQDVNTVVAWYQQKPGKAPKVLISWASTRHTGV PSRFSGSGSGTDYTLTISSLQPEDFATYYCQQHYTTPYTF GGGTKVEIK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
HumAb709-8之VL-CL (VL為加底線的)	153	DIVMTQSPSSLSASVGDRVTITCKASQDVNTVVAWYQQKP GKAPKVLISWASTRHTGVPSRFSGSGSGTDYTLTISSLQP EDFATYYCQQHYTTPYTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ

		ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC

【0213】

實例15.3：PD-1/LAG-3 FIT-Ig結合蛋白FIT107-1-6a-2之產生

使用來自親本抗體HumAb709-8 (人類化抗PD-1)及HumAb747V-72 (人類化抗LAG-3)之免疫球蛋白域之編碼序列，來構築PD-1/LAG-3 FIT-Ig，稱為FIT107-1-6a-2。FIT-Ig FIT107-1-6a-2為包含三組分多肽鏈之六聚體：

多肽鏈1號具有域式：HumAb709-8之VL-CL直接與HumAb747V-72之VH-CH1融合，該VH-CH1直接與突變人類恆定IgG1 (參見表6，見上文)之鉸鏈-CH2-CH3融合；

多肽鏈2號具有域式：HumAb709-8之VH-CH1；及

多肽鏈3號具有域式：HumAb747V-72之輕鏈(VL-CL)。

【0214】 三條所表現FIT107-1-6a-2多肽鏈之胺基酸序列顯示於下表43中。

表43：FIT107-1-6a-2組分鏈之胺基酸序列

多肽	SEQ ID NO:	胺基酸序列 12345678901234567890123456789012345678901234567890
FIT107-1-6a-2 FIT-Ig多肽鏈1號	154	MDMRVPAQLLGLLLLWFPGSRC**DIVMTQSPSSLSASVGDR** **VTITCKASQDVNTVVAWYQQKPGKAPKVLISWASTRHTGV** **PSRFSGSGSGTDYTLTISSLQPEDFATYYCQQHYTTPYTF** **GGGTKVEIK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC**EVQL** **VQSGAEVKKPGATVKLSCTASGFNIKDDYMHWVKQRPEQG** **LDWIGWIVPRNANTVYASKFQGKATITADTSTNTAYLELS** **SLRSEDTAVYYCTVYGDYWGQGTTVTVSS**ASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
mAb HumAb709-8之VL-CL (VL為加底線的)	155	DIVMTQSPSSLSASVGDRVTITCKASQDVNTVVAWYQQKP GKAPKVLISWASTRHTGVPSRFSGSGSGTDYTLTISSLQP EDFATYYCQQHYTTPYTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
mAb HumAb747V-72之VH-CH1 (VH為加底線的)	156	EVQLVQSGAEVKKPGATVKLSCTASGFNIKDDYMHWVKQR PEQGLDWIGWIVPRNANTVYASKFQGKATITADTSTNTAY LELSSLRSEDTAVYYCTVYGDYWGQGTTVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSC
人類IgG1之鉸鏈-CH2-CH3	82	DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK
FIT107-1-6a-2 FIT-Ig多肽鏈2號	157	MEFGLSWLFLVAILKGVQC**EVQLVESGGGLVQPGGSLRLS CAASGFTFSFYTMSWVRQAPGKGLEWVATISGGGRDTYY PDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAGQG GNYLFAYWGQGTLVTVSS**ASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS C
信號序列	84	MEFGLSWLFLVAILKGVQC
HumAb709-8之VH-CH1 (VH為加底線的)	158	EVQLVESGGGLVQPGGSLRLSCAASGFTFSFYTMSWVRQA PGKGLEWVATISGGGRDTYYPDSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCAGQGGNYLFAYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKKVEPKSC
FIT107-1-6a-2 FIT-Ig多肽鏈3號	159	MDMRVPAQLLGLLLLWFPGSRC**DIQMTQSPSSLSASVGDR VTITCRASQEISGYLSWLQQKPGGAIKRLIYAASALDLGV PSRFSGSRSGSDYTLTISSLQPEDFADYYCLQYASYPLTF GQGTKLELK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
HumAb747V-72之VL-CL (VL為加底線的)	160	DIQMTQSPSSLSASVGDRVTITCRASQEISGYLSWLQQKP GGAIKRLIYAASALDLGVPSRFSGSRSGSDYTLTISSLQP EDFADYYCLQYASYPLTFGQGTKLELKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC

【0215】

實例15.4：PD-1/LAG-3 FIT-Ig結合蛋白FIT107-1-6b-2之產生

使用來自親本抗體HumAb709-8 (人類化抗PD-1)及HumAb747V-72 (人類化抗LAG-3)之免疫球蛋白域之編碼序列，來構築PD-1/LAG-3 FIT-Ig，稱為FIT107-1-6b-2。FIT-Ig FIT107-1-6b-2為包含三組分多肽鏈之六聚體：

多肽鏈1號具有域式：HumAb747V-72之VL-CL直接與HumAb709-8之VH-CH1融合，該VH-CH1直接與突變人類恆定IgG1之鉸鏈-CH2-CH3融合；

多肽鏈2號具有域式：HumAb747V-72之VH-CH1；及

多肽鏈3號具有域式：HumAb709-8之輕鏈(VL-CL)。

【0216】 三條所表現FIT107-1-6b-2多肽鏈之胺基酸序列顯示於下表44中。

表44：FIT107-1-6b-2組分鏈之胺基酸序列

多肽	SEQ ID NO:	胺基酸序列 12345678901234567890123456789012345678901234567890
FIT107-1-6b-2 FIT-Ig多肽鏈1號	161	MDMRVPAQLLGLLLLWFPGSRC**DIQMTQSPSSLSASVGDR VTITCRASQEISGYLSWLQQKPGGAIKRLIYAASALDLGV PSRFSGSRSGSDYTLTISSLQPEDFADYYCLQYASYPLTF GQGTKLELK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC**EVQL VESGGGLVQPGGSLRLSCAASGFTFSFYTMSWVRQAPGKG LEWVATISGGGRDTYYPDSVKGRFTISRDNAKNSLYLQMN SLRAEDTAVYYCAGQGGNYLFAYWGQGTLVTVSS**ASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
mAb HumAb747V-72之VL-CL (VL為加底線的)	162	DIQMTQSPSSLSASVGDRVTITCRASQEISGYLSWLQQKP GGAIKRLIYAASALDLGVPSRFSGSRSGSDYTLTISSLQP EDFADYYCLQYASYPLTFGQGTKLELKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG

		LSSPVTKSFNRGEC
mAb HumAb709-8之VH-CH1 (VH為加底線的)	163	EVQLVESGGGLVQPGGSLRLSCAASGFTFSFYTMSWVRQA PGKGLEWVATISGGGRDTYYPDSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCAGQGGNYLFAYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKKVEPKSC
人類IgG1之鉸鏈-CH2-CH3	82	DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK
FIT107-1-6b-2 FIT-Ig多肽鏈2號	164	MEFGLSWLFLVAILKGVQC**EVQLVQSGAEVKKPGATVKLS CTASGFNIKDDYMHWVKQRPEQGLDWIGWIVPRNANTVY ASKFQGKATITADTSTNTAYLELSSLRSEDTAVYYCTVYG DYWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
信號序列	84	MEFGLSWLFLVAILKGVQC
HumAb747V-72之VH-CH1 (VH為加底線的)	165	EVQLVQSGAEVKKPGATVKLSCTASGFNIKDDYMHWVKQR PEQGLDWIGWIVPRNANTVYASKFQGKATITADTSTNTAY LELSSLRSEDTAVYYCTVYGDYWGQGTTVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSC
FIT107-1-6b-2 FIT-Ig多肽鏈3號	166	MDMRVPAQLLGLLLLWFPGSRC**DIVMTQSPSSLSASVGDR VTITCKASQDVNTVVAWYQQKPGKAPKVLISWASTRHTGV PSRFSGSGSGTDYTLTISSLQPEDFATYYCQQHYTTPYTF GGGTKVEIK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
HumAb709-8之VL-CL (VL為加底線的)	167	DIVMTQSPSSLSASVGDRVTITCKASQDVNTVVAWYQQKP GKAPKVLISWASTRHTGVPSRFSGSGSGTDYTLTISSLQP EDFATYYCQQHYTTPYTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC

【0217】

實例15.5：PD-1/LAG-3 FIT-Ig結合蛋白FIT107-1-6a-3之產生

使用來自親本抗體HumAb709-8 (人類化抗PD-1)及HumAb747V-73 (人類化抗LAG-3)之免疫球蛋白域之編碼序列，來構築PD-1/LAG-3 FIT-Ig，稱為FIT107-1-6a-3。FIT-Ig FIT107-1-6a-3為包含三組分多肽鏈之六

聚體：

多肽鏈1號具有域式：HumAb709-8之VL-CL直接與HumAb747V-73之VH-CH1融合，該VH-CH1直接與突變人類恆定IgG1之鉸鏈-CH2-CH3融合；

多肽鏈2號具有域式：HumAb709-8之VH-CH1；及

多肽鏈3號具有域式：HumAb747V-73之輕鏈(VL-CL)。

【0218】 三條所表現FIT107-1-6a-3多肽鏈之胺基酸序列顯示於下表45中。

表45：FIT107-1-6a-3組分鏈之胺基酸序列

多肽	SEQ ID NO:	胺基酸序列 12345678901234567890123456789012345678901234567890
FIT107-1-6a-3 FIT-Ig多肽鏈1號	168	MDMRVPAQLLGLLLLWFPGSRC**DIVMTQSPSSLSASVGDR VTITCKASQDVNTVVAWYQQKPGKAPKVLISWASTRHTGV PSRFSGSGSGTDYTLTISSLQPEDFATYYCQQHYTTPYTF GGGTKVEIK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC**EVQL VQSGAEVKKPGATVKLSCTASGFNIKDDYMHWVKQRPEQG LDWIGWIVPRNANTVYASKFQGKATITADTSTNTAYLELS SLRSEDTAVYYCTVYGDYWGQGTTVTVSS**ASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
mAb HumAb709-8之VL-CL (VL為加底線的)	169	DIVMTQSPSSLSASVGDRVTITCKASQDVNTVVAWYQQKP GKAPKVLISWASTRHTGVPSRFSGSGSGTDYTLTISSLQP EDFATYYCQQHYTTPYTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
mAb HumAb747V-73之VH-CH1 (VH為加底線的)	170	EVQLVQSGAEVKKPGATVKLSCTASGFNIKDDYMHWVKQR PEQGLDWIGWIVPRNANTVYASKFQGKATITADTSTNTAY LELSSLRSEDTAVYYCTVYGDYWGQGTTVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSC

人類IgG1之鉸鏈-CH2-CH3	82	DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK
FIT107-1-6a-3 FIT-Ig多肽鏈2號	171	MEFGLSWLFLVAILKGVQC**EVQLVESGGGLVQPGGSLRLS CAASGFTFSFYTMSWVRQAPGKGLEWVATISGGGRDTYY PDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAGQG GNYLFAYWGQGTLVTVSS**ASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKS C
信號序列	84	MEFGLSWLFLVAILKGVQC
HumAb709-8之VH-CH1 (VH為加底線的)	172	EVQLVESGGGLVQPGGSLRLSCAASGFTFSFYTMSWVRQA PGKGLEWVATISGGGRDTYYPDSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCAGQGGNYLFAYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKKVEPKSC
FIT107-1-6a-3 FIT-Ig多肽鏈3號	173	MDMRVPAQLLGLLLLWFPGSRC**DIQMTQSPSSLSASVGDR VTITCRASQEISGYLSWLQQKPGGAIKRLIYAASTLDSGV PSRFSGSRSGSDYTLTISSLQPEDFADYYCLQYASYPLTF GQGTKLELK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
HumAb747V-73之VL-CL (VL為加底線的)	174	DIQMTQSPSSLSASVGDRVTITCRASQEISGYLSWLQQKP GGAIKRLIYAASTLDSGVPSRFSGSRSGSDYTLTISSLQP EDFADYYCLQYASYPLTFGQGTKLELKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC

【0219】

實例15.6：PD-1/LAG-3 FIT-Ig結合蛋白FIT107-1-6b-3之產生

使用來自親本抗體HumAb709-8 (人類化抗PD-1)及HumAb747V-73 (人類化抗LAG-3)之免疫球蛋白域之編碼序列，來構築PD-1/LAG-3 FIT-Ig，稱為FIT107-1-6b-3。FIT-Ig FIT107-1-6b-3為包含三組分多肽鏈之六聚體：

多肽鏈1號具有域式：HumAb747V-73之VL-CL直接與HumAb709-8之VH-CH1融合，該VH-CH1直接與突變人類恆定IgG1之鉸鏈-CH2-CH3

融合；

多肽鏈2號具有域式：HumAb747V-73之VH-CH1；及

多肽鏈3號具有域式：HumAb709-8之輕鏈(VL-CL)。

【0220】 三條所表現FIT107-1-6b-3多肽鏈之胺基酸序列顯示於下表46中。

表46：FIT107-1-6b-3組分鏈之胺基酸序列

多肽	SEQ ID NO:	胺基酸序列 12345678901234567890123456789012345678901234567890
FIT107-1-6b-3 FIT-Ig多肽鏈1號	175	MDMRVPAQLLGLLLLWFPGSRC**DIQMTQSPSSLSASVGDR VTITCRASQEISGYLSWLQQKPGGAIKRLIYAASTLDSGV PSRFSGSRSGSDYTLTISSLQPEDFADYYCLQYASYPLTF GQGTKLELK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC**EVQL VESGGGLVQPGGSLRLSCAASGFTFSFYTMSWVRQAPGKG LEWVATISGGGRDTYYPDSVKGRFTISRDNAKNSLYLQMN SLRAEDTAVYYCAGQGGNYLFAYWGQGTLVTVSS**ASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
mAb HumAb747V-73之VL-CL (VL為加底線的)	176	DIQMTQSPSSLSASVGDRVTITCRASQEISGYLSWLQQKP GGAIKRLIYAASTLDSGVPSRFSGSRSGSDYTLTISSLQP EDFADYYCLQYASYPLTFGQGTKLELKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
mAb HumAb709-8之VH-CH1 (VH為加底線的)	177	EVQLVESGGGLVQPGGSLRLSCAASGFTFSFYTMSWVRQA PGKGLEWVATISGGGRDTYYPDSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCAGQGGNYLFAYWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKKVEPKSC
人類IgG1之鉸鏈-CH2-CH3	82	DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK

FIT107-1-6b-3 FIT-Ig多肽鏈2號	178	MEFGLSWLFLVAILKGVQC**EVQLVQSGAEVKKPGATVKLS CTASGFNIKDDYMHWVKQRPEQGLDWIGWIVPRNANTVY ASKFQGKATITADTSTNTAYLELSSLRSEDTAVYYCTVYG DYWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
信號序列	84	MEFGLSWLFLVAILKGVQC
HumAb747V-73之 VH-CH1 (VH為加底線的)	179	EVQLVQSGAEVKKPGATVKLSCTASGFNIKDDYMHWVKQR PEQGLDWIGWIVPRNANTVYASKFQGKATITADTSTNTAY LELSSLRSEDTAVYYCTVYGDYWGQGTTVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSC
FIT107-1-6b-3 FIT-Ig多肽鏈3號	180	MDMRVPAQLLGLLLLWFPGSRC**DIVMTQSPSSLSASVGDR VTITCKASQDVNTVVAWYQQKPGKAPKVLISWASTRHTGV PSRFSGSGSGTDYTLTISSLQPEDFATYYCQQHYTTPYTF GGGTKVEIK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
HumAb709-8之 VL-CL (VL為加底線的)	181	DIVMTQSPSSLSASVGDRVTITCKASQDVNTVVAWYQQKP GKAPKVLISWASTRHTGVPSRFSGSGSGTDYTLTISSLQP EDFATYYCQQHYTTPYTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC

【0221】

實例15.7：PD-1/LAG-3 FIT-Ig結合蛋白FIT107-1-7a-1之產生

使用來自親本抗體HumAb713-7 (人類化抗PD-1；參見表9及10，見上文)及HumAb747V-67 (人類化抗LAG-3)之免疫球蛋白域之編碼序列，來構築PD-1/LAG-3 FIT-Ig，稱為FIT107-1-7a-1。FIT-Ig FIT107-1-7a-1為包含三組分多肽鏈之六聚體：

多肽鏈1號具有域式：HumAb713-7之VL-CL直接與HumAb747V-67之VH-CH1融合，該VH-CH1直接與突變人類恆定IgG1之鉸鏈-CH2-CH3融合；

多肽鏈2號具有域式：HumAb713-7之VH-CH1；及

多肽鏈3號具有域式：HumAb747V-67之輕鏈(VL-CL)。

【0222】 三條所表現FIT107-1-7a-1多肽鏈之胺基酸序列顯示於下表47中。

表47：FIT107-1-7a-1組分鏈之胺基酸序列

多肽	SEQ ID NO:	胺基酸序列 12345678901234567890123456789012345678901234567890
FIT107-1-7a-1 FIT-Ig多肽鏈1號	182	MDMRVPAQLLGLLLLWFPGSRC**DIQMTQSPSSLSASVGDR** **VTITCKASDHINNWLAWYQQKPGKAPKLLIYGATSLETGV** **PSRFSGSGSGTDYTFTISSLQPEDIATYYCQQYWSPPYTF** **GGGTKVEIK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC**EVQL** **VQSGAEVKKPGATVKLSCTASGFNIKDDYMHWVKQRPEQG** **LDWIGWIVPENANTVYASKFQGKATITADTSTNTAYLELS** **SLRSEDTAVYYCTVYGDYWGQGTTVTVSS**ASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
mAb HumAb713-7之VL-CL (VL為加底線的)	183	DIQMTQSPSSLSASVGDRVTITCKASDHINNWLAWYQQKP GKAPKLLIYGATSLETGVPSRFSGSGSGTDYTFTISSLQP EDIATYYCQQYWSPPYTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
mAb HumAb747V-67之VH-CH1 (VH為加底線的)	184	EVQLVQSGAEVKKPGATVKLSCTASGFNIKDDYMHWVKQR PEQGLDWIGWIVPENANTVYASKFQGKATITADTSTNTAY LELSSLRSEDTAVYYCTVYGDYWGQGTTVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSC
人類IgG1之鉸鏈-CH2-CH3	82	DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK
FIT107-1-7a-1 FIT-Ig多肽鏈2號	185	MEFGLSWLFLVAILKGVQC**EVQLVESGGGLVQPGGSLRLS** **CAASGFTSSDYGMHWVRQAPGKGLEWVSYISSGSYTIYY** **ADTVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCAKRG** **GSSHVNVMDYWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE PKSC

信號序列	84	MEFGLSWLFLVAILKGVQC
HumAb713-7之VH-CH1 (VH為加底線的)	186	EVQLVESGGGLVQPGGSLRLSCAASGFTSSDYGMHWVRQA PGKGLEWVSYISSGSYTIYYADTVKGRFTISRDNAKNSLY LQMNSLRDEDTAVYYCAKRGGSSHVNVMDYWGQGTTVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSC
FIT107-1-7a-1 FIT-Ig多肽鏈3號	187	MDMRVPAQLLGLLLLWFPGSRC**DIQMTQSPSSLSASVGDR VTITCRASQEISGYLSWLQQKPGGAIKRLIYAASALDSGV PSRFSGSRSGSDYTLTISSLQPEDFADYYCLQYASYPLTF GQGTKLELK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
HumAb747V-67之VL-CL (VL為加底線的)	188	DIQMTQSPSSLSASVGDRVTITCRASQEISGYLSWLQQKP GGAIKRLIYAASALDSGVPSRFSGSRSGSDYTLTISSLQP EDFADYYCLQYASYPLTFGQGTKLELKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC

【0223】

實例15.8：PD-1/LAG-3 FIT-Ig結合蛋白FIT107-1-7b-1之產生

使用來自親本抗體HumAb713-7 (人類化抗PD-1)及HumAb747V-67 (人類化抗LAG-3)之免疫球蛋白域之編碼序列，來構築PD-1/LAG-3 FIT-Ig，稱為FIT107-1-7b-1。FIT-Ig FIT107-1-7b-1為包含三組分多肽鏈之六聚體：

多肽鏈1號具有域式：HumAb747V-67之VL-CL直接與HumAb713-7之VH-CH1融合，該VH-CH1直接與突變人類恆定IgG1之鉸鏈-CH2-CH3融合；

多肽鏈2號具有域式：HumAb747V-67之VH-CH1；及

多肽鏈3號具有域式：HumAb713-7之輕鏈(VL-CL)。

【0224】 三條所表現FIT107-1-7b-1多肽鏈之胺基酸序列顯示於下表48中。

表48：FIT107-1-7b-1組分鏈之胺基酸序列

多肽	SEQ ID NO:	胺基酸序列 12345678901234567890123456789012345678 90
FIT107-1-7b-1 FIT-Ig多肽鏈1號	189	MDMRVPAQLLGLLLLWFPGSRC**DIQMTQSPSSLSASVGDR** **VTITCRASQEISGYLSWLQQKPGGAIKRLIYAASALDSGV** **PSRFSGSRSGSDYTLTISSLQPEDFADYYCLQYASYPLTF** **GQGTKLELK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC**EVQL** **VESGGGLVQPGGSLRLSCAASGFTSSDYGMHWVRQAPGKG** **LEWVSYISSGSYTIYYADTVKGRFTISRDNAKNSLYLQMN** **SLRDEDTAVYYCAKRGGSSHVNVMDYWGQGTTVTVSS**AST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
mAb HumAb747V-67之VL-CL (VL為加底線的)	190	DIQMTQSPSSLSASVGDRVTITCRASQEISGYLSWLQQKP GGAIKRLIYAASALDSGVPSRFSGSRSGSDYTLTISSLQP EDFADYYCLQYASYPLTFGQGTKLELKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
mAb HumAb713-7之VH-CH1 (VH為加底線的)	191	EVQLVESGGGLVQPGGSLRLSCAASGFTSSDYGMHWVRQA PGKGLEWVSYISSGSYTIYYADTVKGRFTISRDNAKNSLY LQMNSLRDEDTAVYYCAKRGGSSHVNVMDYWGQGTTVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSC
人類IgG1之鉸鏈-CH2-CH3	82	DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK
FIT107-1-7b-1 FIT-Ig多肽鏈2號	192	MEFGLSWLFLVAILKGVQC**EVQLVQSGAEVKKPGATVKLS** **CTASGFNIKDDYMHWVKQRPEQGLDWIGWIVPENANTVY** **ASKFQGKATITADTSTNTAYLELSSLRSEDTAVYYCTVYG** **DYWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
信號序列	84	MEFGLSWLFLVAILKGVQC
HumAb747V-67之VH-CH1 (VH為加底線的)	193	EVQLVQSGAEVKKPGATVKLSCTASGFNIKDDYMHWVKQR PEQGLDWIGWIVPENANTVYASKFQGKATITADTSTNTAY LELSSLRSEDTAVYYCTVYGDYWGQGTTVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT

		SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSC
FIT107-1-7b-1 FIT-Ig多肽鏈3號	194	MDMRVPAQLLGLLLLWFPGSRC**DIQMTQSPSSLSASVGDR** **VTITCKASDHINNWLAWYQQKPGKAPKLLIYGATSLETGV** **PSRFSGSGSGTDYTFTISSLQPEDIATYYCQQYWSPPYTF** **GGGTKVEIK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
HumAb713-7之 VL-CL (VL為加底線的)	195	DIQMTQSPSSLSASVGDRVTITCKASDHINNWLAWYQQKP GKAPKLLIYGATSLETGVPSRFSGSGSGTDYTFTISSLQP EDIATYYCQQYWSPPYTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC

【0225】

實例15.9：PD-1/LAG-3 FIT-Ig結合蛋白FIT107-1-7a-2之產生

使用來自親本抗體HumAb713-7 (人類化抗PD-1)及HumAb747V-72 (人類化抗LAG-3)之免疫球蛋白域之編碼序列，來構築PD-1/LAG-3 FIT-Ig，稱為FIT107-1-7a-2。FIT-Ig FIT107-1-7a-2為包含三組分多肽鏈之六聚體：

多肽鏈1號具有域式：HumAb713-7之VL-CL直接與HumAb747V-72之VH-CH1融合，該VH-CH1直接與突變人類恆定IgG1 (參見表6，見上文)之鉸鏈-CH2-CH3融合；

多肽鏈2號具有域式：HumAb713-7之VH-CH1；及

多肽鏈3號具有域式：HumAb747V-72之輕鏈(VL-CL)。

【0226】 三條所表現FIT107-1-7a-2多肽鏈之胺基酸序列顯示於下表49中。

表49：FIT107-1-7a-2組分鏈之胺基酸序列

多肽	SEQ ID NO:	胺基酸序列 12345678901234567890123456789012345678901234567890
FIT107-1-7a-2 FIT-Ig多肽鏈1號	196	MDMRVPAQLLGLLLLWFPGSRC**DIQMTQSPSSLSASVGDR** **VTITCKASDHINNWLAWYQQKPGKAPKLLIYGATSLETGV** **PSRFSGSGSGTDYTFTISSLQPEDIATYYCQQYWSPPYTF**

		GGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC**EVQL VQSGAEVKKPGATVKLSCTASGFNIKDDYMHWVKQRPEQG LDWIGWIVPRNANTVYASKFQGKATITADTSTNTAYLELS SLRSEDTAVYYCTVYGDYWGQGTTVTVSS**ASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
mAb HumAb713-7之VL-CL (VL為加底線的)	197	DIQMTQSPSSLSASVGDRVTITCKASDHINNWLAWYQQKP GKAPKLLIYGATSLETGVPSRFSGSGSGTDYTFTISSLQP EDIATYYCQQYWSPPYTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
mAb HumAb747V-72之VH-CH1 (VH為加底線的)	198	EVQLVQSGAEVKKPGATVKLSCTASGFNIKDDYMHWVKQR PEQGLDWIGWIVPRNANTVYASKFQGKATITADTSTNTAY LELSSLRSEDTAVYYCTVYGDYWGQGTTVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSC
人類IgG1之鉸鏈-CH2-CH3	82	DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK
FIT107-1-7a-2 FIT-Ig多肽鏈2號	199	MEFGLSWLFLVAILKGVQC**EVQLVESGGGLVQPGGSLRLS CAASGFTSSDYGMHWVRQAPGKGLEWVSYISSGSYTIYYA DTVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCAKRGG SSHVNVMDYWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSC
信號序列	84	MEFGLSWLFLVAILKGVQC
HumAb713-7之VH-CH1 (VH為加底線的)	200	EVQLVESGGGLVQPGGSLRLSCAASGFTSSDYGMHWVRQA PGKGLEWVSYISSGSYTIYYADTVKGRFTISRDNAKNSLY LQMNSLRDEDTAVYYCAKRGGSSHVNVMDYWGQGTTVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSC
FIT107-1-7a-2 FIT-Ig多肽鏈3號	201	MDMRVPAQLLGLLLLWFPGSRC**DIQMTQSPSSLSASVGDR VTITCRASQEISGYLSWLQQKPGGAIKRLIYAASALDLGV PSRFSGSRSGSDYTLTISSLQPEDFADYYCLQYASYPLTF GQGTKLELK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
HumAb747V-72之VL-CL (VL為加底線的)	202	DIQMTQSPSSLSASVGDRVTITCRASQEISGYLSWLQQKP GGAIKRLIYAASALDLGVPSRFSGSRSGSDYTLTISSLQP EDFADYYCLQYASYPLTFGQGTKLELKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC

【0227】

實例15.10：PD-1/LAG-3 FIT-Ig結合蛋白FIT107-1-7b-2之產生

使用來自親本抗體HumAb713-7 (人類化抗PD-1)及HumAb747V-72 (人類化抗LAG-3)之免疫球蛋白域之編碼序列，來構築PD-1/LAG-3 FIT-Ig，稱為FIT107-1-7b-2。FIT-Ig FIT107-1-7b-2為包含三組分多肽鏈之六聚體：

多肽鏈1號具有域式：HumAb747V-72之VL-CL直接與HumAb713-7之VH-CH1融合，該VH-CH1直接與突變人類恆定IgG1之鉸鏈-CH2-CH3融合；

多肽鏈2號具有域式：HumAb747V-72之VH-CH1；及

多肽鏈3號具有域式：HumAb713-7之輕鏈(VL-CL)。

【0228】 三條所表現FIT107-1-7b-2多肽鏈之胺基酸序列顯示於下表50中。

表50：FIT107-1-7b-2組分鏈之胺基酸序列

多肽	SEQ ID NO:	胺基酸序列 12345678901234567890123456789012345678901234567890
FIT107-1-7b-2 FIT-Ig多肽鏈1號	203	MDMRVPAQLLGLLLLWFPGSRC**DIQMTQSPSSLSASVGDR VTITCRASQEISGYLSWLQQKPGGAIKRLIYAASALDLGV PSRFSGSRSGSDYTLTISSLQPEDFADYYCLQYASYPLTF GQGTKLELK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC**EVQL VESGGGLVQPGGSLRLSCAASGFTSSDYGMHWVRQAPGKG LEWVSYISSGSYTIYYADTVKGRFTISRDNAKNSLYLQMN SLRDEDTAVYYCAKRGGSSHVNVMDYWGQGTTVTVSS**AST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSV

		FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
mAb HumAb747V-72之VL-CL (VL為加底線的)	204	DIQMTQSPSSLSASVGDRVTITCRASQEISGYLSWLQQKP GGAIKRLIYAASALDLGVPSRFSGSRSGSDYTLTISSLQP EDFADYYCLQYASYPLTFGQGTKLELKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
mAb HumAb713-7之VH-CH1 (VH為加底線的)	205	EVQLVESGGGLVQPGGSLRLSCAASGFTSSDYGMHWVRQA PGKGLEWVSYISSGSYTIYYADTVKGRFTISRDNAKNSLY LQMNSLRDEDTAVYYCAKRGGSSHVNVMDYWGQGTTVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSC
人類IgG1之鉸鏈-CH2-CH3	82	DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK
FIT107-1-7b-2 FIT-Ig多肽鏈2號	206	MEFGLSWLFLVAILKGVQC**EVQLVQSGAEVKKPGATVKLS CTASGFNIKDDYMHWVKQRPEQGLDWIGWIVPRNANTVY ASKFQGKATITADTSTNTAYLELSSLRSEDTAVYYCTVYG DYWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
信號序列	84	MEFGLSWLFLVAILKGVQC
HumAb747V-72之VH-CH1 (VH為加底線的)	207	EVQLVQSGAEVKKPGATVKLSCTASGFNIKDDYMHWVKQR PEQGLDWIGWIVPRNANTVYASKFQGKATITADTSTNTAY LELSSLRSEDTAVYYCTVYGDYWGQGTTVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSC
FIT107-1-7b-2 FIT-Ig多肽鏈3號	208	MDMRVPAQLLGLLLLWFPGSRC**DIQMTQSPSSLSASVGDR VTITCKASDHINNWLAWYQQKPGKAPKLLIYGATSLETGV PSRFSGSGSGTDYTFTISSLQPEDIATYYCQQYWSPPYTF GGGTKVEIK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
HumAb713-7之VL-CL (VL為加底線的)	209	DIQMTQSPSSLSASVGDRVTITCKASDHINNWLAWYQQKP GKAPKLLIYGATSLETGVPSRFSGSGSGTDYTFTISSLQP EDIATYYCQQYWSPPYTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC

【0229】

實例15.11：PD-1/LAG-3 FIT-Ig結合蛋白FIT107-1-7a-3之產生

使用來自親本抗體HumAb713-7 (人類化抗PD-1)及HumAb747V-73 (人類化抗LAG-3)之免疫球蛋白域之編碼序列，來構築PD-1/LAG-3 FIT-Ig，稱為FIT107-1-7a-3。FIT-Ig FIT107-1-7a-3為包含三組分多肽鏈之六聚體：

多肽鏈1號具有域式：HumAb713-7之VL-CL直接與HumAb747V-73之VH-CH1融合，該VH-CH1直接與突變人類恆定IgG1之鉸鏈-CH2-CH3融合；

多肽鏈2號具有域式：HumAb713-7之VH-CH1；及

多肽鏈3號具有域式：HumAb747V-73之輕鏈(VL-CL)。

【0230】 三條所表現FIT107-1-7a-3多肽鏈之胺基酸序列顯示於下表51中。

表51：FIT107-1-7a-3組分鏈之胺基酸序列

多肽	SEQ ID NO:	胺基酸序列 12345678901234567890123456789012345678901234567890
FIT107-1-7a-3 FIT-Ig多肽鏈1號	210	MDMRVPAQLLGLLLLWFPGSRC**DIQMTQSPSSLSASVGDR VTITCKASDHINNWLAWYQQKPGKAPKLLIYGATSLETGV PSRFSGSGSGTDYTFTISSLQPEDIATYYCQQYWSPPYTF GGGTKVEIK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC**EVQL VQSGAEVKKPGATVKLSCTASGFNIKDDYMHWVKQRPEQG LDWIGWIVPRNANTVYASKFQGKATITADTSTNTAYLELS SLRSEDTAVYYCTVYGDYWGQGTTVTVSS**ASTKGPSVFPL APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVH TFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
mAb HumAb713-7	211	DIQMTQSPSSLSASVGDRVTITCKASDHINNWLAWYQQKP

之VL-CL (VL為加底線的)		GKAPKLLIYGATSLETGVPSRFSGSGSGTDYTFTISSLQP EDIATYYCQQYWSPPYTFGGGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
mAb HumAb747V-73之VH-CH1 (VH為加底線的)	212	EVQLVQSGAEVKKPGATVKLSCTASGFNIKDDYMHWVKQR PEQGLDWIGWIVPRNANTVYASKFQGKATITADTSTNTAY LELSSLRSEDTAVYYCTVYGDYWGQGTTVTVSSASTKGPS VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSC
人類IgG1之鉸鏈-CH2-CH3	82	DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK
FIT107-1-7a-3 FIT-Ig多肽鏈2號	213	MEFGLSWLFLVAILKGVQC**EVQLVESGGGLVQPGGSLRLS CAASGFTSSDYGMHWVRQAPGKGLEWVSYISSGSYTIYY ADTVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCAKRG GSSHVNVMDYWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE PKSC
信號序列	84	MEFGLSWLFLVAILKGVQC
HumAb713-7之VH-CH1 (VH為加底線的)	214	EVQLVESGGGLVQPGGSLRLSCAASGFTSSDYGMHWVRQA PGKGLEWVSYISSGSYTIYYADTVKGRFTISRDNAKNSLY LQMNSLRDEDTAVYYCAKRGGSSHVNVMDYWGQGTTVTVS SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSC
FIT107-1-7a-3 FIT-Ig多肽鏈3號	215	MDMRVPAQLLGLLLLWFPGSRC**DIQMTQSPSSLSASVGDR VTITCRASQEISGYLSWLQQKPGGAIKRLIYAASTLDSGV PSRFSGSRSGSDYTLTISSLQPEDFADYYCLQYASYPLTF GQGTKLELK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
HumAb747V-73之VL-CL (VL為加底線的)	216	DIQMTQSPSSLSASVGDRVTITCRASQEISGYLSWLQQKP GGAIKRLIYAASTLDSGVPSRFSGSRSGSDYTLTISSLQP EDFADYYCLQYASYPLTFGQGTKLELKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC

【0231】

實例15.12：PD-1/LAG-3 FIT-Ig結合蛋白FIT107-1-7b-3之產生

使用來自親本抗體HumAb713-7 (人類化抗PD-1)及HumAb747V-73

(人類化抗LAG-3)之免疫球蛋白域之編碼序列，來構築PD-1/LAG-3 FIT-Ig，稱為FIT107-1-7b-3。FIT-Ig FIT107-1-7b-3為包含三組分多肽鏈之六聚體：

多肽鏈1號具有域式：HumAb747V-73之VL-CL直接與HumAb713-7之VH-CH1融合，該VH-CH1直接與突變人類恆定IgG1之鉸鏈-CH2-CH3融合；

多肽鏈2號具有域式：HumAb747V-73之VH-CH1；及

多肽鏈3號具有域式：HumAb713-7之輕鏈(VL-CL)。

【0232】 三條所表現FIT107-1-7b-3多肽鏈之胺基酸序列顯示於下表52中。

表52：FIT107-1-7b-3組分鏈之胺基酸序列

多肽	SEQ ID NO:	胺基酸序列 12345678901234567890123456789012345678901234567890
FIT107-1-7b-3 FIT-Ig多肽鏈1號	217	MDMRVPAQLLGLLLLWFPGSRC**DIQMTQSPSSLSASVGDR VTITCRASQEISGYLSWLQQKPGGAIKRLIYAASTLDSGV PSRFSGSRSGSDYTLTISSLQPEDFADYYCLQYASYPLTF GQGTKLELK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC**EVQL VESGGGLVQPGGSLRLSCAASGFTSSDYGMHWVRQAPGKG LEWVSYISSGSYTIYYADTVKGRFTISRDNAKNSLYLQMN SLRDEDTAVYYCAKRGGSSHVNVMDYWGQGTTVTVSS**AST KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSV FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
mAb HumAb747V-73之VL-CL (VL為加底線的)	218	DIQMTQSPSSLSASVGDRVTITCRASQEISGYLSWLQQKP GGAIKRLIYAASTLDSGVPSRFSGSRSGSDYTLTISSLQP EDFADYYCLQYASYPLTFGQGTKLELKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
mAb HumAb713-7	219	EVQLVESGGGLVQPGGSLRLSCAASGFTSSDYGMHWVRQA PGKGLEWVSYISSGSYTIYYADTVKGRFTISRDNAKNSLY

之VH-CH1 (VH為加底線的)		LQMNSLRDEDTAVYYCAKRGGSSHVNVMDYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
人類IgG1之鉸鏈-CH2-CH3	82	DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
FIT107-1-7b-3 FIT-Ig多肽鏈2號	220	MEFGLSWLFLVAILKGVQC**EVQLVQSGAEVKKPGATVKLSCTASGFNIKDDYMHWVKQRPEQGLDWIGWIVPRNANTVYASKFQGKATITADTSTNTAYLELSSLRSEDTAVYYCTVYGDYWGQGTTVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
信號序列	84	MEFGLSWLFLVAILKGVQC
HumAb747V-73之VH-CH1 (VH為加底線的)	221	EVQLVQSGAEVKKPGATVKLSCTASGFNIKDDYMHWVKQRPEQGLDWIGWIVPRNANTVYASKFQGKATITADTSTNTAYLELSSLRSEDTAVYYCTVYGDYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
FIT107-1-7b-3 FIT-Ig多肽鏈3號	222	MDMRVPAQLLGLLLLWFPGSRC**DIQMTQSPSSLSASVGDRVTITCKASDHINNWLAWYQQKPGKAPKLLIYGATSLETGVPSRFSGSGSGTDYTFTISSLQPEDIATYYCQQYWSPPYTFGGGTKVEIK**RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
信號序列	79	MDMRVPAQLLGLLLLWFPGSRC
HumAb713-7之VL-CL (VL為加底線的)	223	DIQMTQSPSSLSASVGDRVTITCKASDHINNWLAWYQQKPGKAPKLLIYGATSLETGVPSRFSGSGSGTDYTFTISSLQPEDIATYYCQQYWSPPYTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

【0233】

實例16：新穎FIT-Ig蛋白之特徵

【0234】

實例16.1：表現及SEC分析

以與上文實例10.5中所描述相同的方式，來表現上文所描述的12種FIT-Ig結合蛋白(表41-52)，且藉由蛋白A層析來純化。藉由尺寸排阻層析(SEC)，來分析純化FIT-Ig之組成及純度。將含純化FIT-Ig之PBS施加在

TSKgel SuperSW3000, 300 × 4.6 mm管柱(TOSOH)上。DIONEX™ UltiMate 3000 HPLC儀(Thermo Scientific)用於使用在280 nm及214 nm下進行UV偵測來進行SEC。參見下表53。

表53：PD-1/LAG-3 FIT-Ig結合蛋白之表現及SEC分析

FIT-Ig蛋白	DNA莫耳比：鏈1號:2號:3號	表現量(mg/L)	藉由SEC之峰單體部分%
FIT107-1-6a-1	1:2:1.5	6.21	78.9%
FIT107-1-6b-1	1:2:1.5	8.58	55.4%
FIT107-1-6a-2	1:2:1.5	6.11	90.9%
FIT107-1-6b-2	1:2:1.5	15.86	43.2%
FIT107-1-6a-3	1:2:1.5	11.37	43.0%
FIT107-1-6b-3	1:2:1.5	17.22	44.0%
FIT107-1-7a-1	1:2:1.5	14.47	80.0%
FIT107-1-7b-1	1:2:1.5	17.96	94.8%
FIT107-1-7a-2	1:2:1.5	19.25	88.3%
FIT107-1-7b-2	1:2:1.5	22.12	98.5%
FIT107-1-7a-3	1:2:1.5	14.31	80.9%
FIT107-1-7b-3	1:2:1.5	29.20	98.7%

【0235】 具有較低單體部分含量(<80%)之FIT-Ig蛋白排除在進一步表徵外。

【0236】

實例16.2：功能分析

如實例12中所描述，在PBMC活化分析中，使用葡萄球菌腸毒素B(SEB)作為超級抗原，測試PD-1/LAG-3 FIT-Ig活性。結果顯示在圖11中。結果顯示，所有所測試FIT-Ig變體均可增強SEB刺激的PBMC進行IL-2分泌。在某種程度上，在FIT107-1-7b-2及FIT107-1-7b-3之最高劑量中，該增強反轉，因此此等兩種FIT-Ig蛋白不優先作為前導分子。

【0237】

實例16.3：結合活性

藉由生物層干涉法，使用Octet® RED96系統(Pall FortéBio LLC)，來測定FIT-Ig與PD-1及LAG-3目標結合之動力學。針對目標抗原PD-1及

LAG-3兩者之結合親和力顯示於下表54中。所有FIT-Ig蛋白均保留針對huPD-1及huLAG-3兩者之親和力。針對食蟹獼猴抗原測試之所有FIT-Ig蛋白亦顯示與食蟹獼猴抗原之交叉反應性。

表54：PD-1/LAG-3 FIT-Ig結合蛋白之結合親和力

感測器晶片上捕捉之FIT-Ig	分析物	k_{on} (1/Ms)	k_{off} (1/s)	K_D (M)
FIT107-1-7b-1	人類PD-1-His	8.96×10^{4}	9.35×10^{-4}	1.04×10^{-8}
	食蟹獼猴PD-1-his	2.15×10^{5}	7.75×10^{-4}	3.61×10^{-9}
	人類LAG-3-His	2.00×10^{5}	2.43×10^{-4}	1.22×10^{-9}
	食蟹獼猴LAG-3-His	5.19×10^{5}	6.36×10^{-5}	1.23×10^{-10}
FIT107-1-7b-3	人類PD-1-His	1.16×10^{5}	1.03×10^{-3}	8.86×10^{-9}
	食蟹獼猴PD-1-His	2.48×10^{5}	9.19×10^{-4}	3.71×10^{-9}
	人類LAG-3-His	1.44×10^{5}	3.28×10^{-4}	2.28×10^{-9}
	食蟹獼猴LAG-3-His	2.81×10^{5}	4.70×10^{-5}	1.67×10^{-10}
FIT107-1-6a-2	人類PD-1-His	1.87×10^{5}	2.39×10^{-4}	1.28×10^{-9}
	食蟹獼猴PD-1-His	3.06×10^{5}	1.07×10^{-3}	3.49×10^{-9}
	人類LAG-3-His	1.15×10^{5}	1.17×10^{-4}	1.02×10^{-9}
	食蟹獼猴LAG-3-His	1.91×10^{5}	8.17×10^{-5}	4.28×10^{-10}
FIT107-1-7a-1	人類PD-1-His	1.77×10^{5}	5.38×10^{-4}	3.04×10^{-9}
	人類LAG-3-His	1.69×10^{5}	1.24×10^{-4}	7.32×10^{-10}
FIT107-1-7a-2	人類PD-1-His	1.66×10^{5}	5.26×10^{-4}	3.17×10^{-9}
	人類LAG-3-His	1.05×10^{5}	1.28×10^{-4}	1.22×10^{-9}
FIT107-1-7a-3	人類PD-1-His	2.08×10^{5}	6.28×10^{-4}	3.01×10^{-9}
	人類LAG-3-His	9.10×10^{4}	1.34×10^{-4}	1.47×10^{-9}
FIT107-1-7b-2	人類PD-1-His	1.05×10^{5}	8.27×10^{-4}	7.90×10^{-9}
	人類LAG-3-His	1.74×10^{5}	2.46×10^{-4}	1.41×10^{-9}

【0238】

實例16.4：大鼠藥物動力學資料

基於在一步純化後之純度、瞬時轉染中之表現效價、所保留之結合親和力以及在PBMC-SEB分析中之功能活性，選擇FIT107-1-7b-1作為前導分子。在雄性Sprague - Dawley (SD)大鼠中評定FIT107-1-7b-1之藥物

動力學特性。以5 mg/kg之單一靜脈內劑量，向雄性SD大鼠投與FIT-Ig蛋白。經28天時段，在不同時間點採集血清樣本，其中在0、5、15及30分鐘；1、2、4、8及24小時；及2、4、7、10、14、21及28天，經由尾部靜脈連續出血進行取樣，且藉由一般ELISA進行分析。簡言之，在4℃下，ELISA盤用125奈克/孔之山羊抗人類IgG Fc抗體(Rockland，目錄號：609-101-017)塗覆隔夜，用1X PBS/1% BSA/0.05% Tween-20/0.05% ProClin™ 300阻斷。所有血清樣本首先在阻斷緩衝液中稀釋20倍。在5%合併大鼠血清中進行額外稀釋，且在37℃下在培養盤上培育60分鐘。用山羊Fab特異性抗人類IgG-過氧化酶共軛抗體(Sigma-Aldrich；目錄號A0293)進行偵測，且藉助於標準曲線，使用四參數對數擬合來測定濃度。藉由非分室模型，使用WinNonlin軟體(Pharsight Corporation，Mountain View，Calif.)，來測定藥物動力學參數之值。如藉由表55中顯示之此等結果所表明，FIT107-1-7b-1之特性在活體內為穩定的。

表55：FIT107-1-7b-1之藥物動力學特性

PK參數	CL	Vss	β $t_{1/2}$	AUC	MRT
抗體	mL/天/kg	mL/kg	天	天*μg/mL	天
FIT107-1-7b-1	9.17	114	8.82	436	12.4

【0239】

實例16.5：FGL1受體阻斷分析(RBA)

近年來報導，血纖維蛋白原樣蛋白1 (FGL1)為獨立於MHC II類之主要LAG-3功能配位體(Wang J.等人, *Cell*, 176(1):334-47 (2019))。藉由抗體阻斷FGL1/LAG-3相互作用刺激腫瘤免疫性。為了評價抗LAG-3抗體或FIT-Ig之阻斷活性，用杜爾貝科氏(Dulbecco's)磷酸鹽緩衝鹽水將FGL1(Wuhan USCN，目錄號RPD022Hu01)稀釋至5 μg/ml，且將100 μl添加至

96孔盤中並在4℃下培育隔夜。培養盤用300微升/孔PBS+TWEEN 20 (PBST)洗滌三次。添加HumAb747V-67、FIT107-1-7b-1、hIgG (工作濃度：100nM，10nM，1nM及0.1nM)及1 μg/ml生物素標記的LAG-3 (AcroBiosystem，目錄號H82E5)，且在室溫下培育2小時。培養盤用300微升/孔PBST洗滌三次，隨後使用VARIOSKAN™ LUX微量盤讀取器(Thermo Scientific)使用ELISA-Endpoint-TMB/HRP方案讀取。結果顯示於圖12中。結果顯示，FIT107-1-7b-1 FIT-Ig及其親本抗LAG-3抗體HumAb747V-67兩者均可阻斷人類LAG-3與FGL1蛋白結合。

【0240】

實例16.6：FIT107-1-7b-1蛋白之初代細胞結合活性。

前述分析表明，PD-1/LAG-3 FIT-Ig蛋白可結合重組抗原蛋白質。為了進一步評價FIT107-1-7b-1之細胞表面結合能力，親本抗體HumAb713-7、HumAb747V-67及雙特異性FIT-Ig FIT107-1-7b-1用生物素試劑(Sigma，目錄號S3259)進行生物素標記。對於未刺激之PBMC，以5 × 10^6個細胞/毫升將PBMC再懸浮。對於PD-1抗體(HumAb713-7)或LAG-3抗體(HumAb747V-67)測試，添加100 μg/ml抗體，且在37℃下單獨地培育反應混合物40分鐘，隨後用FACS緩衝液洗滌兩次。隨後，將100 μl 5× 10^5個PBMC/孔(未處理組，抗PD-1抗體處理組及抗LAG-3抗體處理組)接種至96孔盤之孔中。添加生物素標記的HumAb713-7、HumAb747V-67及FIT107-1-7b-1，且在37℃下培育40分鐘(最終工作濃度以100nM為起始，3倍連續稀釋)，隨後用FACS緩衝液洗滌兩次。添加FITC-抗生蛋白鏈菌素及BV421-抗人類CD3抗體，且在4℃下培育分析培養盤30分鐘，隨後用FACS緩衝液洗滌兩次。用Beckman Coulter CytoFlex流式細胞儀分析培

養盤。PBMC刺激組用抗-CD3加抗CD28抗體刺激72小時，以誘導T細胞上之PD-1及LAG-3表現。用與未刺激PBMC實驗相同的分組策略(未處理組、抗PD-1抗體處理組及抗LAG-3抗體處理組)，測試刺激PBMC上的HumAb713-7、HumAb747V-67及FIT107-1-7b-1結合。藉由FACS，研究CD3-T細胞上之測試抗體之結合。結果顯示於圖13中。結果顯示，FIT107-7b-1呈現指示與T細胞上之PD-1及LAG-3目標兩者結合之獨特結合模式。

【0241】 本申請案通篇中所引用之所有引用參考文獻(包括文獻參照案、專利、專利申請案及網站)之內容在此明確地以全文引用的方式併入本文中。除非另外指示，否則本發明之實踐將使用此項技術中熟知的免疫學、分子生物學及細胞生物學之習知技術。

【0242】 本發明可在不脫離上文所描述之本發明之基本特徵之情況下以其他特定形式來實施。因此，前述實施例應視為說明性而非限制本文所描述之本發明。本發明之範疇藉由所附申請專利範圍指定。

【序列表】

<110> 中國大陸商上海岸邁生物科技有限公司(Shanghai EpimAb Biotherapeutics Co., Ltd.)

<120> 針對LAG-3之工程化抗體及自其製備之雙特異性PD-1/LAG-3結合蛋白

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Leu His Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Gly Gln Gly Gly Asn Tyr Leu Phe Ala Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ala
115

<210> 9
<211> 107
<212> PRT
<213> 小家鼠

<220>
<223> VL mAb709

<400> 9

Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Ser Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Val
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Leu Lys Val Leu Ile
35 40 45

Ser Trp Ala Ser Thr Arg His Thr Gly Val Pro Ala Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Val Gln Ala
65 70 75 80

Glu Asp Leu Ala Leu Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Gln Leu Glu Ile Lys
100 105

<210> 10
<211> 121
<212> PRT
<213> 小家鼠

<220>
<223> VH mAb713

<400> 10

Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Glu Leu Ser Cys Ala Ala Ser Gly Phe Thr Ser Ser Asp Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Glu Lys Gly Leu Glu Trp Val
35 40 45

Ala Tyr Ile Ser Ser Gly Ser Tyr Thr Ile Tyr Tyr Ala Asp Thr Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Phe
65 70 75 80

Leu Gln Met Thr Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Lys Arg Gly Gly Ser Ser His Val Asn Val Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 11
<211> 107
<212> PRT
<213> 小家鼠

<220>
<223> VL mAb713

<400> 11

Asp Ile Gln Met Thr Gln Ser Ser Ser Tyr Leu Ser Val Ser Leu Gly
1 5 10 15

Gly Arg Val Thr Ile Thr Cys Lys Ala Ser Asp His Ile Asn Asn Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Asn Ala Pro Arg Leu Leu Ile
35 40 45

Ser Gly Ala Thr Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Lys Asp Tyr Thr Leu Ser Ile Thr Ser Leu Gln Thr
65 70 75 80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Gln Tyr Trp Ser Pro Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 12
<211> 117
<212> PRT
<213> 小家鼠

<220>
<223> VH mAb714

<400> 12

Glu Val His Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Phe Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn
20 25 30

Asn Val Glu Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Asp Ile Asn Pro Asn Asn Gly Asp Thr Leu Tyr Ser Gln Tyr Phe
50 55 60

Lys Asp Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Thr Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Thr Gly Leu Tyr Tyr Cys
85 90 95

Ala Arg Gly Lys Ser Asp Gln Phe Asp Tyr Trp Gly Gln Gly Thr Thr
100 105 110

Leu Thr Val Ser Ser
115

<210> 13
<211> 107
<212> PRT

<213> 小家鼠

<220>
<223> VL mAb714

<400> 13

Asp Ile Gln Met Thr Gln Ser Pro Ala Ser Gln Ser Ala Ser Leu Gly
1 5 10 15

Glu Ser Val Thr Ile Thr Cys Leu Ala Ser Gln Thr Ile Gly Thr Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro Gln Leu Leu Ile
35 40 45

Tyr Ala Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Lys Phe Ser Phe Lys Ile Ser Ser Leu Gln Gly
65 70 75 80

Glu Asp Phe Val Ser Tyr Tyr Cys Gln Gln Leu Tyr Ser Ser Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 14
<211> 118
<212> PRT
<213> 小家鼠

<220>
<223> VH mAb715

<400> 14

Glu Val Met Leu Val Glu Ser Gly Gly Gly Leu Leu Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr

20 25 30

Ala Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Gly Gly Gly Arg Asp Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Thr Ser Leu Arg Ser Glu Asp Thr Ala Phe Tyr Tyr Cys
85 90 95

Ala Gly Gln Gly Gly Thr Tyr Leu Phe Ala Ser Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ala
115

<210> 15
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> VL mAb715

<400> 15

Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Ser Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Ala
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Val Leu Ile
35 40 45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly

50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Val Gln Ala
65 70 75 80

Glu Asp Leu Ala Leu Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 16
<211> 120
<212> PRT
<213> 小家鼠

<220>
<223> VH mAb718

<400> 16

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
1 5 10 15

Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Ala Lys Gln Thr Pro Val His Gly Leu Glu Trp Ile
35 40 45

Gly Val Ile Glu Pro Glu Ser Gly Gly Thr Val Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Lys Leu Thr Ala Asp Lys Ser Ser Arg Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Glu Gly Phe Asn Ser Asp His Tyr Phe Asp Tyr Trp Gly Gln

100 105 110

Gly Thr Thr Leu Thr Val Ser Ser
115 120

<210> 17
<211> 112
<212> PRT
<213> 小家鼠

<220>
<223> VL mAb718

<400> 17

Asp Val Leu 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 Asn Ile Val His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Phe 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 Tyr Cys Phe Gln Gly
85 90 95

Ser His Val Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 18
<211> 116
<212> PRT
<213> 小家鼠

<220>
<223> VH mAb719

<400> 18

Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Thr Ala Ser Gly Phe Ser Phe Ser Ser His
20 25 30

Leu Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

Ala Ala Ile Ser Gly Gly Gly Ala Asp Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Arg Ser Leu Arg Ser Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Thr Arg Gln Ile Leu Ala Phe Asp Ser Trp Gly Gln Gly Thr Thr Leu
100 105 110

Thr Val Ser Ser
115

<210> 19
<211> 107
<212> PRT
<213> 小家鼠

<220>
<223> VL mAb719

<400> 19

Asp Ile Gln Met Asn Gln Ser Pro Ser Ser Leu Ser Val Ser Leu Gly
1 5 10 15

Asp Thr Ile Thr Ile Thr Cys His Ala Ser Gln Asn Ile Tyr Val Trp
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Asn Ile Pro Lys Leu Leu Ile
35 40 45

Tyr Lys Ala Ser Asn Leu His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Gly Gly Ser Gly Thr Gly Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Gly Gln Ser Tyr Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 20
<211> 118
<212> PRT
<213> 人工序列

<220>
<223> VH mAb709 VH.1

<400> 20

Glu Val Gln Leu Val 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 Phe Tyr
20 25 30

Thr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Gly Gly Gly Arg Asp Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser 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 Gln Gly Gly Asn Tyr Leu Phe Ala Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 21
<211> 118
<212> PRT
<213> 人工序列

<220>
<223> VH mAb709 VH.1A

<400> 21

Glu Val Gln Leu Val 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 Phe Tyr
20 25 30

Thr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Gly Gly Gly Arg Asp Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser 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 Gly Gln Gly Gly Asn Tyr Leu Phe Ala Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 22
<211> 118
<212> PRT
<213> 人工序列

<220>
<223> VH mAb709 VH.1B

<400> 22

Glu Val Gln Leu Val 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 Phe Tyr
20 25 30

Thr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Arg Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Gly Gly Gly Arg Asp Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser 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 Gly Gln Gly Gly Asn Tyr Leu Phe Ala Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 23
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> VK mAb709 VK.1A

<400> 23

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Val
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 24
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> VK mAb709 VK.1B

<400> 24

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Val
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Ser Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 25
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> VK mAb709 VK.1C

<400> 25

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Val
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Val Leu Ile
35 40 45

Ser Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 26
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> VK mAb709 VK.1D

<400> 26

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Val
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Val Leu Ile
35 40 45

Ser Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys

100 105

<210> 27
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> VK mAb709 VK.1E

<400> 27

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Val
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ser Leu Lys Val Leu Ile
35 40 45

Ser Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 28
<211> 330
<212> PRT
<213> 智人

<400> 28

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

```
Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205
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Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225 230 235 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> 29
<211> 107
<212> PRT
<213> 智人

<400> 29

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1 5 10 15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
20 25 30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
35 40 45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
50 55 60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65 70 75 80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
85 90 95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
100 105

<210> 30
<211> 121
<212> PRT
<213> 人工序列

<220>
<223> VH mAb713 VH.1

<400> 30

Glu Val Gln Leu Val 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 Asp Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Gly Ser Tyr Thr Ile Tyr Tyr Ala Asp Thr Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Gly Gly Ser Ser His Val Asn Val Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 31
<211> 121
<212> PRT
<213> 人工序列

<220>
<223> VH mAb713 VH.1A

<400> 31

Glu Val Gln Leu Val 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 Asp Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Gly Ser Tyr Thr Ile Tyr Tyr Ala Asp Thr Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Arg Gly Gly Ser Ser His Val Asn Val Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 32
<211> 121
<212> PRT
<213> 人工序列

<220>
<223> VH mAb713 VH.1B

<400> 32

Glu Val Gln Leu Val 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 Ser Ser Asp Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Gly Ser Tyr Thr Ile Tyr Tyr Ala Asp Thr Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Arg Gly Gly Ser Ser His Val Asn Val Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 33
<211> 121
<212> PRT
<213> 人工序列

<220>
<223> VH mAb713 VH.1C

<400> 33

Glu Val Gln Leu Val 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 Ser Ser Asp Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Tyr Ile Ser Ser Gly Ser Tyr Thr Ile Tyr Tyr Ala Asp Thr Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Arg Gly Gly Ser Ser His Val Asn Val Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 34
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> VK mAb713 VK.1

<400> 34

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Asp His Ile Asn Asn Trp

20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Gly Ala Thr Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Trp Ser Pro Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 35
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> VK mAb713 VK.1A

<400> 35

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Asp His Ile Asn Asn Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Gly Ala Thr Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Phe Thr Ile Ser Ser Leu Gln Pro

65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Trp Ser Pro Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 36
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> VK mAb713 VK.1B

<400> 36

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Asp His Ile Asn Asn Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Ser Gly Ala Thr Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Trp Ser Pro Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 37

<211> 107
<212> PRT
<213> 人工序列

<220>
<223> VK mAb713 VK.1C

<400> 37

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Asp His Ile Asn Asn Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Ser Gly Ala Thr Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Lys Asp Tyr Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Trp Ser Pro Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 38
<211> 122
<212> PRT
<213> 人工序列

<220>
<223> VH mAb703 VH.1A

<400> 38

Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Tyr Ser Ile Ser Thr Gly
20 25 30

Tyr Tyr Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45

Ile Gly Tyr Met Ser Tyr Asp Gly Asn Asn Asn Tyr Asn Pro Ser Leu
50 55 60

Lys Asn Arg Val Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Arg Gly Thr Thr Ile Leu Gly Gly Thr Met Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 39
<211> 122
<212> PRT
<213> 人工序列

<220>
<223> VH mAb703 VH.1B

<400> 39

Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Tyr Ser Ile Ser Thr Gly
20 25 30

Tyr Tyr Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45

Ile Gly Tyr Met Ser Tyr Asp Gly Asn Asn Asn Tyr Asn Pro Ser Leu
50 55 60

Lys Asn Arg Ile Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Arg Gly Thr Thr Ile Leu Gly Gly Thr Met Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 40
<211> 122
<212> PRT
<213> 人工序列

<220>
<223> VH mAb703 VH.1C

<400> 40

Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Tyr Ser Ile Ser Thr Gly
20 25 30

Tyr Tyr Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45

Met Gly Tyr Met Ser Tyr Asp Gly Asn Asn Asn Tyr Asn Pro Ser Leu
50 55 60

Lys Asn Arg Ile Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Arg Gly Thr Thr Ile Leu Gly Gly Thr Met Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 41
<211> 122
<212> PRT
<213> 人工序列

<220>
<223> VH mAb703 VH.1D

<400> 41

Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Tyr Ser Ile Thr Thr Gly
20 25 30

Tyr Tyr Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45

Met Gly Tyr Met Ser Tyr Asp Gly Asn Asn Asn Tyr Asn Pro Ser Leu
50 55 60

Lys Asn Arg Ile Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Arg Gly Thr Thr Ile Leu Gly Gly Thr Met Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 42
<211> 122
<212> PRT
<213> 人工序列

<220>
<223> VH mAb703 VH.1E

<400> 42

Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Tyr Ser Ile Thr Thr Gly
20 25 30

Tyr Tyr Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Lys Leu Glu Trp
35 40 45

Met Gly Tyr Met Ser Tyr Asp Gly Asn Asn Asn Tyr Asn Pro Ser Leu
50 55 60

Lys Asn Arg Ile Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Phe Ser
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ala Arg Asp Arg Gly Thr Thr Ile Leu Gly Gly Thr Met Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 43
<211> 107
<212> PRT

<213> 人工序列

<220>
<223> VK mAb703 VK.1

<400> 43

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn Asp
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Tyr Ala Phe Tyr Arg Tyr Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Asp Tyr Ser Ser Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 44
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> VK mAb703 VK.1A

<400> 44

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn Asp

20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Tyr Ala Phe Tyr Arg Tyr Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Asp Tyr Ser Ser Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 45
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> VK mAb703 VK.1B

<400> 45

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn Asp
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Tyr Ala Phe Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro

65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Asp Tyr Ser Ser Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 46
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> VK mAb703 VK.1C

<400> 46

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn Asp
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Tyr Ala Phe Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 47

<211> 107
<212> PRT
<213> 人工序列

<220>
<223> VK mAb703 VK.1D

<400> 47

Ser Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn Asp
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Tyr Ala Phe Tyr Arg Tyr Thr Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Tyr Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 48
<211> 116
<212> PRT
<213> 人工序列

<220>
<223> VH mAb719 VH.1

<400> 48

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 Ser His
20 25 30

Leu Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Gly Gly Ala Asp Thr Tyr Tyr Pro 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 Lys Gln Ile Leu Ala Phe Asp Ser Trp Gly Gln Gly Thr Thr Val
100 105 110

Thr Val Ser Ser
115

<210> 49
<211> 116
<212> PRT
<213> 人工序列

<220>
<223> VH mAb719 VH.1A

<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 Phe Ser Ser His
20 25 30

Leu Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Gly Gly Ala Asp Thr Tyr Tyr Pro 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

Thr Arg Gln Ile Leu Ala Phe Asp Ser Trp Gly Gln Gly Thr Thr Val
100 105 110

Thr Val Ser Ser
115

<210> 50
<211> 116
<212> PRT
<213> 人工序列

<220>
<223> VH mAb719 VH.1B

<400> 50

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 Ser Phe Ser Ser His
20 25 30

Leu Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Gly Gly Ala Asp Thr Tyr Tyr Pro 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

Thr Arg Gln Ile Leu Ala Phe Asp Ser Trp Gly Gln Gly Thr Thr Val
100 105 110

Thr Val Ser Ser
115

<210> 51
<211> 116
<212> PRT
<213> 人工序列

<220>
<223> VH mAb719 VH.1C

<400> 51

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 Ser Phe Ser Ser His
20 25 30

Leu Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Ala Ile Ser Gly Gly Gly Ala Asp Thr Tyr Tyr Pro 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

Thr Arg Gln Ile Leu Ala Phe Asp Ser Trp Gly Gln Gly Thr Thr Val
100 105 110

Thr Val Ser Ser
115

<210> 52
<211> 116
<212> PRT
<213> 人工序列

<220>
<223> VH mAb719 VH.1D

<400> 52

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 Ser Phe Ser Ser His
20 25 30

Leu Met Ser Trp Val Arg Gln Ala Pro Gly Lys Arg Leu Glu Trp Val
35 40 45

Ala Ala Ile Ser Gly Gly Gly Ala Asp Thr Tyr Tyr Pro 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

Thr Arg Gln Ile Leu Ala Phe Asp Ser Trp Gly Gln Gly Thr Thr Val
100 105 110

Thr Val Ser Ser
115

<210> 53
<211> 116
<212> PRT

<213> 人工序列

<220>
<223> VH mAb719 VH.1E

<400> 53

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 Ser Phe Ser Ser His
20 25 30

Leu Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Ala Ile Ser Gly Gly Gly Ala Asp Thr Tyr Tyr Pro Ala 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

Thr Arg Gln Ile Leu Ala Phe Asp Ala Trp Gly Gln Gly Thr Thr Val
100 105 110

Thr Val Ser Ser
115

<210> 54
<211> 116
<212> PRT
<213> 人工序列

<220>
<223> VH mAb719 VH.1F

<400> 54

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 Ser Phe Ser Ser His
20 25 30

Leu Met Ser Trp Val Arg Gln Ala Pro Gly Lys Arg Leu Glu Trp Val
35 40 45

Ala Ala Ile Ser Gly Gly Gly Ala Asp Thr Tyr Tyr Pro Ala 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

Thr Arg Gln Ile Leu Ala Phe Asp Ala Trp Gly Gln Gly Thr Thr Val
100 105 110

Thr Val Ser Ser
115

<210> 55
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> VK mAb719 VK.1

<400> 55

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys His Ala Ser Gln Asn Ile Tyr Val Trp
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile

35 40 45

Tyr Lys Ala Ser Asn Leu His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Gly Gln Ser Tyr Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 56
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> VK mAb719 VK.1A

<400> 56

Asp Ile Gln Met Asn Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys His Ala Ser Gln Asn Ile Tyr Val Trp
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Lys Ala Ser Asn Leu His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Gly Gln Ser Tyr Pro Trp

85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 57
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> VK mAb719 VK.1B

<400> 57

Asp Ile Gln Met Asn Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys His Ala Ser Gln Asn Ile Tyr Val Trp
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ile Pro Lys Leu Leu Ile
35 40 45

Tyr Lys Ala Ser Asn Leu His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Gly Gln Ser Tyr Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 58
<211> 665
<212> PRT
<213> 人工序列

<220>
<223> 人類LAG-3 /Fc融合蛋白

<400> 58

Leu Gln Pro Gly Ala Glu Val Pro Val Val Trp Ala Gln Glu Gly Ala
1 5 10 15

Pro Ala Gln Leu Pro Cys Ser Pro Thr Ile Pro Leu Gln Asp Leu Ser
20 25 30

Leu Leu Arg Arg Ala Gly Val Thr Trp Gln His Gln Pro Asp Ser Gly
35 40 45

Pro Pro Ala Ala Ala Pro Gly His Pro Leu Ala Pro Gly Pro His Pro
50 55 60

Ala Ala Pro Ser Ser Trp Gly Pro Arg Pro Arg Arg Tyr Thr Val Leu
65 70 75 80

Ser Val Gly Pro Gly Gly Leu Arg Ser Gly Arg Leu Pro Leu Gln Pro
85 90 95

Arg Val Gln Leu Asp Glu Arg Gly Arg Gln Arg Gly Asp Phe Ser Leu
100 105 110

Trp Leu Arg Pro Ala Arg Arg Ala Asp Ala Gly Glu Tyr Arg Ala Ala
115 120 125

Val His Leu Arg Asp Arg Ala Leu Ser Cys Arg Leu Arg Leu Arg Leu
130 135 140

Gly Gln Ala Ser Met Thr Ala Ser Pro Pro Gly Ser Leu Arg Ala Ser
145 150 155 160

Asp Trp Val Ile Leu Asn Cys Ser Phe Ser Arg Pro Asp Arg Pro Ala
165 170 175

Ser Val His Trp Phe Arg Asn Arg Gly Gln Gly Arg Val Pro Val Arg

180 185 190

Glu Ser Pro His His His Leu Ala Glu Ser Phe Leu Phe Leu Pro Gln
195 200 205

Val Ser Pro Met Asp Ser Gly Pro Trp Gly Cys Ile Leu Thr Tyr Arg
210 215 220

Asp Gly Phe Asn Val Ser Ile Met Tyr Asn Leu Thr Val Leu Gly Leu
225 230 235 240

Glu Pro Pro Thr Pro Leu Thr Val Tyr Ala Gly Ala Gly Ser Arg Val
245 250 255

Gly Leu Pro Cys Arg Leu Pro Ala Gly Val Gly Thr Arg Ser Phe Leu
260 265 270

Thr Ala Lys Trp Thr Pro Pro Gly Gly Gly Pro Asp Leu Leu Val Thr
275 280 285

Gly Asp Asn Gly Asp Phe Thr Leu Arg Leu Glu Asp Val Ser Gln Ala
290 295 300

Gln Ala Gly Thr Tyr Thr Cys His Ile His Leu Gln Glu Gln Gln Leu
305 310 315 320

Asn Ala Thr Val Thr Leu Ala Ile Ile Thr Val Thr Pro Lys Ser Phe
325 330 335

Gly Ser Pro Gly Ser Leu Gly Lys Leu Leu Cys Glu Val Thr Pro Val
340 345 350

Ser Gly Gln Glu Arg Phe Val Trp Ser Ser Leu Asp Thr Pro Ser Gln
355 360 365

Arg Ser Phe Ser Gly Pro Trp Leu Glu Ala Gln Glu Ala Gln Leu Leu
370 375 380

Ser Gln Pro Trp Gln Cys Gln Leu Tyr Gln Gly Glu Arg Leu Leu Gly
385 390 395 400

Ala Ala Val Tyr Phe Thr Glu Leu Ser Ser Pro Gly Ala Gln Arg Ser
405 410 415

Gly Arg Ala Pro Gly Ala Leu Pro Ala Gly His Leu Ile Glu Gly Arg
420 425 430

Met Asp Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
435 440 445

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
450 455 460

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
465 470 475 480

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
485 490 495

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
500 505 510

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
515 520 525

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
530 535 540

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
545 550 555 560

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
565 570 575

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro

580 585 590

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
595 600 605

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
610 615 620

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
625 630 635 640

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
645 650 655

Lys Ser Leu Ser Leu Ser Pro Gly Lys
660 665

<210> 59
<211> 665
<212> PRT
<213> 人工序列

<220>
<223> 食蟹獼猴LAG-3 /Fc融合蛋白

<220>
<221> misc_feature
<222> (52)..(52)
<223> Xaa可爲任何天然存在之胺基酸

<400> 59

Pro Gln Pro Gly Ala Glu Ile Ser Val Val Trp Ala Gln Glu Gly Ala
1 5 10 15

Pro Ala Gln Leu Pro Cys Ser Pro Thr Ile Pro Leu Gln Asp Leu Ser
20 25 30

Leu Leu Arg Arg Ala Gly Val Thr Trp Gln His Gln Pro Asp Ser Gly
35 40 45

Pro Pro Ala Xaa Ala Pro Gly His Pro Pro Val Pro Gly His Arg Pro
50 55 60

Ala Ala Pro Tyr Ser Trp Gly Pro Arg Pro Arg Arg Tyr Thr Val Leu
65 70 75 80

Ser Val Gly Pro Gly Gly Leu Arg Ser Gly Arg Leu Pro Leu Gln Pro
85 90 95

Arg Val Gln Leu Asp Glu Arg Gly Arg Gln Arg Gly Asp Phe Ser Leu
100 105 110

Trp Leu Arg Pro Ala Arg Arg Ala Asp Ala Gly Glu Tyr Arg Ala Thr
115 120 125

Val His Leu Arg Asp Arg Ala Leu Ser Cys Arg Leu Arg Leu Arg Val
130 135 140

Gly Gln Ala Ser Met Thr Ala Ser Pro Pro Gly Ser Leu Arg Thr Ser
145 150 155 160

Asp Trp Val Ile Leu Asn Cys Ser Phe Ser Arg Pro Asp Arg Pro Ala
165 170 175

Ser Val His Trp Phe Arg Ser Arg Gly Gln Gly Arg Val Pro Val Gln
180 185 190

Gly Ser Pro His His His Leu Ala Glu Ser Phe Leu Phe Leu Pro His
195 200 205

Val Gly Pro Met Asp Ser Gly Leu Trp Gly Cys Ile Leu Thr Tyr Arg
210 215 220

Asp Gly Phe Asn Val Ser Ile Met Tyr Asn Leu Thr Val Leu Gly Leu
225 230 235 240

Glu Pro Ala Thr Pro Leu Thr Val Tyr Ala Gly Ala Gly Ser Arg Val

245 250 255

Glu Leu Pro Cys Arg Leu Pro Pro Ala Val Gly Thr Gln Ser Phe Leu
260 265 270

Thr Ala Lys Trp Ala Pro Pro Gly Gly Gly Pro Asp Leu Leu Val Ala
275 280 285

Gly Asp Asn Gly Asp Phe Thr Leu Arg Leu Glu Asp Val Ser Gln Ala
290 295 300

Gln Ala Gly Thr Tyr Ile Cys His Ile Arg Leu Gln Gly Gln Gln Leu
305 310 315 320

Asn Ala Thr Val Thr Leu Ala Ile Ile Thr Val Thr Pro Lys Ser Phe
325 330 335

Gly Ser Pro Gly Ser Leu Gly Lys Leu Leu Cys Glu Val Thr Pro Ala
340 345 350

Ser Gly Gln Glu His Phe Val Trp Ser Pro Leu Asn Thr Pro Ser Gln
355 360 365

Arg Ser Phe Ser Gly Pro Trp Leu Glu Ala Gln Glu Ala Gln Leu Leu
370 375 380

Ser Gln Pro Trp Gln Cys Gln Leu His Gln Gly Glu Arg Leu Leu Gly
385 390 395 400

Ala Ala Val Tyr Phe Thr Glu Leu Ser Ser Pro Gly Ala Gln Arg Ser
405 410 415

Gly Arg Ala Pro Gly Ala Leu Arg Ala Gly His Leu Ile Glu Gly Arg
420 425 430

Met Asp Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
435 440 445

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Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
    450                 455                 460

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
465                 470                 475                 480

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
                485                 490                 495

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
            500                 505                 510

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
        515                 520                 525

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
    530                 535                 540

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
545                 550                 555                 560

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
                565                 570                 575

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
            580                 585                 590

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
        595                 600                 605

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
    610                 615                 620

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
625                 630                 635                 640

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
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645 650 655

Lys Ser Leu Ser Leu Ser Pro Gly Lys
660 665

<210> 60
<211> 113
<212> PRT
<213> 小家鼠

<220>
<223> VH mAb746及VH mAb747

<400> 60

Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Thr Ala Ser Asp Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile
35 40 45

Gly Trp Ile Val Pro Glu Asn Gly Asn Thr Glu Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65 70 75 80

Leu Gln Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser
100 105 110

Ser

<210> 61

<211> 107
<212> PRT
<213> 小家鼠

<220>
<223> VL mAb746

<400> 61

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Ser Leu Asn Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Ser Asp Gly Thr Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val Pro Lys Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
65 70 75 80

Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 62
<211> 107
<212> PRT
<213> 小家鼠

<220>
<223> VL mAb747

<400> 62

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Leu Gly
1 5 10 15

Glu Arg Val Ser Leu Asn Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Asp Gly Thr Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val Pro Lys Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
65 70 75 80

Glu Asp Phe Ala Ala Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 63
<211> 116
<212> PRT
<213> 小家鼠

<220>
<223> VH mAb742

<400> 63

Gln Gly Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
1 5 10 15

Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Asn Asp Tyr
20 25 30

Glu Met His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Pro Glu Thr Gly Gly Thr Ala Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Ile Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ile Arg Trp Gly Ser Thr Val Phe Pro Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser
115

<210> 64
<211> 112
<212> PRT
<213> 小家鼠

<220>
<223> VL mAb742

<400> 64

Asp Gly Val Leu Thr Gln Thr Pro Leu Ser Leu Pro Val Asn Ile Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Lys Ser Thr Lys Ser Leu Leu Asn Ser
20 25 30

Asp Gly Phe Thr Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu 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 Tyr Cys Phe Gln Ser
85 90 95

Asn Tyr Leu Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 65
<211> 116
<212> PRT
<213> 小家鼠

<220>
<223> VH mAb744

<400> 65

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Thr
1 5 10 15

Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Met His Trp Met Lys Gln Thr Pro Val His Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Asp Pro Ala Thr Gly Gly Thr Ala Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Ile Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Asp Phe Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ile Arg Trp Gly Thr Thr Val Phe Pro Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser
115

<210> 66
<211> 112
<212> PRT

<213> 小家鼠

<220>
<223> VL mAb744

<400> 66

Asp Val Val Leu Thr Gln Thr Pro Leu Ser Leu Pro Val Asn Ile Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Lys Ser Thr Lys Ser Leu Leu Asn Ser
20 25 30

Asp Gly Phe Thr Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu 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 Tyr Cys Phe Gln Ser
85 90 95

Asn Tyr Leu Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 67
<211> 112
<212> PRT
<213> 小家鼠

<220>
<223> VH mAb748

<400> 67

Glu Val Gln Met Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Thr Val Ser Gly Phe Asn Ile Lys Asp Asp

20 25 30

Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Asp Pro Glu Asn Gly Asp Thr Glu Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65 70 75 80

Leu Gln Leu Asn Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser
100 105 110

<210> 68
<211> 112
<212> PRT
<213> 小家鼠

<220>
<223> VL mAb748及VL mAb750

<400> 68

Asp Val Val Met Thr Gln Thr Pro Leu Thr Leu Ser Val Thr Ile Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Asp Gly Lys Thr Tyr Leu Asn Trp Leu Leu Gln Arg Pro Gly Gln Ser
35 40 45

Pro Lys Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Val Pro
50 55 60

Asp Arg Phe Thr 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 Tyr Cys Trp Gln Gly
85 90 95

Ser His Phe Pro Gln Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 69
<211> 116
<212> PRT
<213> 小家鼠

<220>
<223> VH mAb749

<400> 69

Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Thr Ala Ser Asp Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Val His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Asp Pro Glu Asn Gly Asp Thr Glu Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65 70 75 80

Leu Gln Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Phe Cys
85 90 95

Ser Thr Trp Asp Ala Glu Glu Asn Tyr Trp Gly Gln Gly Thr Thr Leu
100 105 110

Ser Val Ser Ser

115

<210> 70
<211> 112
<212> PRT
<213> 小家鼠

<220>
<223> VL mAb749

<400> 70

Asp Ile Val Leu Thr Gln Ala Ala Pro Ser Val Pro Val Thr Pro Gly
1 5 10 15

Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser
35 40 45

Pro Gln Val Leu Ile Tyr Arg Met Ser Asn Leu Ala Ser Gly Val Pro
50 55 60

Val Arg Phe Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Arg Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln His
85 90 95

Leu Glu Tyr Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 71
<211> 116
<212> PRT
<213> 小家鼠

<220>
<223> VH mAb750

<400> 71

Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Thr Pro Ser Gly Leu Asn Ile Lys Asp Asp
20 25 30

Tyr Ile His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Asp Pro Glu Asn Gly Asp Thr Glu Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65 70 75 80

Leu Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Cys Thr Ala Asp Tyr Arg Asn Trp Tyr Trp Gly Gln Gly Thr Thr Leu
100 105 110

Thr Val Ser Ser
115

<210> 72
<211> 113
<212> PRT
<213> 人工序列

<220>
<223> VH mAb747 VH.2A

<400> 72

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Asp Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Val Pro Glu Asn Gly Asn Thr Glu Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Ile Asn Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser

<210> 73
<211> 113
<212> PRT
<213> 人工序列

<220>
<223> VH mAb747 VH.2B

<400> 73

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Asp Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Val Pro Glu Asn Gly Asn Thr Glu Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Ile Asn Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser

<210> 74
<211> 113
<212> PRT
<213> 人工序列

<220>
<223> VH mAb747 VH.1G

<400> 74

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Ala Ser Asp Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Val Pro Glu Asn Gly Asn Thr Glu Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser

<210> 75
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> VK mAb747 VK.1E

<400> 75

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Asn Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Gly Lys Thr Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 76
<211> 107
<212> PRT

<213> 人工序列

<220>
<223> VK mAb747 VK.2A

<400> 76

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Asn Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Glu Lys Thr Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 77
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> Vk mAb747 VK.2B

<400> 77

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Asn Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr

20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Glu Gly Thr Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 78
<211> 679
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-2a FIT-Ig多肽鏈1號

<400> 78

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ser Arg Cys Asp Ile Val Met Thr Gln Ser His Lys Phe
20 25 30

Met Ser Thr Ser Val Gly Asp Ser Val Thr Ile Thr Cys Lys Ala Ser
35 40 45

Gln Asp Val Asn Thr Val Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln
50 55 60

Ser Leu Lys Val Leu Ile Ser Trp Ala Ser Thr Arg His Thr Gly Val

65 70 75 80

Pro Ala Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr
85 90 95

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Leu Tyr Tyr Cys Gln Gln
100 105 110

His Tyr Thr Thr Pro Tyr Thr Phe Gly Gly Gly Thr Gln Leu Glu Ile
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Glu Val Gln Leu
225 230 235 240

Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala Ser Val Lys Leu
245 250 255

Ser Cys Thr Ala Ser Asp Phe Asn Ile Lys Asp Asp Tyr Met His Trp
260 265 270

Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile Gly Trp Ile Val
275 280 285

Pro Glu Asn Gly Asn Thr Glu Tyr Ala Ser Lys Phe Gln Gly Lys Ala
290 295 300

Thr Ile Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr Leu Gln Leu Ser
305 310 315 320

Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys Thr Val Tyr Gly
325 330 335

Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Ala Ser Thr
340 345 350

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
355 360 365

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
370 375 380

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
385 390 395 400

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
405 410 415

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
420 425 430

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
435 440 445

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
450 455 460

Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys

465 470 475 480

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
485 490 495

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
500 505 510

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
515 520 525

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
530 535 540

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
545 550 555 560

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
565 570 575

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
580 585 590

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
595 600 605

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
610 615 620

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
625 630 635 640

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
645 650 655

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
660 665 670

Leu Ser Leu Ser Pro Gly Lys
675

<210> 79
<211> 22
<212> PRT
<213> 人工序列

<220>
<223> 信號序列

<400> 79

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ser Arg Cys
20

<210> 80
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> mAb709之VL-CL

<400> 80

Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Ser Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Val
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Leu Lys Val Leu Ile
35 40 45

Ser Trp Ala Ser Thr Arg His Thr Gly Val Pro Ala Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Val Gln Ala

65 70 75 80

Glu Asp Leu Ala Leu Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Gln 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> 81
<211> 216
<212> PRT
<213> 人工序列

<220>
<223> mAb746之VH-CH1

<400> 81

Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala

1 5 10 15

Ser Val Lys Leu Ser Cys Thr Ala Ser Asp Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile
35 40 45

Gly Trp Ile Val Pro Glu Asn Gly Asn Thr Glu Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65 70 75 80

Leu Gln Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
115 120 125

Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
180 185 190

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Lys Val Glu Pro Lys Ser Cys
210 215

<210> 82
<211> 227
<212> PRT
<213> 人工序列

<220>
<223> 人類IgG1之鉸鏈-CH2-CH3

<400> 82

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65 70 75 80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85 90 95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
100 105 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
115 120 125

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
130 135 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145 150 155 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
165 170 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
180 185 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
195 200 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
210 215 220

Pro Gly Lys
225

<210> 83
<211> 240
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-2a FIT-Ig多肽鏈2號

<400> 83

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1 5 10 15

Val Gln Cys Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys
20 25 30

Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

Ser Phe Tyr Thr Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu
50 55 60

Glu Trp Val Ala Thr Ile Ser Gly Gly Gly Arg Asp Thr Tyr Tyr Pro
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
85 90 95

Thr Leu Tyr Leu His Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Leu
100 105 110

Tyr Tyr Cys Ala Gly Gln Gly Gly Asn Tyr Leu Phe Ala Tyr Trp Gly
115 120 125

Gln Gly Thr Leu Val Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser
130 135 140

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
145 150 155 160

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
165 170 175

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
180 185 190

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
195 200 205

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
210 215 220

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
225 230 235 240

<210> 84
<211> 19
<212> PRT
<213> 人工序列

<220>
<223> 信號序列

<400> 84

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1 5 10 15

Val Gln Cys

<210> 85
<211> 221
<212> PRT
<213> 人工序列

<220>
<223> 鼠類mAb709之VH-CH1

<400> 85

Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Phe Tyr
20 25 30

Thr Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Gly Gly Gly Arg Asp Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu His Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Gly Gln Gly Gly Asn Tyr Leu Phe Ala Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ala 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
210 215 220

<210> 86
<211> 236
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-2a FIT-Ig多肽鏈3號

<400> 86

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ser Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Leu Gly Glu Arg Val Ser Leu Asn Cys Arg Ala Ser
35 40 45

Gln Glu Ile Ser Gly Tyr Leu Ser Trp Leu Gln Gln Lys Ser Asp Gly
50 55 60

Thr Ile Lys Arg Leu Ile Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val
65 70 75 80

Pro Lys Arg Phe Ser Gly Ser Arg Ser Gly Ser Asp Tyr Ser Leu Thr
85 90 95

Ile Ser Ser Leu Glu Ser Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln
100 105 110

Tyr Ala Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 87

<211> 214
<212> PRT
<213> 人工序列

<220>
<223> 鼠類mAb746之VL-CL

<400> 87

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Leu Gly
1               5                  10                  15

Glu Arg Val Ser Leu Asn Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
            20                  25                  30

Leu Ser Trp Leu Gln Gln Lys Ser Asp Gly Thr Ile Lys Arg Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val Pro Lys Arg Phe Ser Gly
    50                  55                  60

Ser Arg Ser Gly Ser Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
65                  70                  75                  80

Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
                85                  90                  95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu 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
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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> 88
<211> 684
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-2b FIT-Ig多肽鏈1號

<400> 88

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ser Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Leu Gly Glu Arg Val Ser Leu Asn Cys Arg Ala Ser
35 40 45

Gln Glu Ile Ser Gly Tyr Leu Ser Trp Leu Gln Gln Lys Ser Asp Gly
50 55 60

Thr Ile Lys Arg Leu Ile Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val
65 70 75 80

Pro Lys Arg Phe Ser Gly Ser Arg Ser Gly Ser Asp Tyr Ser Leu Thr
85 90 95

Ile Ser Ser Leu Glu Ser Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln

100 105 110

Tyr Ala Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Glu Val Lys Leu
225 230 235 240

Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly Ser Leu Lys Leu
245 250 255

Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Phe Tyr Thr Met Ser Trp
260 265 270

Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val Ala Thr Ile Ser
275 280 285

Gly Gly Gly Arg Asp Thr Tyr Tyr Pro Asp Ser Val Lys Gly Arg Phe
290 295 300

Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu His Met Ser
305 310 315 320

Ser Leu Arg Ser Glu Asp Thr Ala Leu Tyr Tyr Cys Ala Gly Gln Gly
325 330 335

Gly Asn Tyr Leu Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
340 345 350

Ser Ala Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser
355 360 365

Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys
370 375 380

Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
385 390 395 400

Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
405 410 415

Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr
420 425 430

Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val
435 440 445

Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro
450 455 460

Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe
465 470 475 480

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
485 490 495

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe

500 505 510

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
515 520 525

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
530 535 540

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
545 550 555 560

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
565 570 575

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
580 585 590

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
595 600 605

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
610 615 620

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
625 630 635 640

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
645 650 655

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
660 665 670

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
675 680

<210> 89
<211> 214
<212> PRT

<213> 人工序列

<220>
<223> mAb746之VL-CL

<400> 89

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Leu Gly
1               5                  10                  15

Glu Arg Val Ser Leu Asn Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
            20                  25                  30

Leu Ser Trp Leu Gln Gln Lys Ser Asp Gly Thr Ile Lys Arg Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val Pro Lys Arg Phe Ser Gly
    50                  55                  60

Ser Arg Ser Gly Ser Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Ser
65                  70                  75                  80

Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
                85                  90                  95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu 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> 90
<211> 221
<212> PRT
<213> 人工序列

<220>
<223> mAb709之VH-CH1

<400> 90

Glu Val Lys Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Phe Tyr
20 25 30

Thr Met Ser Trp Val Arg Gln Thr Pro Glu Lys Arg Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Gly Gly Gly Arg Asp Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu His Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Gly Gln Gly Gly Asn Tyr Leu Phe Ala Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ala 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
210 215 220

<210> 91
<211> 235
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-2b FIT-Ig多肽鏈2號

<400> 91

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1 5 10 15

Val Gln Cys Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg
20 25 30

Pro Gly Ala Ser Val Lys Leu Ser Cys Thr Ala Ser Asp Phe Asn Ile
35 40 45

Lys Asp Asp Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu
50 55 60

Asp Trp Ile Gly Trp Ile Val Pro Glu Asn Gly Asn Thr Glu Tyr Ala
65 70 75 80

Ser Lys Phe Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Ser Asn
85 90 95

Thr Ala Tyr Leu Gln Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Leu
115 120 125

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
130 135 140

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
145 150 155 160

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
165 170 175

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
180 185 190

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
195 200 205

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
210 215 220

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
225 230 235

<210> 92

<211> 216
<212> PRT
<213> 人工序列

<220>
<223> mAb746之VH-CH1

<400> 92

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Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ala
1               5                  10                  15

Ser Val Lys Leu Ser Cys Thr Ala Ser Asp Phe Asn Ile Lys Asp Asp
            20                  25                  30

Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile
        35                  40                  45

Gly Trp Ile Val Pro Glu Asn Gly Asn Thr Glu Tyr Ala Ser Lys Phe
    50                  55                  60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65                  70                  75                  80

Leu Gln Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser
            100                 105                 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
        115                 120                 125

Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
    130                 135                 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145                 150                 155                 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
```

165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
180 185 190

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Lys Val Glu Pro Lys Ser Cys
210 215

<210> 93
<211> 236
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-2b FIT-Ig多肽鏈3號

<400> 93

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ser Arg Cys Asp Ile Val Met Thr Gln Ser His Lys Phe
20 25 30

Met Ser Thr Ser Val Gly Asp Ser Val Thr Ile Thr Cys Lys Ala Ser
35 40 45

Gln Asp Val Asn Thr Val Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln
50 55 60

Ser Leu Lys Val Leu Ile Ser Trp Ala Ser Thr Arg His Thr Gly Val
65 70 75 80

Pro Ala Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr
85 90 95

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Leu Tyr Tyr Cys Gln Gln

100 105 110

His Tyr Thr Thr Pro Tyr Thr Phe Gly Gly Gly Thr Gln Leu Glu Ile
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 94
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> mAb709之VL-CL

<400> 94

Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Ser Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Val

20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Leu Lys Val Leu Ile
35 40 45

Ser Trp Ala Ser Thr Arg His Thr Gly Val Pro Ala Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Val Gln Ala
65 70 75 80

Glu Asp Leu Ala Leu Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Gln 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> 95
<211> 679
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-5a FIT-Ig多肽鏈1號

<400> 95

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Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                  10                  15

Phe Pro Gly Ser Arg Cys Asp Ile Val Met Thr Gln Ser Pro Ser Ser
            20                  25                  30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser
        35                  40                  45

Gln Asp Val Asn Thr Val Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys
    50                  55                  60

Ala Pro Lys Val Leu Ile Ser Trp Ala Ser Thr Arg His Thr Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr
                85                  90                  95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            100                 105                 110

His Tyr Thr Thr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
        115                 120                 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160
```

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Glu Val Gln Leu
225 230 235 240

Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val
245 250 255

Ser Cys Lys Ala Ser Asp Phe Asn Ile Lys Asp Asp Tyr Met His Trp
260 265 270

Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile Gly Trp Ile Val
275 280 285

Pro Glu Asn Gly Asn Thr Glu Tyr Ala Ser Lys Phe Gln Gly Lys Ala
290 295 300

Thr Ile Thr Ala Asp Thr Ser Ile Asn Thr Ala Tyr Met Glu Leu Ser
305 310 315 320

Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys Thr Val Tyr Gly
325 330 335

Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
340 345 350

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser

355 360 365

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
370 375 380

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
385 390 395 400

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
405 410 415

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
420 425 430

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
435 440 445

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
450 455 460

Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
465 470 475 480

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
485 490 495

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
500 505 510

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
515 520 525

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
530 535 540

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
545 550 555 560

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
565 570 575

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
580 585 590

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
595 600 605

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
610 615 620

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
625 630 635 640

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
645 650 655

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
660 665 670

Leu Ser Leu Ser Pro Gly Lys
675

<210> 96
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> HumAb709-8之VL-CL

<400> 96

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Val
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Val Leu Ile
35 40 45

Ser Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val 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> 97

<211> 216
<212> PRT
<213> 人工序列

<220>
<223> mAb HumAb747-42之VH-CH1

<400> 97

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Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                  10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Asp Phe Asn Ile Lys Asp Asp
            20                  25                  30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Trp Ile Val Pro Glu Asn Gly Asn Thr Glu Tyr Ala Ser Lys Phe
    50                  55                  60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Ile Asn Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
            100                 105                 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
        115                 120                 125

Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
    130                 135                 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145                 150                 155                 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
```

165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
180 185 190

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Lys Val Glu Pro Lys Ser Cys
210 215

<210> 98
<211> 240
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-5a FIT-Ig多肽鏈2號

<400> 98

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1 5 10 15

Val Gln Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

Ser Phe Tyr Thr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ala Thr Ile Ser Gly Gly Gly Arg Asp Thr Tyr Tyr Pro
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
85 90 95

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

100 105 110

Tyr Tyr Cys Ala Gly Gln Gly Gly Asn Tyr Leu Phe Ala Tyr Trp Gly
115 120 125

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
130 135 140

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
145 150 155 160

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
165 170 175

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
180 185 190

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
195 200 205

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
210 215 220

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
225 230 235 240

<210> 99
<211> 221
<212> PRT
<213> 人工序列

<220>
<223> HumAb709-8之VH-CH1

<400> 99

Glu Val Gln Leu Val 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 Phe Tyr

20 25 30

Thr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Gly Gly Gly Arg Asp Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser 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 Gly Gln Gly Gly Asn Tyr Leu Phe Ala 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
210 215 220

<210> 100
<211> 236
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-5a FIT-Ig多肽鏈3號

<400> 100

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ser Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Asn Cys Arg Ala Ser
35 40 45

Gln Glu Ile Ser Gly Tyr Leu Ser Trp Leu Gln Gln Lys Pro Glu Gly
50 55 60

Thr Ile Lys Arg Leu Ile Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln
100 105 110

Tyr Ala Ser Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 101
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> HumAb747-42之VL-CL

<400> 101

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Asn Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Glu Gly Thr Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val 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> 102
<211> 684
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-5b FIT-Ig多肽鏈1號

<400> 102

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

```
Phe Pro Gly Ser Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20                  25                  30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Asn Cys Arg Ala Ser
        35                  40                  45

Gln Glu Ile Ser Gly Tyr Leu Ser Trp Leu Gln Gln Lys Pro Glu Gly
    50                  55                  60

Thr Ile Lys Arg Leu Ile Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr
                85                  90                  95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln
            100                 105                 110

Tyr Ala Ser Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
        115                 120                 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        195                 200                 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
```

210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Glu Val Gln Leu
225 230 235 240

Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu
245 250 255

Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Phe Tyr Thr Met Ser Trp
260 265 270

Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Thr Ile Ser
275 280 285

Gly Gly Gly Arg Asp Thr Tyr Tyr Pro Asp Ser Val Lys Gly Arg Phe
290 295 300

Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn
305 310 315 320

Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Gly Gln Gly
325 330 335

Gly Asn Tyr Leu Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
340 345 350

Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser
355 360 365

Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys
370 375 380

Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
385 390 395 400

Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
405 410 415

Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr
420 425 430

Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val
435 440 445

Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro
450 455 460

Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe
465 470 475 480

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
485 490 495

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
500 505 510

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
515 520 525

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
530 535 540

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
545 550 555 560

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
565 570 575

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
580 585 590

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
595 600 605

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro

610 615 620

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
625 630 635 640

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
645 650 655

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
660 665 670

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
675 680

<210> 103
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> HumAb747-42之VL-CL

<400> 103

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Asn Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Glu Gly Thr Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu

85 90 95

Thr Phe Gly Gly Gly Thr Lys Val 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> 104
<211> 221
<212> PRT
<213> 人工序列

<220>
<223> HumAb709-8之VH-CH1

<400> 104

Glu Val Gln Leu Val 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 Phe Tyr

20 25 30

Thr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Gly Gly Gly Arg Asp Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser 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 Gly Gln Gly Gly Asn Tyr Leu Phe Ala 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
210 215 220

<210> 105
<211> 235
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-5b FIT-Ig多肽鏈2號

<400> 105

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Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1               5                  10                  15

Val Gln Cys Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Asp Phe Asn Ile
        35                  40                  45

Lys Asp Asp Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60

Glu Trp Ile Gly Trp Ile Val Pro Glu Asn Gly Asn Thr Glu Tyr Ala
65                  70                  75                  80

Ser Lys Phe Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Ile Asn
                85                  90                  95

Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val
        115                 120                 125

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
    130                 135                 140

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
145                 150                 155                 160
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Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
165 170 175

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
180 185 190

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
195 200 205

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
210 215 220

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
225 230 235

<210> 106
<211> 216
<212> PRT
<213> 人工序列

<220>
<223> HumAb747-42之VH-CH1

<400> 106

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Asp Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Val Pro Glu Asn Gly Asn Thr Glu Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Ile Asn Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
115 120 125

Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
180 185 190

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Lys Val Glu Pro Lys Ser Cys
210 215

<210> 107
<211> 236
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-5b FIT-Ig多肽鏈3號

<400> 107

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

```
Phe Pro Gly Ser Arg Cys Asp Ile Val Met Thr Gln Ser Pro Ser Ser
            20                  25                  30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser
        35                  40                  45

Gln Asp Val Asn Thr Val Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys
    50                  55                  60

Ala Pro Lys Val Leu Ile Ser Trp Ala Ser Thr Arg His Thr Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr
                85                  90                  95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            100                 105                 110

His Tyr Thr Thr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
        115                 120                 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        195                 200                 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
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210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 108
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> mAb HuMAb709-8之VL-CL

<400> 108

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Val
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Val Leu Ile
35 40 45

Ser Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val 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> 109
<211> 113
<212> PRT
<213> 人工序列

<220>
<223> 用於huEpi001-VHv1之VH

<400> 109

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Val Ser Asp Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Val Pro Glu Asn Gly Asn Thr Glu Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr

65 70 75 80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser

<210> 110
<211> 113
<212> PRT
<213> 人工序列

<220>
<223> 用於huEpi001-VHv2之VH

<400> 110

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Leu Ser Cys Lys Ala Ser Asp Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Val Pro Glu Asn Gly Asn Thr Glu Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser

100 105 110

Ser

<210> 111
<211> 113
<212> PRT
<213> 人工序列

<220>
<223> 用於huEpi001-VHv3之VH

<400> 111

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Leu Ser Cys Thr Ala Ser Asp Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Gln Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Val Pro Glu Asn Gly Asn Thr Glu Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser

<210> 112

<211> 113
<212> PRT
<213> 人工序列

<220>
<223> 用於huEpi001-VHv4之VH

<400> 112

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Leu Ser Cys Thr Ala Ser Asp Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Val Pro Glu Asn Gly Asn Thr Glu Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Arg Ala Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr
65 70 75 80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser

<210> 113
<211> 113
<212> PRT
<213> 人工序列

<220>
<223> 用於huEpi001-VHv5之VH

<400> 113

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Leu Ser Cys Thr Ala Ser Asp Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Val Pro Glu Asn Gly Asn Thr Glu Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Arg Ala Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr
65 70 75 80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser

<210> 114
<211> 113
<212> PRT
<213> 人工序列

<220>
<223> 用於huEpi001-VHv6之VH

<400> 114

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Leu Ser Cys Thr Ala Ser Asp Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile
35 40 45

Gly Trp Ile Val Pro Glu Asn Gly Asn Thr Glu Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr
65 70 75 80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser

<210> 115
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> 用於huEpi001 VLv1之VL

<400> 115

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Gly Lys Ala Ile Lys Ser Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 116
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> 用於huEpi001 VLv2之VL

<400> 116

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Gly Lys Ala Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 117
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> 用於huEpi001 VLv3之VL

<400> 117

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly Ala Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 118
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> 用於huEpi001 VLv4之VL

<400> 118

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly Ala Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 119
<211> 113
<212> PRT
<213> 人工序列

<220>
<223> 用於抗體B2-53之VH

<400> 119

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Val Pro Glu Asn Gly Asn Thr Val Tyr Ala Ser Lys Phe

50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Ile Asn Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser

<210> 120
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> 用於抗體B2-53之VL

<400> 120

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Asn Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Glu Gly Thr Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Ala Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu

85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 121
<211> 113
<212> PRT
<213> 人工序列

<220>
<223> 用於抗體B3-21之VH

<400> 121

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Asp Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Val Pro Glu Asn Gly Asn Thr Glu Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Ile Asn Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser

<210> 122

<211> 107
<212> PRT
<213> 人工序列

<220>
<223> 用於抗體B3-21之VL

<400> 122

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Asn Cys Arg Ala Met Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Glu Gly Thr Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Tyr Ala Tyr Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 123
<211> 113
<212> PRT
<213> 人工序列

<220>
<223> 用於抗體B3-43之VH

<400> 123

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Cys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Val Pro Glu Asn Gly Asn Thr Glu Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Ile Asn Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser

<210> 124
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> 用於抗體B3-43之VL

<400> 124

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Asn Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Glu Gly Thr Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser His Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 125
<211> 113
<212> PRT
<213> 人工序列

<220>
<223> 用於抗體B3-46之VH

<400> 125

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Val Pro Glu Asn Gly Leu Thr Glu Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Ile Asn Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser

<210> 126
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> 用於抗體B3-46之VL

<400> 126

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Asn Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Glu Gly Thr Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Thr Ser Thr Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 127
<211> 113
<212> PRT

<213> 人工序列

<220>
<223> 用於抗體B3-48之VH

<400> 127

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Asp Phe Ser Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Val Pro Glu Asn Gly Lys Thr Glu Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Ile Asn Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser

<210> 128
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> 用於抗體B3-48之VL

<400> 128

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly

1 5 10 15

Asp Arg Val Thr Ile Asn Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Glu Gly Thr Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Met Thr Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 129
<211> 113
<212> PRT
<213> 人工序列

<220>
<223> 用於抗體B3-69之VH

<400> 129

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Val Pro Glu Asn Gly Asn Thr His Tyr Ala Ser Lys Phe

50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Ile Asn Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser

<210> 130
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> 用於抗體B3-69之VL

<400> 130

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Asn Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Glu Gly Thr Ile Lys Arg Leu Ile
35 40 45

Tyr Glu Ala Ser Thr Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu

85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 131
<211> 113
<212> PRT
<213> 人工序列

<220>
<223> 用於抗體D1-70之VH

<400> 131

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Val Pro Arg Asn Gly Asn Thr Met Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Ile Asn Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser

<210> 132

<211> 107
<212> PRT
<213> 人工序列

<220>
<223> 用於抗體D1-70之VL

<400> 132

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Asn Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Glu Gly Thr Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Asp Leu Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 133
<211> 113
<212> PRT
<213> 人工序列

<220>
<223> 用於huEpi001-VHv6(G55A)之VH

<400> 133

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Leu Ser Cys Thr Ala Ser Asp Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile
35 40 45

Gly Trp Ile Val Pro Glu Asn Ala Asn Thr Glu Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr
65 70 75 80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser

<210> 134
<211> 113
<212> PRT
<213> 人工序列

<220>
<223> 用於huEpi001-VHv6.1之VH

<400> 134

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile
35 40 45

Gly Trp Ile Val Pro Arg Asn Gly Asn Thr Met Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr
65 70 75 80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser

<210> 135
<211> 113
<212> PRT
<213> 人工序列

<220>
<223> 用於huEpi001-VHv6.2之VH

<400> 135

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile
35 40 45

Gly Trp Ile Val Pro Glu Asn Gly Asn Thr Val Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr
65 70 75 80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser

<210> 136
<211> 113
<212> PRT
<213> 人工序列

<220>
<223> 用於huEpi001-VHv6.3之VH

<400> 136

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile
35 40 45

Gly Trp Ile Val Pro Arg Asn Gly Asn Thr Val Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr
65 70 75 80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser

<210> 137
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> 用於huEpi001-VLv3.4之VL

<400> 137

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly Ala Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Asp Leu Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 138
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> 用於huEpi001-VLv3.5之VL

<400> 138

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly Ala Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Ala Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 139
<211> 107
<212> PRT
<213> 人工序列

<220>
<223> 用於huEpi001-VLv3.6之VL

<400> 139

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly Ala Ile Lys Arg Leu Ile

35 40 45

Tyr Ala Ala Ser Ala Leu Asp Leu Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 140
<211> 679
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-6a-1 FIT-Ig多肽鏈1號

<400> 140

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ser Arg Cys Asp Ile Val Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser
35 40 45

Gln Asp Val Asn Thr Val Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Val Leu Ile Ser Trp Ala Ser Thr Arg His Thr Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr

85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

His Tyr Thr Thr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Glu Val Gln Leu
225 230 235 240

Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Thr Val Lys Leu
245 250 255

Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Asp Tyr Met His Trp
260 265 270

Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile Gly Trp Ile Val
275 280 285

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Pro Glu Asn Ala Asn Thr Val Tyr Ala Ser Lys Phe Gln Gly Lys Ala
    290                 295                 300

Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr Leu Glu Leu Ser
305                 310                 315                 320

Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Thr Val Tyr Gly
                325                 330                 335

Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
            340                 345                 350

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
        355                 360                 365

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
    370                 375                 380

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
385                 390                 395                 400

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
                405                 410                 415

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
            420                 425                 430

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
        435                 440                 445

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
    450                 455                 460

Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
465                 470                 475                 480

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
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485 490 495

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
500 505 510

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
515 520 525

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
530 535 540

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
545 550 555 560

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
565 570 575

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
580 585 590

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
595 600 605

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
610 615 620

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
625 630 635 640

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
645 650 655

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
660 665 670

Leu Ser Leu Ser Pro Gly Lys
675

<210> 141
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> HumAb709-8之VL-CL

<400> 141

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Val
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Val Leu Ile
35 40 45

Ser Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val 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> 142
<211> 216
<212> PRT
<213> 人工序列

<220>
<223> HumAb747V-67之VH-CH1

<400> 142

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile
35 40 45

Gly Trp Ile Val Pro Glu Asn Ala Asn Thr Val Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr
65 70 75 80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
115 120 125

Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
180 185 190

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Lys Val Glu Pro Lys Ser Cys
210 215

<210> 143
<211> 240
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-6a-1 FIT-Ig多肽鏈2號

<400> 143

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1 5 10 15

Val Gln Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

Ser Phe Tyr Thr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ala Thr Ile Ser Gly Gly Gly Arg Asp Thr Tyr Tyr Pro
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
85 90 95

Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Gly Gln Gly Gly Asn Tyr Leu Phe Ala Tyr Trp Gly
115 120 125

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
130 135 140

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
145 150 155 160

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
165 170 175

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
180 185 190

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
195 200 205

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
210 215 220

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys

225 230 235 240

<210> 144
<211> 221
<212> PRT
<213> 人工序列

<220>
<223> HumAb709-8之VH-CH1

<400> 144

Glu Val Gln Leu Val 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 Phe Tyr
20 25 30

Thr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Gly Gly Gly Arg Asp Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser 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 Gly Gln Gly Gly Asn Tyr Leu Phe Ala 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
210 215 220

<210> 145
<211> 236
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-6a-1 FIT-Ig多肽鏈3號

<400> 145

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ser Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Gln Glu Ile Ser Gly Tyr Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly
50 55 60

Ala Ile Lys Arg Leu Ile Tyr Ala Ala Ser Ala Leu Asp Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr

85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln
100 105 110

Tyr Ala Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 146
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> HumAb747V-67之VL-CL

<400> 146

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly Ala Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Ala Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu 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> 147
<211> 684
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-6b-1 FIT-Ig多肽鏈1號

<400> 147

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ser Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Gln Glu Ile Ser Gly Tyr Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly
50 55 60

Ala Ile Lys Arg Leu Ile Tyr Ala Ala Ser Ala Leu Asp Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln
100 105 110

Tyr Ala Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Glu Val Gln Leu
225 230 235 240

Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu
245 250 255

Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Phe Tyr Thr Met Ser Trp
260 265 270

Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Thr Ile Ser
275 280 285

Gly Gly Gly Arg Asp Thr Tyr Tyr Pro Asp Ser Val Lys Gly Arg Phe
290 295 300

Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn
305 310 315 320

Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Gly Gln Gly
325 330 335

Gly Asn Tyr Leu Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val

340 345 350

Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser
355 360 365

Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys
370 375 380

Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
385 390 395 400

Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
405 410 415

Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr
420 425 430

Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val
435 440 445

Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro
450 455 460

Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe
465 470 475 480

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
485 490 495

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
500 505 510

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
515 520 525

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
530 535 540

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
545 550 555 560

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
565 570 575

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
580 585 590

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
595 600 605

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
610 615 620

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
625 630 635 640

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
645 650 655

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
660 665 670

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
675 680

<210> 148
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> HumAb747V-67之VL-CL

<400> 148

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

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Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
            20                  25                  30

Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly Ala Ile Lys Arg Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Ala Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu 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
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210

<210> 149
<211> 221
<212> PRT
<213> 人工序列

<220>
<223> HumAb709-8之VH-CH1

<400> 149

Glu Val Gln Leu Val 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 Phe Tyr
20 25 30

Thr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Gly Gly Gly Arg Asp Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser 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 Gly Gln Gly Gly Asn Tyr Leu Phe Ala 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
210 215 220

<210> 150
<211> 235
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-6b-1 FIT-Ig多肽鏈2號

<400> 150

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1 5 10 15

Val Gln Cys Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30

Pro Gly Ala Thr Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile
35 40 45

Lys Asp Asp Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu
50 55 60

Asp Trp Ile Gly Trp Ile Val Pro Glu Asn Ala Asn Thr Val Tyr Ala
65 70 75 80

Ser Lys Phe Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Thr Asn

85 90 95

Thr Ala Tyr Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val
115 120 125

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
130 135 140

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
145 150 155 160

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
165 170 175

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
180 185 190

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
195 200 205

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
210 215 220

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
225 230 235

<210> 151
<211> 216
<212> PRT
<213> 人工序列

<220>
<223> HumAb747V-67之VH-CH1

<400> 151

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala

1 5 10 15

Thr Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile
35 40 45

Gly Trp Ile Val Pro Glu Asn Ala Asn Thr Val Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr
65 70 75 80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
115 120 125

Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
180 185 190

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Lys Val Glu Pro Lys Ser Cys
210 215

<210> 152
<211> 236
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-6b-1 FIT-Ig多肽鏈3號

<400> 152

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ser Arg Cys Asp Ile Val Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser
35 40 45

Gln Asp Val Asn Thr Val Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Val Leu Ile Ser Trp Ala Ser Thr Arg His Thr Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

His Tyr Thr Thr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 153
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> HumAb709-8之VL-CL

<400> 153

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Val
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Val Leu Ile
35 40 45

Ser Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val 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> 154
<211> 679
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-6a-2 FIT-Ig多肽鏈1號

<400> 154

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Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                  10                  15

Phe Pro Gly Ser Arg Cys Asp Ile Val Met Thr Gln Ser Pro Ser Ser
            20                  25                  30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser
        35                  40                  45

Gln Asp Val Asn Thr Val Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys
    50                  55                  60

Ala Pro Lys Val Leu Ile Ser Trp Ala Ser Thr Arg His Thr Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr
                85                  90                  95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            100                 105                 110

His Tyr Thr Thr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
        115                 120                 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
```

195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Glu Val Gln Leu
225 230 235 240

Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Thr Val Lys Leu
245 250 255

Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Asp Tyr Met His Trp
260 265 270

Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile Gly Trp Ile Val
275 280 285

Pro Arg Asn Ala Asn Thr Val Tyr Ala Ser Lys Phe Gln Gly Lys Ala
290 295 300

Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr Leu Glu Leu Ser
305 310 315 320

Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Thr Val Tyr Gly
325 330 335

Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
340 345 350

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
355 360 365

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
370 375 380

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
385 390 395 400

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
405 410 415

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
420 425 430

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
435 440 445

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
450 455 460

Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
465 470 475 480

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
485 490 495

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
500 505 510

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
515 520 525

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
530 535 540

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
545 550 555 560

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
565 570 575

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
580 585 590

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp

595 600 605

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
610 615 620

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
625 630 635 640

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
645 650 655

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
660 665 670

Leu Ser Leu Ser Pro Gly Lys
675

<210> 155
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> HumAb709-8之VL-CL

<400> 155

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Val
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Val Leu Ile
35 40 45

Ser Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro

65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val 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> 156
<211> 216
<212> PRT
<213> 人工序列

<220>
<223> HumAb747V-72之VH-CH1

<400> 156

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala

1 5 10 15

Thr Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile
35 40 45

Gly Trp Ile Val Pro Arg Asn Ala Asn Thr Val Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr
65 70 75 80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
115 120 125

Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
180 185 190

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Lys Val Glu Pro Lys Ser Cys
210 215

<210> 157
<211> 240
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-6a-2 FIT-Ig多肽鏈2號

<400> 157

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1 5 10 15

Val Gln Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

Ser Phe Tyr Thr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ala Thr Ile Ser Gly Gly Gly Arg Asp Thr Tyr Tyr Pro
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
85 90 95

Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Gly Gln Gly Gly Asn Tyr Leu Phe Ala Tyr Trp Gly
115 120 125

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
130 135 140

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
145 150 155 160

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
165 170 175

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
180 185 190

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
195 200 205

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
210 215 220

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
225 230 235 240

<210> 158
<211> 221
<212> PRT
<213> 人工序列

<220>
<223> HumAb709-8之VH-CH1

<400> 158

Glu Val Gln Leu Val 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 Phe Tyr
20 25 30

Thr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Gly Gly Gly Arg Asp Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser 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 Gly Gln Gly Gly Asn Tyr Leu Phe Ala 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
210 215 220

<210> 159
<211> 236
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-6a-2 FIT-Ig多肽鏈3號

<400> 159

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Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                  10                  15

Phe Pro Gly Ser Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20                  25                  30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35                  40                  45

Gln Glu Ile Ser Gly Tyr Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly
    50                  55                  60

Ala Ile Lys Arg Leu Ile Tyr Ala Ala Ser Ala Leu Asp Leu Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr
                85                  90                  95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln
            100                 105                 110

Tyr Ala Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu
        115                 120                 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
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195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 160
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> HumAb747V-72之VL-CL

<400> 160

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly Ala Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Ala Leu Asp Leu Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu 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> 161
<211> 684
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-6b-2 FIT-Ig多肽鏈1號

<400> 161

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ser Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Gln Glu Ile Ser Gly Tyr Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly

50 55 60

Ala Ile Lys Arg Leu Ile Tyr Ala Ala Ser Ala Leu Asp Leu Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln
100 105 110

Tyr Ala Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Glu Val Gln Leu
225 230 235 240

Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu
245 250 255

Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Phe Tyr Thr Met Ser Trp
260 265 270

Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Thr Ile Ser
275 280 285

Gly Gly Gly Arg Asp Thr Tyr Tyr Pro Asp Ser Val Lys Gly Arg Phe
290 295 300

Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn
305 310 315 320

Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Gly Gln Gly
325 330 335

Gly Asn Tyr Leu Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
340 345 350

Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser
355 360 365

Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys
370 375 380

Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
385 390 395 400

Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
405 410 415

Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr
420 425 430

Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val
435 440 445

Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro

450 455 460

Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe
465 470 475 480

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
485 490 495

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
500 505 510

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
515 520 525

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
530 535 540

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
545 550 555 560

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
565 570 575

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
580 585 590

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
595 600 605

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
610 615 620

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
625 630 635 640

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
645 650 655

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
660 665 670

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
675 680

<210> 162
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> HumAb747V-72之VL-CL

<400> 162

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly Ala Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Ala Leu Asp Leu Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu 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> 163
<211> 221
<212> PRT
<213> 人工序列

<220>
<223> HumAb709-8之VH-CH1

<400> 163

Glu Val Gln Leu Val 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 Phe Tyr
20 25 30

Thr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Gly Gly Gly Arg Asp Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser 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 Gly Gln Gly Gly Asn Tyr Leu Phe Ala 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
210 215 220

<210> 164
<211> 235
<212> PRT
<213> 人工序列

<220>
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<400> 164

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Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1               5                  10                  15

Val Gln Cys Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30

Pro Gly Ala Thr Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile
        35                  40                  45

Lys Asp Asp Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu
    50                  55                  60

Asp Trp Ile Gly Trp Ile Val Pro Arg Asn Ala Asn Thr Val Tyr Ala
65                  70                  75                  80

Ser Lys Phe Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Thr Asn
                85                  90                  95

Thr Ala Tyr Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val
        115                 120                 125

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
    130                 135                 140

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
145                 150                 155                 160

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
                165                 170                 175

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
            180                 185                 190

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
```

195 200 205

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
210 215 220

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
225 230 235

<210> 165
<211> 216
<212> PRT
<213> 人工序列

<220>
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<400> 165

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile
35 40 45

Gly Trp Ile Val Pro Arg Asn Ala Asn Thr Val Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr
65 70 75 80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser

115 120 125

Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
180 185 190

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Lys Val Glu Pro Lys Ser Cys
210 215

<210> 166
<211> 236
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-6b-2 FIT-Ig多肽鏈3號

<400> 166

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ser Arg Cys Asp Ile Val Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser
35 40 45

Gln Asp Val Asn Thr Val Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys

50 55 60

Ala Pro Lys Val Leu Ile Ser Trp Ala Ser Thr Arg His Thr Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

His Tyr Thr Thr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 167
<211> 214
<212> PRT

<213> 人工序列

<220>
<223> HumAb709-8之VL-CL

<400> 167

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Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Val
            20                  25                  30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Val Leu Ile
        35                  40                  45

Ser Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Tyr
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val 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> 168
<211> 679
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-6a-3 FIT-Ig多肽鏈1號

<400> 168

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ser Arg Cys Asp Ile Val Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser
35 40 45

Gln Asp Val Asn Thr Val Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Val Leu Ile Ser Trp Ala Ser Thr Arg His Thr Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

His Tyr Thr Thr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Glu Val Gln Leu
225 230 235 240

Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Thr Val Lys Leu
245 250 255

Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Asp Tyr Met His Trp
260 265 270

Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile Gly Trp Ile Val
275 280 285

Pro Arg Asn Ala Asn Thr Val Tyr Ala Ser Lys Phe Gln Gly Lys Ala
290 295 300

Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr Leu Glu Leu Ser

305 310 315 320

Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Thr Val Tyr Gly
325 330 335

Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
340 345 350

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
355 360 365

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
370 375 380

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
385 390 395 400

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
405 410 415

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
420 425 430

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
435 440 445

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
450 455 460

Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
465 470 475 480

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
485 490 495

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
500 505 510

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
515 520 525

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
530 535 540

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
545 550 555 560

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
565 570 575

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
580 585 590

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
595 600 605

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
610 615 620

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
625 630 635 640

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
645 650 655

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
660 665 670

Leu Ser Leu Ser Pro Gly Lys
675

<210> 169
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> HumAb709-8之VL-CL

<400> 169

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Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Val
            20                  25                  30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Val Leu Ile
        35                  40                  45

Ser Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Tyr
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val 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
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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> 170
<211> 216
<212> PRT
<213> 人工序列

<220>
<223> HumAb747V-73之VH-CH1

<400> 170

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile
35 40 45

Gly Trp Ile Val Pro Arg Asn Ala Asn Thr Val Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr
65 70 75 80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser

115 120 125

Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
180 185 190

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Lys Val Glu Pro Lys Ser Cys
210 215

<210> 171
<211> 240
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-6a-3 FIT-Ig多肽鏈2號

<400> 171

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1 5 10 15

Val Gln Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

Ser Phe Tyr Thr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu

50 55 60

Glu Trp Val Ala Thr Ile Ser Gly Gly Gly Arg Asp Thr Tyr Tyr Pro
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
85 90 95

Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Gly Gln Gly Gly Asn Tyr Leu Phe Ala Tyr Trp Gly
115 120 125

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
130 135 140

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
145 150 155 160

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
165 170 175

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
180 185 190

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
195 200 205

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
210 215 220

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
225 230 235 240

<210> 172
<211> 221
<212> PRT

<213> 人工序列

<220>
<223> HumAb709-8之VH-CH1

<400> 172

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Glu Val Gln Leu Val 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 Phe Tyr
            20                  25                  30

Thr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Thr Ile Ser Gly Gly Gly Arg Asp Thr Tyr Tyr Pro Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser 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 Gly Gln Gly Gly Asn Tyr Leu Phe Ala 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
210 215 220

<210> 173
<211> 236
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-6a-3 FIT-Ig多肽鏈3號

<400> 173

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ser Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Gln Glu Ile Ser Gly Tyr Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly
50 55 60

Ala Ile Lys Arg Leu Ile Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln
100 105 110

Tyr Ala Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 174
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> HumAb747V-73之VL-CL

<400> 174

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly Ala Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu 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> 175

<211> 684
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-6b-3 FIT-Ig多肽鏈1號

<400> 175

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Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                  10                  15

Phe Pro Gly Ser Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20                  25                  30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35                  40                  45

Gln Glu Ile Ser Gly Tyr Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly
    50                  55                  60

Ala Ile Lys Arg Leu Ile Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr
                85                  90                  95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln
            100                 105                 110

Tyr Ala Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu
        115                 120                 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
```

165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Glu Val Gln Leu
225 230 235 240

Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu
245 250 255

Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Phe Tyr Thr Met Ser Trp
260 265 270

Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Thr Ile Ser
275 280 285

Gly Gly Gly Arg Asp Thr Tyr Tyr Pro Asp Ser Val Lys Gly Arg Phe
290 295 300

Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn
305 310 315 320

Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Gly Gln Gly
325 330 335

Gly Asn Tyr Leu Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
340 345 350

Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser
355 360 365

Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys
370 375 380

Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu
385 390 395 400

Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu
405 410 415

Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr
420 425 430

Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val
435 440 445

Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro
450 455 460

Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe
465 470 475 480

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
485 490 495

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
500 505 510

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
515 520 525

Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr
530 535 540

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
545 550 555 560

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala

565 570 575

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
580 585 590

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
595 600 605

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
610 615 620

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
625 630 635 640

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
645 650 655

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
660 665 670

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
675 680

<210> 176
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> HumAb747V-73之VL-CL

<400> 176

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly Ala Ile Lys Arg Leu Ile

35 40 45

Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu 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> 177
<211> 221
<212> PRT

<213> 人工序列

<220>
<223> HumAb709-8之VH-CH1

<400> 177

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Glu Val Gln Leu Val 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 Phe Tyr
            20                  25                  30

Thr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Thr Ile Ser Gly Gly Gly Arg Asp Thr Tyr Tyr Pro Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser 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 Gly Gln Gly Gly Asn Tyr Leu Phe Ala 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
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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
210 215 220

<210> 178
<211> 235
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-6b-3 FIT-Ig多肽鏈2號

<400> 178

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1 5 10 15

Val Gln Cys Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30

Pro Gly Ala Thr Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile
35 40 45

Lys Asp Asp Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu
50 55 60

Asp Trp Ile Gly Trp Ile Val Pro Arg Asn Ala Asn Thr Val Tyr Ala
65 70 75 80

Ser Lys Phe Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Thr Asn
85 90 95

Thr Ala Tyr Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val
115 120 125

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
130 135 140

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
145 150 155 160

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
165 170 175

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
180 185 190

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
195 200 205

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
210 215 220

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
225 230 235

<210> 179
<211> 216
<212> PRT
<213> 人工序列

<220>
<223> HumAb747V-73之VH-CH1

<400> 179

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile
35 40 45

Gly Trp Ile Val Pro Arg Asn Ala Asn Thr Val Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr
65 70 75 80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
115 120 125

Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
180 185 190

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Lys Val Glu Pro Lys Ser Cys
210 215

<210> 180

<211> 236
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-6b-3 FIT-Ig多肽鏈3號

<400> 180

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Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                  10                  15

Phe Pro Gly Ser Arg Cys Asp Ile Val Met Thr Gln Ser Pro Ser Ser
            20                  25                  30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser
        35                  40                  45

Gln Asp Val Asn Thr Val Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys
    50                  55                  60

Ala Pro Lys Val Leu Ile Ser Trp Ala Ser Thr Arg His Thr Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr
                85                  90                  95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            100                 105                 110

His Tyr Thr Thr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
        115                 120                 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
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165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 181
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> HumAb709-8之VL-CL

<400> 181

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Asn Thr Val
20 25 30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Val Leu Ile
35 40 45

Ser Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Tyr

85 90 95

Thr Phe Gly Gly Gly Thr Lys Val 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> 182
<211> 679
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-7a-1 FIT-Ig多肽鏈1號

<400> 182

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ser Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser

20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser
35 40 45

Asp His Ile Asn Asn Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Leu Leu Ile Tyr Gly Ala Thr Ser Leu Glu Thr Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Phe Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

Tyr Trp Ser Pro Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Glu Val Gln Leu
225 230 235 240

Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Thr Val Lys Leu
245 250 255

Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Asp Tyr Met His Trp
260 265 270

Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile Gly Trp Ile Val
275 280 285

Pro Glu Asn Ala Asn Thr Val Tyr Ala Ser Lys Phe Gln Gly Lys Ala
290 295 300

Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr Leu Glu Leu Ser
305 310 315 320

Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Thr Val Tyr Gly
325 330 335

Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
340 345 350

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
355 360 365

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
370 375 380

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
385 390 395 400

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
405 410 415

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys

420 425 430

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
435 440 445

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
450 455 460

Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
465 470 475 480

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
485 490 495

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
500 505 510

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
515 520 525

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
530 535 540

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
545 550 555 560

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
565 570 575

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
580 585 590

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
595 600 605

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
610 615 620

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
625 630 635 640

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
645 650 655

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
660 665 670

Leu Ser Leu Ser Pro Gly Lys
675

<210> 183
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> mAb HumAb713-7之VL-CL

<400> 183

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Asp His Ile Asn Asn Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Gly Ala Thr Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Trp Ser Pro Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val 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> 184
<211> 216
<212> PRT
<213> 人工序列

<220>
<223> HumAb747V-67之VH-CH1

<400> 184

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile
35 40 45

Gly Trp Ile Val Pro Glu Asn Ala Asn Thr Val Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr
65 70 75 80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
115 120 125

Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
180 185 190

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Lys Val Glu Pro Lys Ser Cys
210 215

<210> 185

<211> 243
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-7a-1 FIT-Ig多肽鏈2號

<400> 185

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1 5 10 15

Val Gln Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ser
35 40 45

Ser Asp Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Tyr Ile Ser Ser Gly Ser Tyr Thr Ile Tyr Tyr Ala
65 70 75 80

Asp Thr Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
85 90 95

Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Lys Arg Gly Gly Ser Ser His Val Asn Val Met Asp
115 120 125

Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys
130 135 140

Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
145 150 155 160

Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro

165 170 175

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
180 185 190

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
195 200 205

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
210 215 220

Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
225 230 235 240

Lys Ser Cys

<210> 186
<211> 224
<212> PRT
<213> 人工序列

<220>
<223> HumAb713-7之VH-CH1

<400> 186

Glu Val Gln Leu Val 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 Ser Ser Asp Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Gly Ser Tyr Thr Ile Tyr Tyr Ala Asp Thr Val
50 55 60

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

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Arg Gly Gly Ser Ser His Val Asn Val Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
210 215 220

<210> 187
<211> 236
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-7a-1 FIT-Ig多肽鏈3號

<400> 187

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp

1 5 10 15

Phe Pro Gly Ser Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Gln Glu Ile Ser Gly Tyr Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly
50 55 60

Ala Ile Lys Arg Leu Ile Tyr Ala Ala Ser Ala Leu Asp Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln
100 105 110

Tyr Ala Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 188
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> HumAb747V-67之VL-CL

<400> 188

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly Ala Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Ala Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu 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> 189
<211> 687
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-7b-1 FIT-Ig多肽鏈1號

<400> 189

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ser Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Gln Glu Ile Ser Gly Tyr Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly
50 55 60

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Ala Ile Lys Arg Leu Ile Tyr Ala Ala Ser Ala Leu Asp Ser Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr
                85                  90                  95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln
            100                 105                 110

Tyr Ala Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu
        115                 120                 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        195                 200                 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
    210                 215                 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Glu Val Gln Leu
225                 230                 235                 240

Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu
                245                 250                 255

Ser Cys Ala Ala Ser Gly Phe Thr Ser Ser Asp Tyr Gly Met His Trp
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260 265 270

Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Tyr Ile Ser
275 280 285

Ser Gly Ser Tyr Thr Ile Tyr Tyr Ala Asp Thr Val Lys Gly Arg Phe
290 295 300

Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn
305 310 315 320

Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys Arg Gly
325 330 335

Gly Ser Ser His Val Asn Val Met Asp Tyr Trp Gly Gln Gly Thr Thr
340 345 350

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
355 360 365

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
370 375 380

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
385 390 395 400

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
405 410 415

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
420 425 430

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
435 440 445

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
450 455 460

Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
465 470 475 480

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
485 490 495

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
500 505 510

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
515 520 525

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
530 535 540

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
545 550 555 560

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
565 570 575

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
580 585 590

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
595 600 605

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
610 615 620

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
625 630 635 640

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
645 650 655

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu

660 665 670

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
675 680 685

<210> 190
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> HumAb747V-67之VL-CL

<400> 190

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly Ala Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Ala Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu 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> 191
<211> 224
<212> PRT
<213> 人工序列

<220>
<223> HumAb713-7之VH-CH1

<400> 191

Glu Val Gln Leu Val 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 Ser Ser Asp Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Gly Ser Tyr Thr Ile Tyr Tyr Ala Asp Thr Val
50 55 60

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

65 70 75 80

Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Arg Gly Gly Ser Ser His Val Asn Val Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
210 215 220

<210> 192
<211> 235
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<400> 192

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly

1 5 10 15

Val Gln Cys Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30

Pro Gly Ala Thr Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile
35 40 45

Lys Asp Asp Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu
50 55 60

Asp Trp Ile Gly Trp Ile Val Pro Glu Asn Ala Asn Thr Val Tyr Ala
65 70 75 80

Ser Lys Phe Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Thr Asn
85 90 95

Thr Ala Tyr Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val
115 120 125

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
130 135 140

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
145 150 155 160

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
165 170 175

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
180 185 190

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
195 200 205

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
210 215 220

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
225 230 235

<210> 193
<211> 216
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<213> 人工序列

<220>
<223> HumAb747V-67之VH-CH1

<400> 193

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile
35 40 45

Gly Trp Ile Val Pro Glu Asn Ala Asn Thr Val Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr
65 70 75 80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
115 120 125

Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
180 185 190

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Lys Val Glu Pro Lys Ser Cys
210 215

<210> 194
<211> 236
<212> PRT
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<220>
<223> FIT107-1-7b-1 FIT-Ig多肽鏈3號

<400> 194

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ser Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser
35 40 45

Asp His Ile Asn Asn Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Leu Leu Ile Tyr Gly Ala Thr Ser Leu Glu Thr Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Phe Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

Tyr Trp Ser Pro Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 195
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<400> 195

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Asp His Ile Asn Asn Trp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Gly Ala Thr Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Tyr Thr Phe Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Trp Ser Pro Pro Tyr
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val 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
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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> 196
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<220>
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<400> 196

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ser Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser
35 40 45

Asp His Ile Asn Asn Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Leu Leu Ile Tyr Gly Ala Thr Ser Leu Glu Thr Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Phe Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

Tyr Trp Ser Pro Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile

115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Glu Val Gln Leu
225 230 235 240

Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Thr Val Lys Leu
245 250 255

Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Asp Tyr Met His Trp
260 265 270

Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile Gly Trp Ile Val
275 280 285

Pro Arg Asn Ala Asn Thr Val Tyr Ala Ser Lys Phe Gln Gly Lys Ala
290 295 300

Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr Leu Glu Leu Ser
305 310 315 320

Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Thr Val Tyr Gly
325 330 335

Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
340 345 350

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
355 360 365

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
370 375 380

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
385 390 395 400

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
405 410 415

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
420 425 430

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
435 440 445

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
450 455 460

Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
465 470 475 480

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
485 490 495

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
500 505 510

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr

515 520 525

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
530 535 540

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
545 550 555 560

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
565 570 575

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
580 585 590

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
595 600 605

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
610 615 620

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
625 630 635 640

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
645 650 655

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
660 665 670

Leu Ser Leu Ser Pro Gly Lys
675

<210> 197
<211> 214
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<223> HumAb713-7之VL-CL

<400> 197

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Asp His Ile Asn Asn Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Gly Ala Thr Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Trp Ser Pro Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val 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> 198
<211> 216
<212> PRT
<213> 人工序列

<220>
<223> HumAb747V-72之VH-CH1

<400> 198

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile
35 40 45

Gly Trp Ile Val Pro Arg Asn Ala Asn Thr Val Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr
65 70 75 80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
115 120 125

Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
180 185 190

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Lys Val Glu Pro Lys Ser Cys
210 215

<210> 199
<211> 243
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-7a-2 FIT-Ig多肽鏈2號

<400> 199

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1 5 10 15

Val Gln Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ser
35 40 45

Ser Asp Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Tyr Ile Ser Ser Gly Ser Tyr Thr Ile Tyr Tyr Ala
65 70 75 80

Asp Thr Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
85 90 95

Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Lys Arg Gly Gly Ser Ser His Val Asn Val Met Asp
115 120 125

Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys
130 135 140

Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
145 150 155 160

Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
165 170 175

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
180 185 190

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
195 200 205

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
210 215 220

Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
225 230 235 240

Lys Ser Cys

<210> 200

<211> 224
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<213> 人工序列

<220>
<223> HumAb713-7之VH-CH1

<400> 200

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Glu Val Gln Leu Val 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 Ser Ser Asp Tyr
            20                  25                  30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Ser Gly Ser Tyr Thr Ile Tyr Tyr Ala Asp Thr Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Arg Gly Gly Ser Ser His Val Asn Val Met Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
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165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
210 215 220

<210> 201
<211> 236
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-7a-2 FIT-Ig多肽鏈3號

<400> 201

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ser Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Gln Glu Ile Ser Gly Tyr Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly
50 55 60

Ala Ile Lys Arg Leu Ile Tyr Ala Ala Ser Ala Leu Asp Leu Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln

100 105 110

Tyr Ala Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 202
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> HumAb747V-72之VL-CL

<400> 202

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr

20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly Ala Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Ala Leu Asp Leu Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu 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> 203
<211> 687
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-7b-2 FIT-Ig多肽鏈1號

<400> 203

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Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                  10                  15

Phe Pro Gly Ser Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20                  25                  30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35                  40                  45

Gln Glu Ile Ser Gly Tyr Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly
    50                  55                  60

Ala Ile Lys Arg Leu Ile Tyr Ala Ala Ser Ala Leu Asp Leu Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr
                85                  90                  95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln
            100                 105                 110

Tyr Ala Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu
        115                 120                 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160
```

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Glu Val Gln Leu
225 230 235 240

Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu
245 250 255

Ser Cys Ala Ala Ser Gly Phe Thr Ser Ser Asp Tyr Gly Met His Trp
260 265 270

Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Tyr Ile Ser
275 280 285

Ser Gly Ser Tyr Thr Ile Tyr Tyr Ala Asp Thr Val Lys Gly Arg Phe
290 295 300

Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn
305 310 315 320

Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys Arg Gly
325 330 335

Gly Ser Ser His Val Asn Val Met Asp Tyr Trp Gly Gln Gly Thr Thr
340 345 350

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu

355 360 365

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
370 375 380

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
385 390 395 400

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
405 410 415

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
420 425 430

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
435 440 445

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
450 455 460

Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
465 470 475 480

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
485 490 495

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
500 505 510

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
515 520 525

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
530 535 540

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
545 550 555 560

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
565 570 575

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
580 585 590

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
595 600 605

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
610 615 620

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
625 630 635 640

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
645 650 655

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
660 665 670

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
675 680 685

<210> 204
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> mAb HumAb747V-72之VL-CL

<400> 204

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly Ala Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Ala Leu Asp Leu Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu 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> 205

<211> 224
<212> PRT
<213> 人工序列

<220>
<223> HumAb713-7之VH-CH1

<400> 205

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Glu Val Gln Leu Val 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 Ser Ser Asp Tyr
            20                  25                  30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Ser Gly Ser Tyr Thr Ile Tyr Tyr Ala Asp Thr Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Arg Gly Gly Ser Ser His Val Asn Val Met Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
        115                 120                 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
    130                 135                 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145                 150                 155                 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
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165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
210 215 220

<210> 206
<211> 235
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-7b-2 FIT-Ig多肽鏈2號

<400> 206

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1 5 10 15

Val Gln Cys Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30

Pro Gly Ala Thr Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile
35 40 45

Lys Asp Asp Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu
50 55 60

Asp Trp Ile Gly Trp Ile Val Pro Arg Asn Ala Asn Thr Val Tyr Ala
65 70 75 80

Ser Lys Phe Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Thr Asn
85 90 95

Thr Ala Tyr Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val

100 105 110

Tyr Tyr Cys Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val
115 120 125

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
130 135 140

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
145 150 155 160

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
165 170 175

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
180 185 190

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
195 200 205

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
210 215 220

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
225 230 235

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<400> 207

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Asp

20 25 30

Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile
35 40 45

Gly Trp Ile Val Pro Arg Asn Ala Asn Thr Val Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr
65 70 75 80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
115 120 125

Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
180 185 190

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Lys Val Glu Pro Lys Ser Cys
210 215

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<223> FIT107-1-7b-2 FIT-Ig多肽鏈3號

<400> 208

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ser Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser
35 40 45

Asp His Ile Asn Asn Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Leu Leu Ile Tyr Gly Ala Thr Ser Leu Glu Thr Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Phe Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

Tyr Trp Ser Pro Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 209
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<400> 209

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Asp His Ile Asn Asn Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Gly Ala Thr Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Trp Ser Pro Pro Tyr
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val 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> 210
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Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ser Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser
35 40 45

Asp His Ile Asn Asn Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Leu Leu Ile Tyr Gly Ala Thr Ser Leu Glu Thr Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Phe Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

Tyr Trp Ser Pro Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser

210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Glu Val Gln Leu
225 230 235 240

Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Thr Val Lys Leu
245 250 255

Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Asp Tyr Met His Trp
260 265 270

Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile Gly Trp Ile Val
275 280 285

Pro Arg Asn Ala Asn Thr Val Tyr Ala Ser Lys Phe Gln Gly Lys Ala
290 295 300

Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr Leu Glu Leu Ser
305 310 315 320

Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Thr Val Tyr Gly
325 330 335

Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
340 345 350

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
355 360 365

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
370 375 380

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
385 390 395 400

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
405 410 415

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
420 425 430

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
435 440 445

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
450 455 460

Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
465 470 475 480

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
485 490 495

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
500 505 510

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
515 520 525

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
530 535 540

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
545 550 555 560

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
565 570 575

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys
580 585 590

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
595 600 605

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys

610 615 620

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
625 630 635 640

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
645 650 655

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
660 665 670

Leu Ser Leu Ser Pro Gly Lys
675

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<400> 211

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Asp His Ile Asn Asn Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Gly Ala Thr Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Phe Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Trp Ser Pro Pro Tyr

85 90 95

Thr Phe Gly Gly Gly Thr Lys Val 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> 212
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<220>
<223> HumAb747V-73之VH-CH1

<400> 212

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Asp

20 25 30

Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile
35 40 45

Gly Trp Ile Val Pro Arg Asn Ala Asn Thr Val Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr
65 70 75 80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
115 120 125

Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
180 185 190

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Lys Val Glu Pro Lys Ser Cys
210 215

<210> 213
<211> 243
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-7a-3 FIT-Ig多肽鏈2號

<400> 213

Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1 5 10 15

Val Gln Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ser
35 40 45

Ser Asp Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Tyr Ile Ser Ser Gly Ser Tyr Thr Ile Tyr Tyr Ala
65 70 75 80

Asp Thr Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
85 90 95

Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Lys Arg Gly Gly Ser Ser His Val Asn Val Met Asp
115 120 125

Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys
130 135 140

Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
145 150 155 160

Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
165 170 175

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
180 185 190

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
195 200 205

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
210 215 220

Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
225 230 235 240

Lys Ser Cys

<210> 214
<211> 224
<212> PRT
<213> 人工序列

<220>
<223> HumAb713-7之VH-CH1

<400> 214

Glu Val Gln Leu Val 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 Ser Ser Asp Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Gly Ser Tyr Thr Ile Tyr Tyr Ala Asp Thr Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Arg Gly Gly Ser Ser His Val Asn Val Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
210 215 220

<210> 215
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<400> 215

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Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                  10                  15

Phe Pro Gly Ser Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20                  25                  30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35                  40                  45

Gln Glu Ile Ser Gly Tyr Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly
    50                  55                  60

Ala Ile Lys Arg Leu Ile Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr
                85                  90                  95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln
            100                 105                 110

Tyr Ala Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu
        115                 120                 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
    130                 135                 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
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195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 216
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<212> PRT
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<223> HumAb747V-73之VL-CL

<400> 216

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly Ala Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu 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> 217
<211> 687
<212> PRT
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<220>
<223> FIT107-1-7b-3 FIT-Ig多肽鏈1號

<400> 217

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ser Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Gln Glu Ile Ser Gly Tyr Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly

50 55 60

Ala Ile Lys Arg Leu Ile Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln
100 105 110

Tyr Ala Ser Tyr Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Glu Val Gln Leu
225 230 235 240

Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu
245 250 255

```
Ser Cys Ala Ala Ser Gly Phe Thr Ser Ser Asp Tyr Gly Met His Trp
            260                 265                 270

Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Tyr Ile Ser
        275                 280                 285

Ser Gly Ser Tyr Thr Ile Tyr Tyr Ala Asp Thr Val Lys Gly Arg Phe
    290                 295                 300

Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn
305                 310                 315                 320

Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys Arg Gly
                325                 330                 335

Gly Ser Ser His Val Asn Val Met Asp Tyr Trp Gly Gln Gly Thr Thr
            340                 345                 350

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        355                 360                 365

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    370                 375                 380

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
385                 390                 395                 400

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                405                 410                 415

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            420                 425                 430

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        435                 440                 445

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His
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450 455 460

Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val
465 470 475 480

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
485 490 495

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
500 505 510

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
515 520 525

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
530 535 540

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
545 550 555 560

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
565 570 575

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
580 585 590

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
595 600 605

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
610 615 620

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
625 630 635 640

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
645 650 655

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
660 665 670

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
675 680 685

<210> 218
<211> 214
<212> PRT
<213> 人工序列

<220>
<223> HumAb747V-73之VL-CL

<400> 218

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Glu Ile Ser Gly Tyr
20 25 30

Leu Ser Trp Leu Gln Gln Lys Pro Gly Gly Ala Ile Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Thr Leu Asp Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Arg Ser Gly Ser Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Asp Tyr Tyr Cys Leu Gln Tyr Ala Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Leu 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> 219
<211> 224
<212> PRT
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<220>
<223> HumAb713-7之VH-CH1

<400> 219

Glu Val Gln Leu Val 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 Ser Ser Asp Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Gly Ser Tyr Thr Ile Tyr Tyr Ala Asp Thr Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Arg Gly Gly Ser Ser His Val Asn Val Met Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
210 215 220

<210> 220
<211> 235
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<213> 人工序列

<220>
<223> FIT107-1-7b-3 FIT-Ig多肽鏈2號

<400> 220

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Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
1               5                  10                  15

Val Gln Cys Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30

Pro Gly Ala Thr Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile
        35                  40                  45

Lys Asp Asp Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu
    50                  55                  60

Asp Trp Ile Gly Trp Ile Val Pro Arg Asn Ala Asn Thr Val Tyr Ala
65                  70                  75                  80

Ser Lys Phe Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Thr Asn
                85                  90                  95

Thr Ala Tyr Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val
        115                 120                 125

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
    130                 135                 140

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
145                 150                 155                 160

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
                165                 170                 175

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
            180                 185                 190

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
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195 200 205

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
210 215 220

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
225 230 235

<210> 221
<211> 216
<212> PRT
<213> 人工序列

<220>
<223> HumAb747V-73之VH-CH1

<400> 221

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile
35 40 45

Gly Trp Ile Val Pro Arg Asn Ala Asn Thr Val Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr
65 70 75 80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser

115 120 125

Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
130 135 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145 150 155 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
165 170 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
180 185 190

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
195 200 205

Lys Lys Val Glu Pro Lys Ser Cys
210 215

<210> 222
<211> 236
<212> PRT
<213> 人工序列

<220>
<223> FIT107-1-7b-3 FIT-Ig多肽鏈3號

<400> 222

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Phe Pro Gly Ser Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser
35 40 45

Asp His Ile Asn Asn Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys

50 55 60

Ala Pro Lys Leu Leu Ile Tyr Gly Ala Thr Ser Leu Glu Thr Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Phe Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

Tyr Trp Ser Pro Pro Tyr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145 150 155 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
165 170 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
180 185 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
195 200 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
210 215 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 223
<211> 214
<212> PRT

<213> 人工序列

<220>
<223> HumAb713-7之VL-CL

<400> 223

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Asp His Ile Asn Asn Trp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Gly Ala Thr Ser Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Tyr Thr Phe Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Trp Ser Pro Pro Tyr
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val 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
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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> 224
<211> 16
<212> PRT
<213> 人工序列

<220>
<223> 抗LAG-3抗體HumAb747V-67之CDR-H2，具有G55A取代(Kabat編號)

<400> 224
Trp Ile Val Pro Glu Asn Ala Asn Thr Val Tyr Ala Ser Lys Phe Gln
1 5 10 15

Gly

<210> 225
<211> 16
<212> PRT
<213> 人工序列

<220>
<223> 抗LAG-3抗體HumAb747V-72或HumAb747V-73之CDR-H2，具有G55A取代(Kabat編號)

<400> 225
Trp Ile Val Pro Arg Asn Ala Asn Thr Va Tyr Ala Ser Lys Phe Gln
1 5 10 15

Gly

<210> 226
<211> 113
<212> PRT
<213> 人工序列

<220>
<223> 具有G55A取代之VH(Kabat編號)

<400> 226

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile
35 40 45

Gly Trp Ile Val Pro Glu Asn Ala Asn Thr Val Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr
65 70 75 80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser

<210> 227
<211> 113
<212> PRT
<213> 人工序列

<220>
<223> 具有G55A取代之VH(Kabat編號)

<400> 227

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Asp
20 25 30

Tyr Met His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Asp Trp Ile
35 40 45

Gly Trp Ile Val Pro Arg Asn Ala Asn Thr Val Tyr Ala Ser Lys Phe
50 55 60

Gln Gly Lys Ala Thr Ile Thr Ala Asp Thr Ser Thr Asn Thr Ala Tyr
65 70 75 80

Leu Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Val Tyr Gly Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser

【發明申請專利範圍】

【請求項1】

一種結合蛋白，其包含第一、第二及第三多肽鏈，其中

該第一多肽鏈自胺基端至羧基端包含：(i) VL_A-CL-VH_B-CH1-Fc，其中CL直接與VH_B融合；或(ii) VH_B-CH1-VL_A-CL-Fc，其中CH1直接與VL_A融合；

該第二多肽鏈自胺基端至羧基端包含VH_A-CH1；及

該第三多肽鏈自胺基端至羧基端包含VL_B-CL；

其中VL為輕鏈可變域，CL為輕鏈恆定域，VH為重鏈可變域，CH1為重鏈恆定域，Fc為免疫球蛋白Fc區，A為PD-1或LAG-3之抗原決定位且B為PD-1或LAG-3之抗原決定位，其限制條件為A與B不同，該結合蛋白為雙特異性及多價，能夠與PD-1及LAG-3兩者結合：

其中當A為LAG-3之抗原決定位且B為PD-1之抗原決定位時，VH_A和VL_A分別表示VH_{LAG-3}及VL_{LAG-3}且VH_B和VL_B分別表示VH_{PD-1}及VL_{PD-1}，或

當B為LAG-3之抗原決定位且A為PD-1之抗原決定位時，VL_B和VH_B分別表示VL_{LAG-3}及VH_{LAG-3}且VL_A和VH_A分別表示VL_{PD-1}及VH_{PD-1}，且

其中該VH_{LAG-3}和VL_{LAG-3}分別包含CDR-H1、CDR-H2及CDR-H3，以及CDR-L1、CDR-L2及CDR-L3，且該等CDR選自以下CDR組之群組：

a)包含DDYMH(SEQ ID NO:135之殘基31-35)之CDR-H1、包含WIVPENANTVYASKFQG(SEQ ID NO:224)之CDR-H2、包含YGDY(SEQ ID NO:135之殘基99-102)之CDR-H3、包含

RASQEISGYLS(SEQ ID NO:138之殘基24-34)之CDR-L1、包含AASALDS(SEQ ID NO:138之殘基50-56)之CDR-L2及包LQYASYPLT(SEQ ID NO:138之殘基89-97)之CDR-L3；

b)包含DDYMH(SEQ ID NO:136之殘基31-35)之CDR-H1、包含WIVPRNANTVYASKFQG(SEQ ID NO:225)之CDR-H2、包含YGDY(SEQ ID NO:136之殘基99-102)之CDR-H3、包含RASQEISGYLS(SEQ ID NO:139之殘基24-34)之CDR-L1、包含AASALDL(SEQ ID NO:139之殘基50-56)之CDR-L2及包含LQYASYPLT(SEQ ID NO:139之殘基89-97)之CDR-L3；及

c)包含DDYMH(SEQ ID NO:136之殘基31-35)之CDR-H1、包含WIVPRNANTVYASKFQG(SEQ ID NO:225)之CDR-H2、包含YGDY(SEQ ID NO:136之殘基99-102)之CDR-H3、包含RASQEISGYLS(SEQ ID NO:117之殘基24-34)之CDR-L1、包含AASTLDS(SEQ ID NO:117之殘基50-56)之CDR-L2及包含 LQYASYPLT(SEQ ID NO:117之殘基89-97)之CDR-L3;且

其中該VH_{PD-1}和VL_{PD-1}分別包含CDR-H1、CDR-H2及CDR-H3，以及CDR-L1、CDR-L2及CDR-L3，且該等CDR分別為：

包含DYGMH (SEQ ID NO:10之殘基31-35)之CDR-H1、包含YISSGSYTIYYADTVKG(SEQ ID NO:10之殘基50-66)之CDR-H2、包含RGGSSHVNVMDY（SEQ ID NO:10之殘基99-110）之CDR-H3、包含KASDHINNWLA (SEQ ID NO:11之殘基24-34)之CDR-L1、包含GATSLET (SEQ ID NO:11之殘基50-56)之CDR-L2及包含QQYWSPPYT(SEQ ID NO:11之殘基89-97)之CDR-L3。

【請求項2】

如請求項1之結合蛋白，其中該VL_A-CL域及VH_A-CH1域與和抗原靶標PD-1及LAG-3中一者結合的親本抗體相同，且該VL_B-CL域及VH_B-CH1域與和抗原靶標PD-1及LAG-3中另一者結合的不同親本抗體相同。

【請求項3】

如請求項2之結合蛋白，其包含第一、第二及第三多肽鏈，其中該第一多肽鏈自胺基端至羧基端包含VL_{PD-1}-CL-VH_{LAG-3}-CH1-Fc，其中CL直接與VH_{LAG-3}融合，

其中該第二多肽鏈自胺基端至羧基端包含VH_{PD-1}-CH1；及

其中該第三多肽鏈自胺基端至羧基端包含VL_{LAG-3}-CL；

其中VL_{PD-1}為抗PD-1抗體之輕鏈可變域，CL為輕鏈恆定域，VH_{PD-1}為抗PD-1抗體之重鏈可變域，CH1為重鏈恆定域，VL_{LAG-3}為抗LAG-3抗體之輕鏈可變域，VH_{LAG-3}為抗LAG-3抗體之重鏈可變域且Fc為免疫球蛋白Fc區。

【請求項4】

如請求項3之結合蛋白，其中在該第一多肽鏈中，該等VL_{PD-1}-CL域與抗PD-1親本抗體之輕鏈相同，該等VH_{PD-1}-CH1域與抗PD-1親本抗體之重鏈可變域及重鏈恆定域相同，該等VL_{LAG-3}-CL域與抗LAG-3親本抗體之輕鏈相同，且該等VH_{LAG-3}-CH1域與抗LAG-3親本抗體之重鏈可變域及重鏈恆定域相同。

【請求項5】

如請求項2之結合蛋白，其包含第一、第二及第三多肽鏈，其中該第一多肽鏈自胺基端至羧基端包含VL_{LAG-3}-CL-VH_{PD-1}-CH1-Fc，其中CL直

接與VH_{PD-1}融合，

其中該第二多肽鏈自胺基端至羧基端包含VH_{LAG-3}-CH1；及

其中該第三多肽鏈自胺基端至羧基端包含VL_{PD-1}-CL；

其中VL_{PD-1}為抗PD-1抗體之輕鏈可變域，CL為輕鏈恆定域，VH_{PD-1}為抗PD-1抗體之重鏈可變域，CH1為重鏈恆定域，VL_{LAG-3}為抗LAG-3抗體之輕鏈可變域，VH_{LAG-3}為抗LAG-3抗體之重鏈可變域且Fc為免疫球蛋白Fc區。

【請求項6】

如請求項5之結合蛋白，其中在該第一多肽鏈中，該等VL_{LAG-3}-CL域與抗LAG-3親本抗體之輕鏈相同，該等VH_{LAG-3}-CH1域與抗LAG-3親本抗體之重鏈可變域及重鏈恆定域相同，該等VL_{PD-1}-CL域與抗PD-1親本抗體之輕鏈相同，且該等VH_{PD-1}-CH1域與抗PD-1親本抗體之重鏈可變域及重鏈恆定域相同。

【請求項7】

如請求項2之結合蛋白，其包含第一、第二及第三多肽鏈，其中該第一多肽鏈自胺基端至羧基端包含VH_{LAG-3}-CH1-VL_{PD-1}-CL-Fc，其中CH1直接與VL_{PD-1}融合，

其中該第二多肽鏈自胺基端至羧基端包含VL_{LAG-3}-CL；及

其中該第三多肽鏈自胺基端至羧基端包含VH_{PD-1}-CH1；

其中VL_{PD-1}為抗PD-1抗體之輕鏈可變域，CL為輕鏈恆定域，VH_{PD-1}為抗PD-1抗體之重鏈可變域，CH1為重鏈恆定域，VL_{LAG-3}為抗LAG-3抗體之輕鏈可變域，VH_{LAG-3}為抗LAG-3抗體之重鏈可變域且Fc為免疫球蛋白Fc區。

【請求項8】

如請求項7之結合蛋白，其中在該第一多肽鏈中，該等VL_{LAG-3}-CL域與抗LAG-3親本抗體之輕鏈相同，該等VH_{LAG-3}-CH1域與抗LAG-3親本抗體之重鏈可變域及重鏈恆定域相同，該等VL_{PD-1}-CL域與抗PD-1親本抗體之輕鏈相同，且該等VH_{PD-1}-CH1域與抗PD-1親本抗體之重鏈可變域及重鏈恆定域相同。

【請求項9】

如請求項2之結合蛋白，其包含第一、第二及第三多肽鏈，其中該第一多肽鏈自胺基端至羧基端包含VH_{PD-1}-CH1-VL_{LAG-3}-CL-Fc，其中CH1直接與VL_{LAG-3}融合，

其中該第二多肽鏈自胺基端至羧基端包含VL_{PD-1}-CL；及

其中該第三多肽鏈自胺基端至羧基端包含VH_{LAG-3}-CH1；

其中VL_{PD-1}為抗PD-1抗體之輕鏈可變域，CL為輕鏈恆定域，VH_{PD-1}為抗PD-1抗體之重鏈可變域，CH1為重鏈恆定域，VL_{LAG-3}為抗LAG-3抗體之輕鏈可變域，VH_{LAG-3}為抗LAG-3抗體之重鏈可變域且Fc為免疫球蛋白Fc區。

【請求項10】

如請求項9之結合蛋白，其中在該第一多肽鏈中，該等VL_{LAG-3}-CL域與抗LAG-3親本抗體之輕鏈相同，該等VH_{LAG-3}-CH1域與抗LAG-3親本抗體之重鏈可變域及重鏈恆定域相同，該等VL_{PD-1}-CL域與抗PD-1親本抗體之輕鏈相同，且該等VH_{PD-1}-CH1域與抗PD-1親本抗體之重鏈可變域及重鏈恆定域相同。

【請求項11】

如請求項1之結合蛋白，其中該第一多肽鏈包含SEQ ID NO:189之胺基酸23-687的胺基酸序列；該第二多肽鏈包含SEQ ID NO:193的胺基酸序列；及該第三多肽鏈包含SEQ ID NO:195的胺基酸序列。

【請求項12】

如請求項1之結合蛋白，其中該第一多肽鏈包含SEQ ID NO:196之胺基酸23-679的胺基酸序列；該第二多肽鏈包含SEQ ID NO:200的胺基酸序列；及該第三多肽鏈包含SEQ ID NO:202的胺基酸序列。

【請求項13】

如請求項1之結合蛋白，其中該第一多肽鏈包含SEQ ID NO:203之胺基酸23-687的胺基酸序列；該第二多肽鏈包含SEQ ID NO:207的胺基酸序列；及該第三多肽鏈包含SEQ ID NO:209的胺基酸序列。

【請求項14】

如請求項1之結合蛋白，其中該第一多肽鏈包含SEQ ID NO:210之胺基酸23-679的胺基酸序列；該第二多肽鏈包含SEQ ID NO:214的胺基酸序列；及該第三多肽鏈包含SEQ ID NO:216的胺基酸序列。

【請求項15】

如請求項1之結合蛋白，其中該第一多肽鏈包含SEQ ID NO:217之胺基酸23-687的胺基酸序列；該第二多肽鏈包含SEQ ID NO:221的胺基酸序列；及該第三多肽鏈包含SEQ ID NO:223的胺基酸序列。

【請求項16】

如請求項1之結合蛋白，其中該第一多肽鏈包含SEQ ID NO:154之胺基酸23-687的胺基酸序列；該第二多肽鏈包含SEQ ID NO:158的胺基酸序列；及該第三多肽鏈包含SEQ ID NO:160的胺基酸序列。

【請求項17】

一種抗LAG3抗體或其抗原結合部分，其能夠結合人類LAG-3，其中該抗體之該抗原結合部分包含一組六個CDR，即 CDR-H1、CDR-H2、CDR-H3、CDR-L1、CDR-L2及CDR-L3，該等CDR選自以下CDR組的群組：

a)包含DFNIKDDYMH(SEQ ID NO:114之殘基26-35)之CDR-H1、包含WIVPENGNTEYASKFQG(SEQ ID NO:114之殘基50-66)之CDR-H2、包含YGDY(SEQ ID NO:114之殘基99-102)之CDR-H3、包含RASQEISGYLS(SEQ ID NO:117之殘基24-34)之CDR-L1、包含AASTLDS(SEQ ID NO:117之殘基50-56)之CDR-L2及包含LQYASYPLT(SEQ ID NO:117之殘基89-97)之CDR-L3；

b)包含DDYMH(SEQ ID NO:135之殘基31-35)之CDR-H1、包含WIVPENANTVYASKFQG(SEQ ID NO:224)之CDR-H2、包含YGDY(SEQ ID NO:135之殘基99-102)之CDR-H3、包含RASQEISGYLS(SEQ ID NO:138之殘基24-34)之CDR-L1、包含AASALDS(SEQ ID NO:138之殘基50-56)之CDR-L2及包LQYASYPLT(SEQ ID NO:138之殘基89-97)之CDR-L3；

c)包含DDYMH(SEQ ID NO:136之殘基31-35)之CDR-H1、包含WIVPRNANTVYASKFQG(SEQ ID NO:225)之CDR-H2、包含YGDY(SEQ ID NO:136之殘基99-102)之CDR-H3、包含RASQEISGYLS(SEQ ID NO:139之殘基24-34)之CDR-L1、包含AASALDL(SEQ ID NO:139之殘基50-56)之CDR-L2及包含LQYASYPLT(SEQ ID NO:139之殘基89-97)之CDR-L3；及

d)包含DDYMH(SEQ ID NO:136之殘基31-35)之CDR-H1、包含WIVPRNANTVYASKFQG(SEQ ID NO:225)之CDR-H2、包含YGDY(SEQ ID NO:136之殘基99-102)之CDR-H3、包含RASQEISGYLS(SEQ ID NO:117之殘基24-34)之CDR-L1、包含AASTLDS(SEQ ID NO:117之殘基50-56)之CDR-L2及包含 LQYASYPLT(SEQ ID NO:117之殘基 89-97)之CDR-L3。

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【請求項18】

一種抗LAG-3抗體或其抗原結合部分，其包含VH域及VL域，其中：

-該 VH 域包含 SEQ ID NO: 135 之胺基酸序列，且該 VL 域包含 SEQ ID NO: 138 之胺基酸序列；

-該 VH 域包含 SEQ ID NO: 136 之胺基酸序列，且該 VL 域包含 SEQ ID NO: 139 之胺基酸序列；

-該 VH 域包含 SEQ ID NO: 136 之胺基酸序列，且該 VL 域包含 SEQ ID NO: 117 之胺基酸序列；

-該 VH 域包含 SEQ ID NO: 226 之胺基酸序列，且該 VL 域包含 SEQ ID NO: 138 之胺基酸序列；

-該 VH 域包含 SEQ ID NO: 227 之胺基酸序列，且該 VL 域包含 SEQ ID NO: 139 之胺基酸序列；或

-該 VH 域包含 SEQ ID NO: 227 之胺基酸序列，且該 VL 域包含 SEQ ID NO: 117 之胺基酸序列。

。

【請求項19】

如請求項1至16中任一項之結合蛋白，其進一步包含含有SEQ ID NO:28之胺基酸序列之Fc區。

【請求項20】

如請求項17或18之抗LAG-3抗體或其抗原結合部分，其進一步包含含有SEQ ID NO:28之胺基酸序列之Fc區。

【請求項21】

一種醫藥組合物，其包含至少一種如請求項1至10中任一項之結合蛋白及醫藥學上可接受之載劑。

【請求項22】

一種醫藥組合物，其包含至少一種如請求項11至16中任一項之結合蛋白及醫藥學上可接受之載劑。

【請求項23】

一種醫藥組合物，其包含至少一種如請求項17之抗LAG-3抗體或其抗原結合部分及醫藥學上可接受之載劑。

【請求項24】

一種如請求項1之結合蛋白之用途，其用於製造用以治療其中PD-1介導的活性及/或LAG-3介導的活性有害的疾病或病症的藥物。

【請求項第25】

如請求項24之用途，其中該疾病為癌症。

【請求項26】

如請求項25之用途，其中該癌症為：黑素瘤、腎癌、前列腺癌、胰臟腺癌、乳癌、結腸癌、肺癌、食道癌、頭頸部鱗狀細胞癌、肝癌、卵巢癌、宮頸癌、甲狀腺癌、神經膠母細胞瘤、神經膠瘤、白血病、淋巴瘤或原發性骨癌。

【請求項27】

如請求項25之用途，其中該癌症為非小細胞肺癌。

【請求項28】

如請求項25之用途，其中該癌症為骨肉瘤、尤文氏肉瘤(Ewing sarcoma)、惡性纖維組織細胞瘤或軟骨肉瘤。

【請求項29】

一種醫藥組合物，其包含如請求項1之至少一種結合蛋白及醫藥學上可接受之載劑，其用於治療其中PD-1介導的活性及/或LAG-3介導的活性有害的病症。

【請求項30】

如請求項29之醫藥組合物，其中該病症為癌症。

【請求項31】

如請求項30之醫藥組合物，其中該癌症為：黑素瘤、腎癌、前列腺癌、胰臟腺癌、乳癌、結腸癌、肺癌、食道癌、頭頸部鱗狀細胞癌、肝癌、卵巢癌、宮頸癌、甲狀腺癌、神經膠母細胞瘤、神經膠瘤、白血病、淋巴瘤或原發性骨癌。

【請求項32】

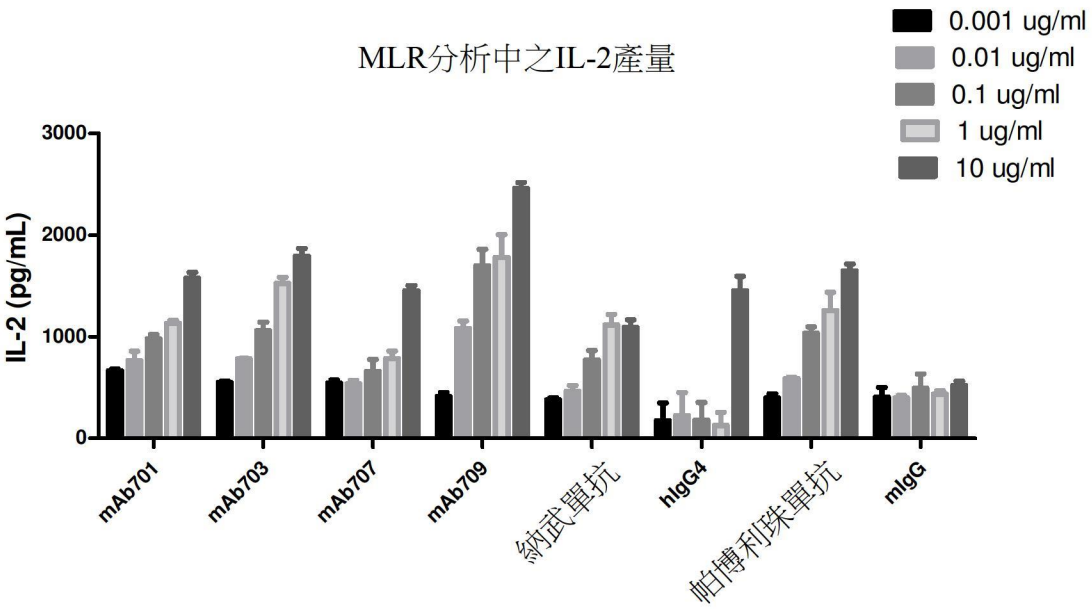
如請求項30之醫藥組合物，其中該癌症為非小細胞肺癌。

【請求項33】

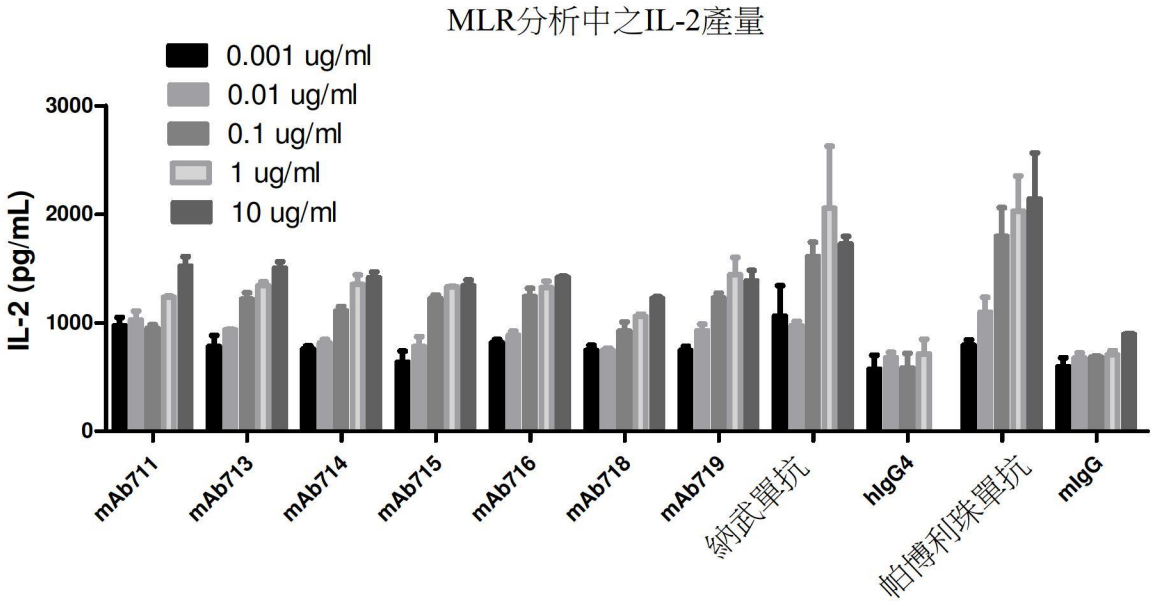
如請求項30之醫藥組合物，其中該癌症為骨肉瘤、尤文氏肉瘤、惡性纖維組織細胞瘤或軟骨肉瘤。

【發明圖式】

A

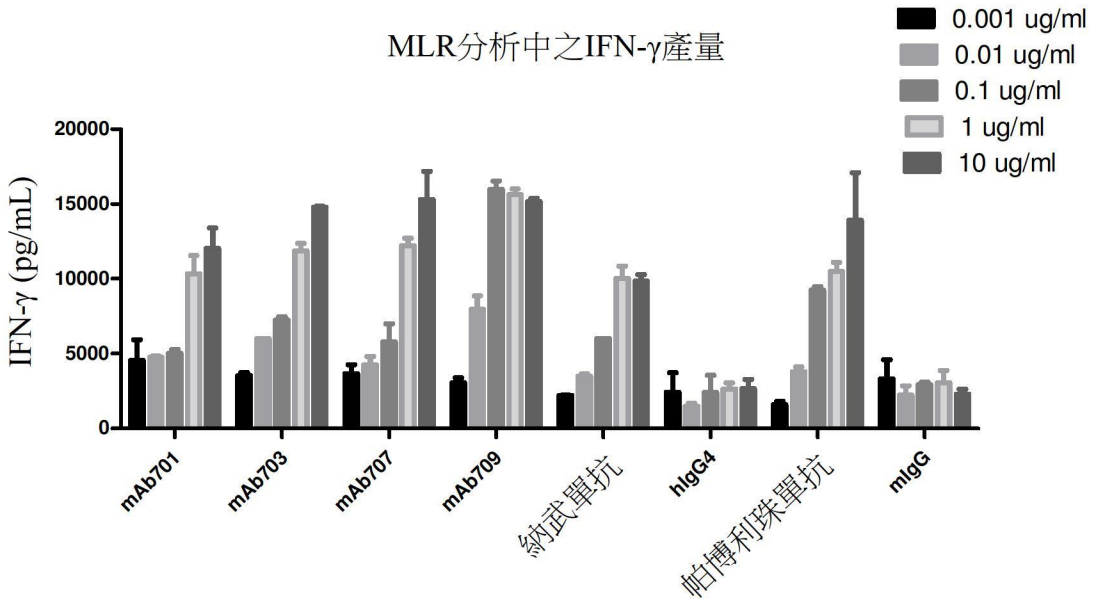

MLR分析中之IL-2產量
0.001 ug/ml
0.01 ug/ml
0.1 ug/ml
1 ug/ml
10 ug/ml
IL-2 (pg/mL)
3000
2000
1000
0
mAb701
mAb703
mAb707
mAb709
納武單抗
hIgG4
帕博利珠單抗
mIgG

B

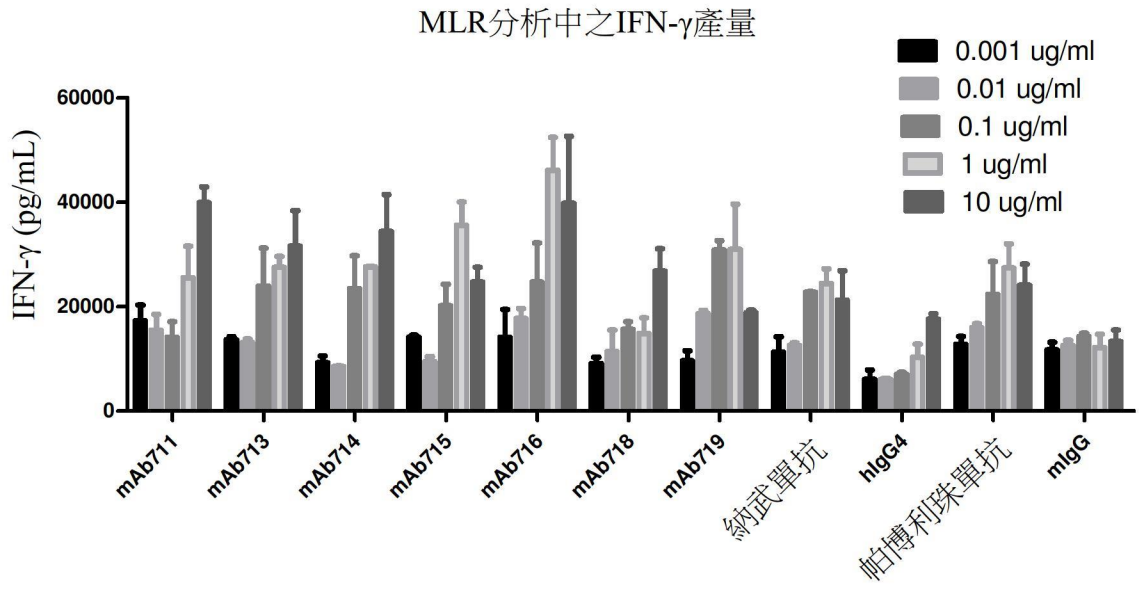

MLR分析中之IL-2產量
0.001 ug/ml
0.01 ug/ml
0.1 ug/ml
1 ug/ml
10 ug/ml
IL-2 (pg/mL)
3000
2000
1000
0
mAb711
mAb713
mAb714
mAb715
mAb716
mAb718
mAb719
納武單抗
hIgG4
帕博利珠單抗
mIgG

【圖1】

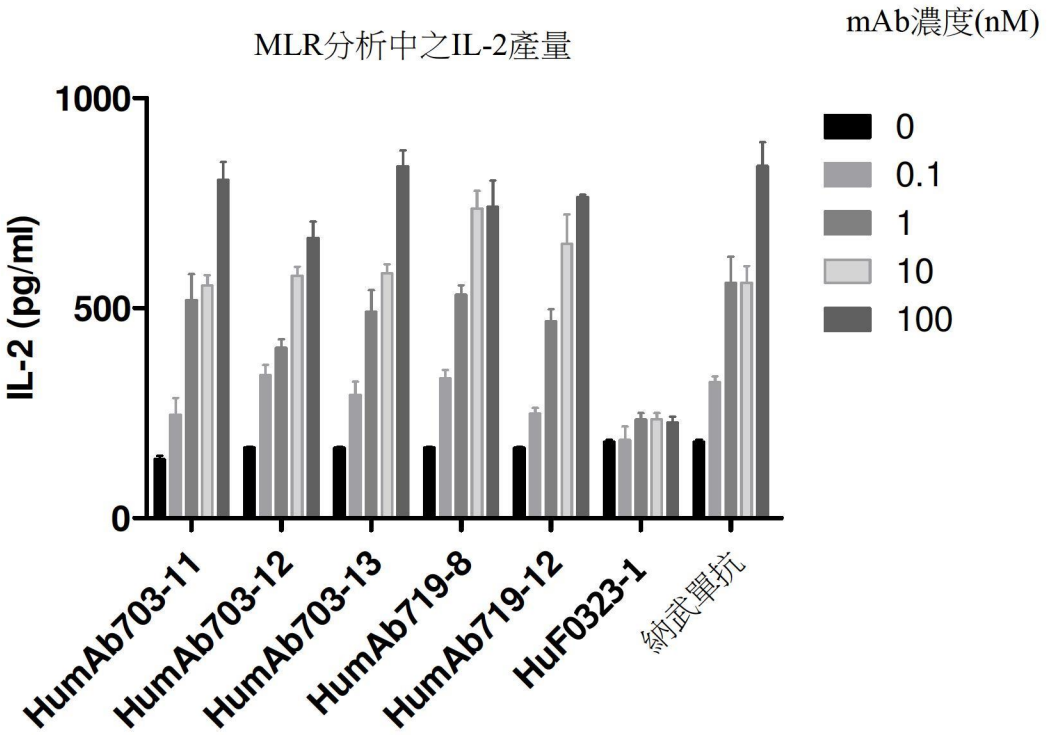
A


MLR分析中之IFN-γ產量
0.001 ug/ml
0.01 ug/ml
0.1 ug/ml
1 ug/ml
10 ug/ml
IFN-γ (pg/mL)
20000
15000
10000
5000
0
mAb701
mAb703
mAb707
mAb709
納武單抗
hIgG4
帕博利珠單抗
mIgG

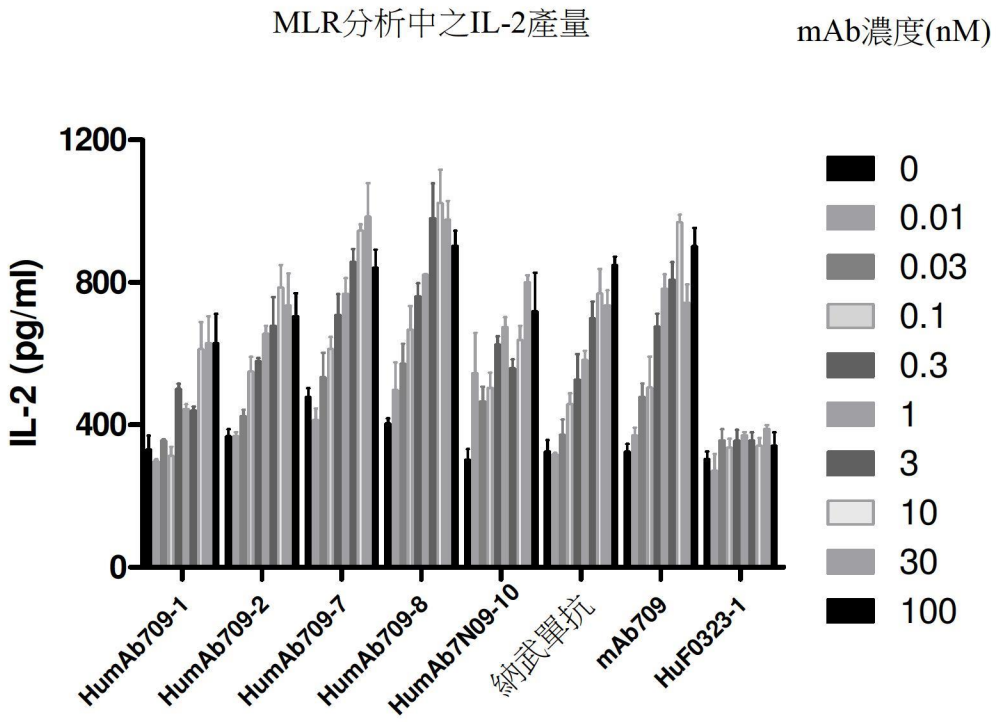
B


MLR分析中之IFN-γ產量
0.001 ug/ml
0.01 ug/ml
0.1 ug/ml
1 ug/ml
10 ug/ml
IFN-γ (pg/mL)
60000
40000
20000
0
mAb711
mAb713
mAb714
mAb715
mAb716
mAb718
mAb719
納武單抗
hIgG4
帕博利珠單抗
mIgG

【圖2】

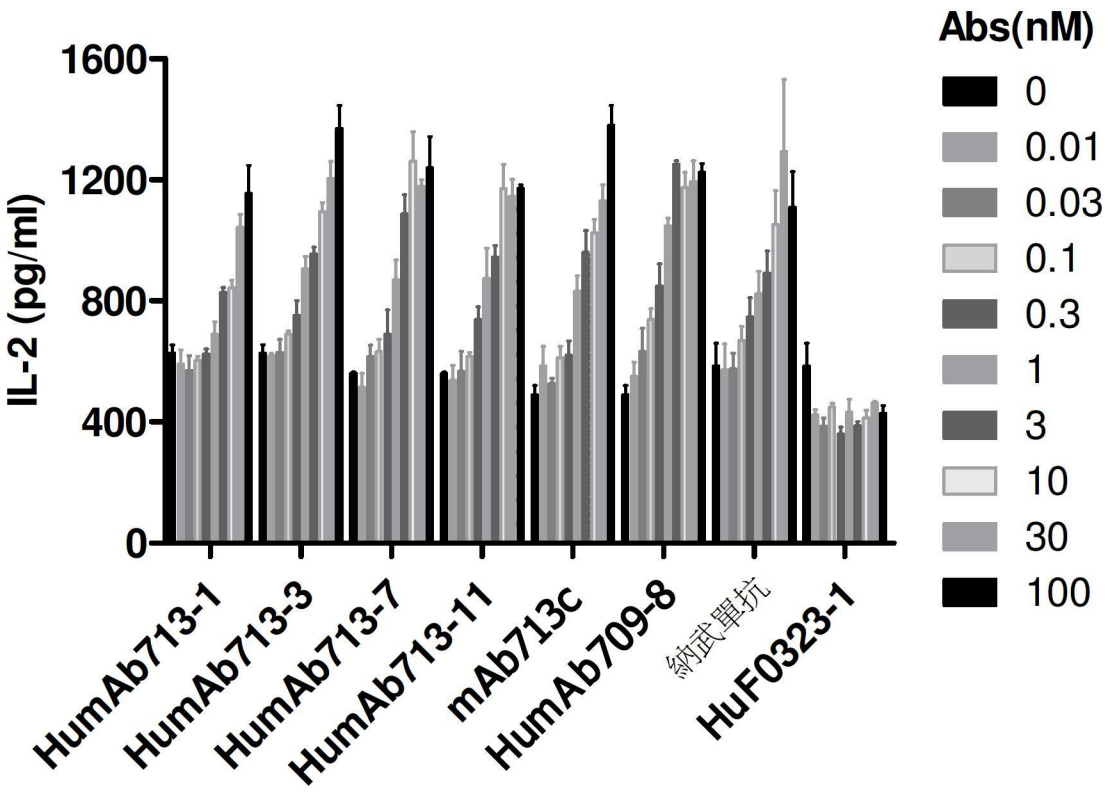

MLR分析中之IL-2產量
mAb濃度(nM)
0
0.1
1
10
100
IL-2 (pg/ml)
1000
500
0
HumAb703-11
HumAb703-12
HumAb703-13
HumAb719-8
HumAb719-12
HuF0323-1
納武單抗

【圖3】

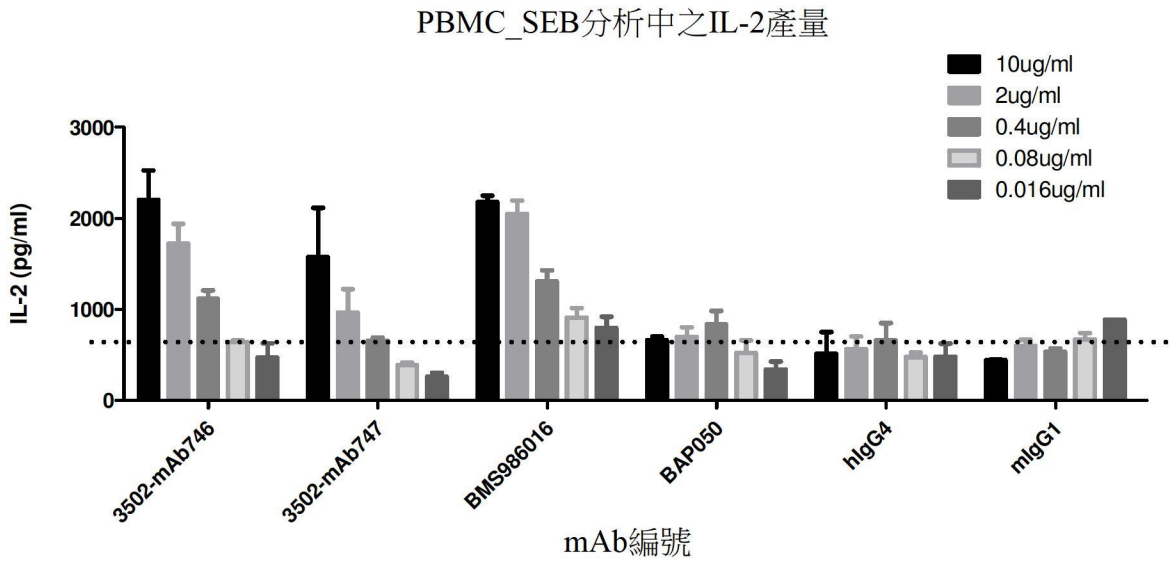

MLR分析中之IL-2產量
mAb濃度(nM)
IL-2 (pg/ml)
1200
800
400
0
0
0.01
0.03
0.1
0.3
1
3
10
30
100
HumAb709-1
HumAb709-2
HumAb709-7
HumAb709-8
HumAb7N09-10
納武單抗
mAb709
HuF0323-1

【圖4】

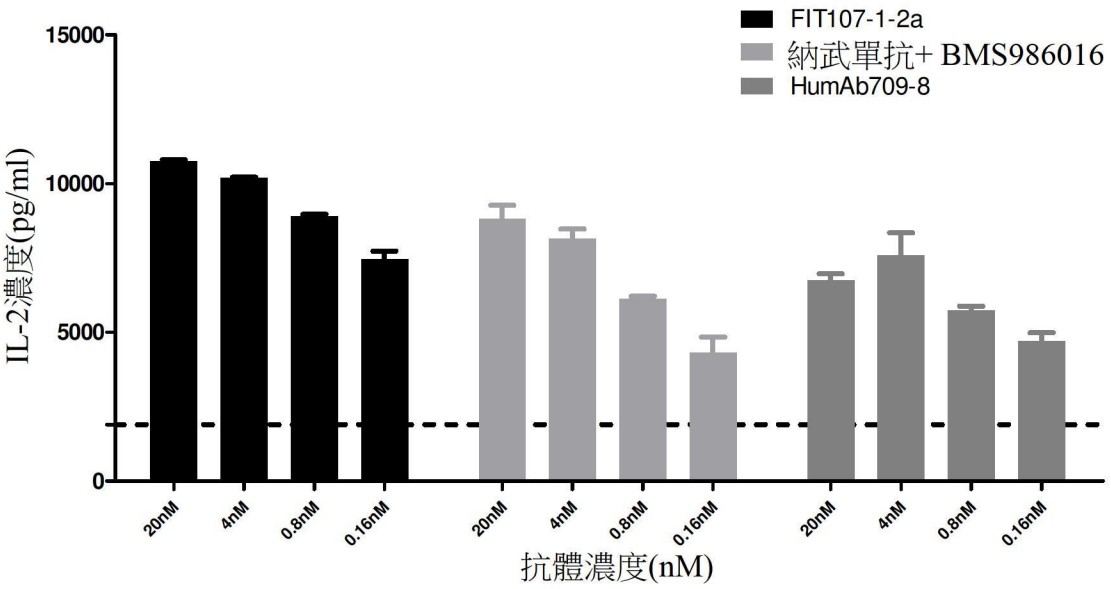
MLR分析中之IL-2產量



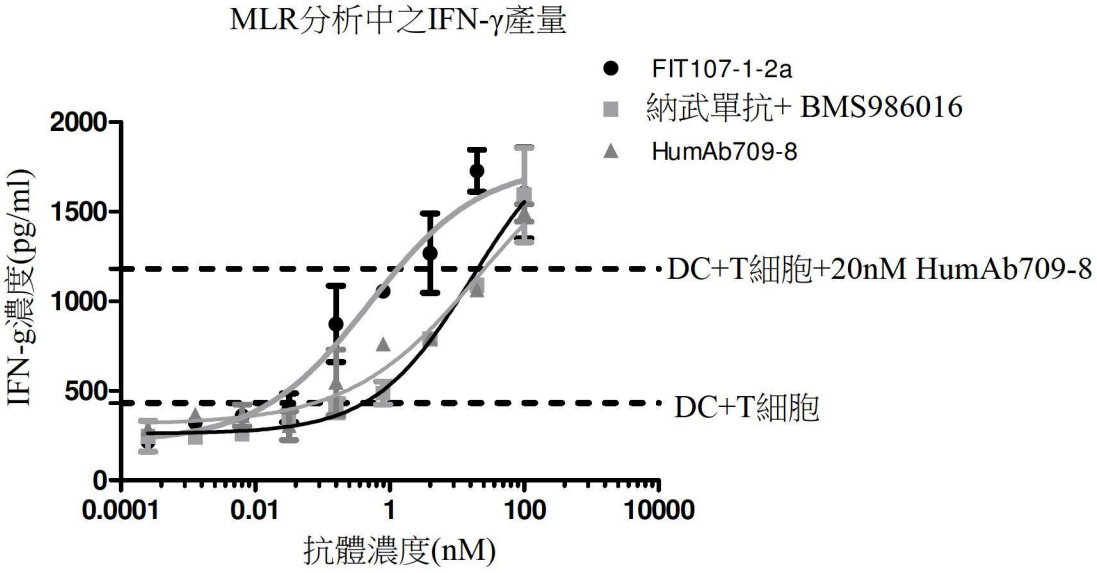
【圖5】


PBMC_SEB分析中之IL-2產量
10ug/ml
2ug/ml
0.4ug/ml
0.08ug/ml
0.016ug/ml
IL-2 (pg/ml)
3000
2000
1000
0
3502-mAb746
3502-mAb747
BMS986016
BAP050
hIgG4
mIgG1
mAb編號

【圖6】

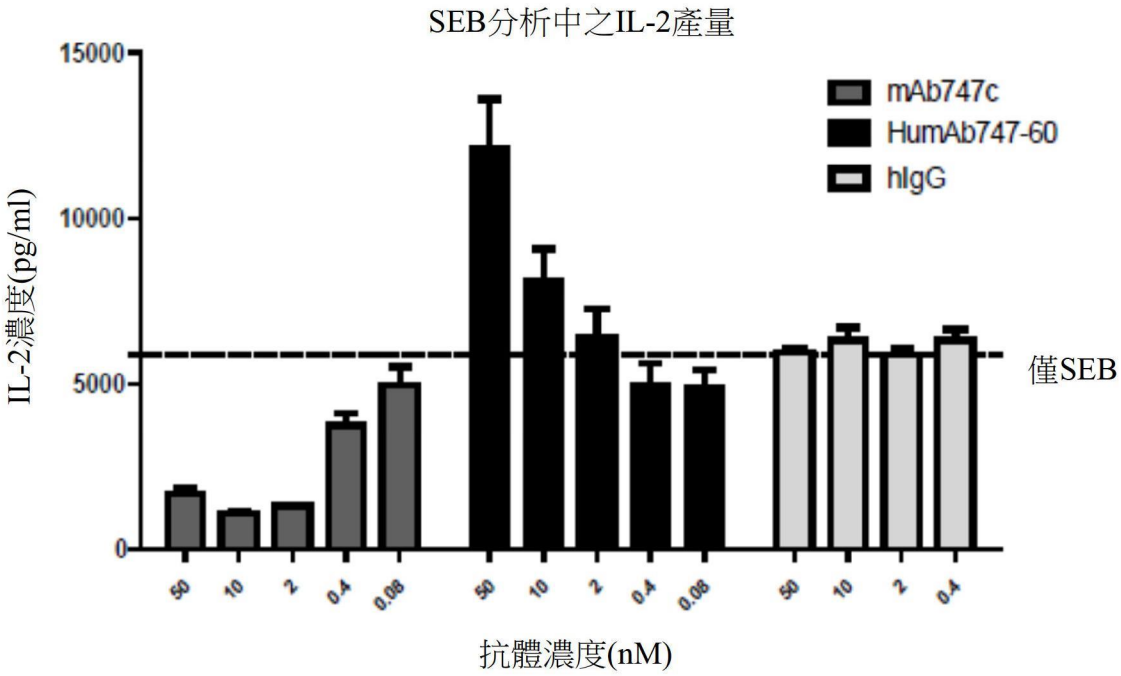

PBMC_SEB分析中之IL-2產量
FIT107-1-2a
納武單抗+ BMS986016
HumAb709-8
IL-2濃度(pg/ml)
15000
10000
5000
0
20nM
4nM
0.8nM
0.16nM
抗體濃度(nM)

【圖7】

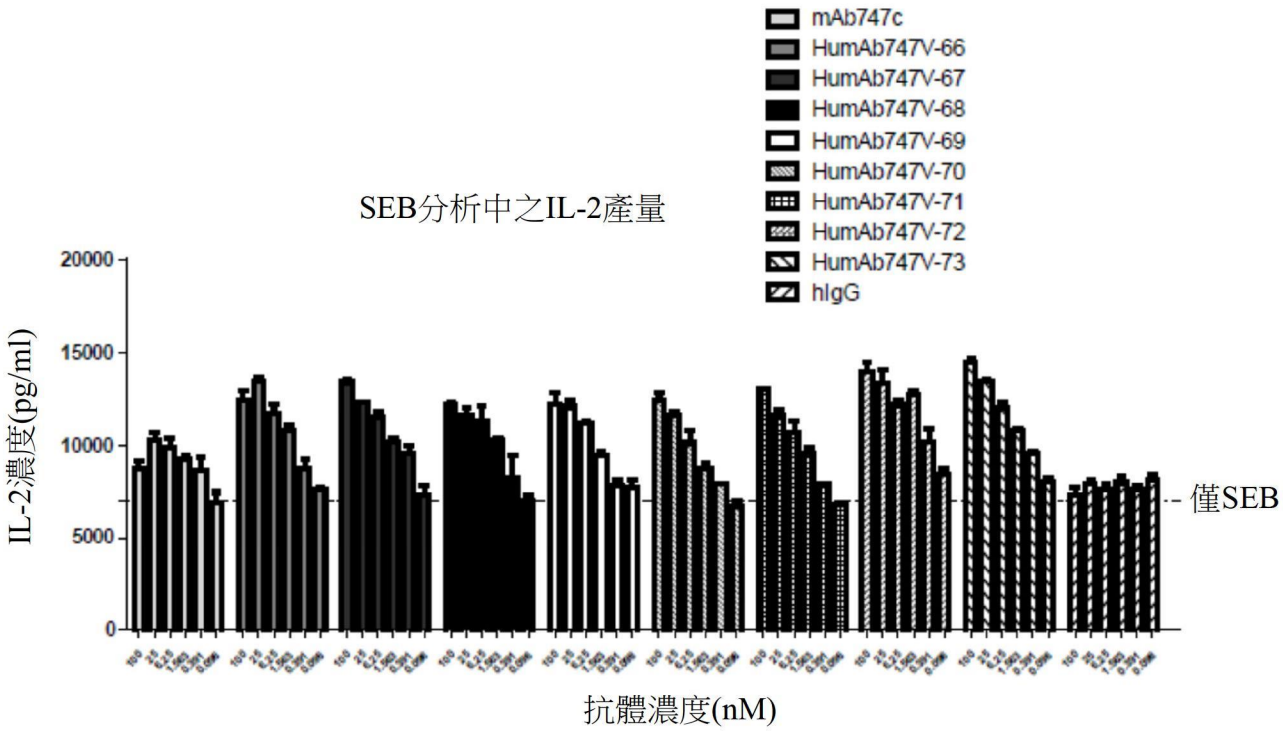


	FIT107-1-2a	納武單抗+ BMS986016	HumAb709-8
EC50	0.5084	16.84	22.62

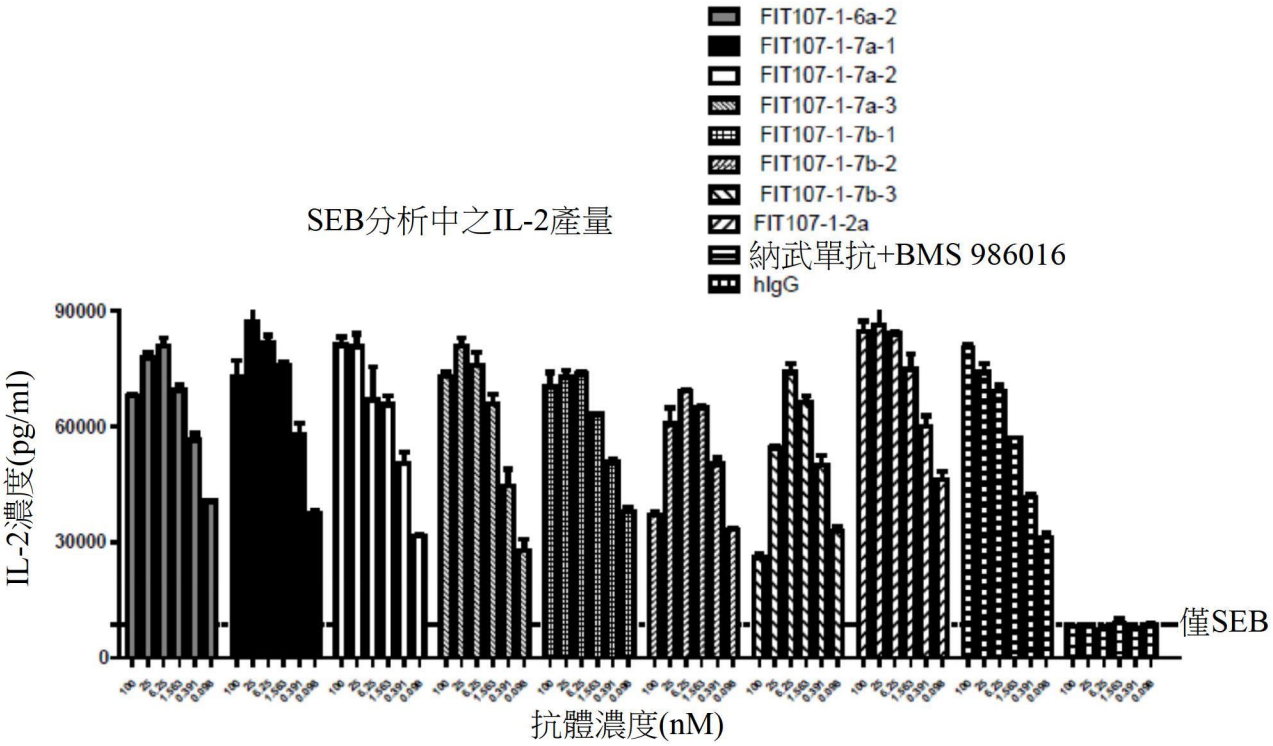
【圖8】


SEB分析中之IL-2產量
15000
10000
5000
0
IL-2濃度(pg/ml)
mAb747c
HumAb747-60
hIgG
僅SEB
50
10
2
0.4
0.08
抗體濃度(nM)

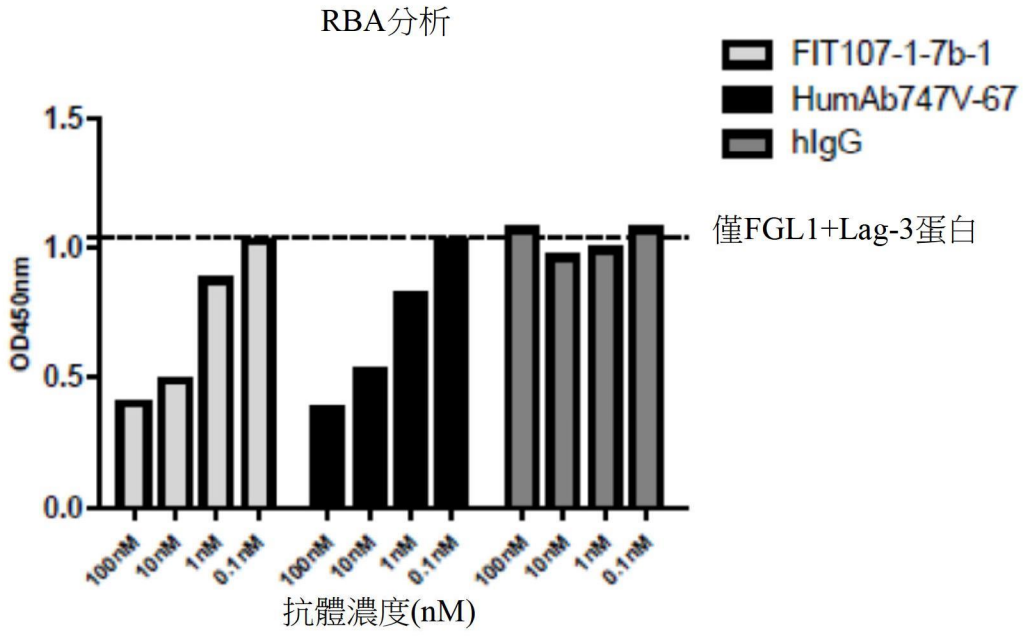
【圖9】


mAb747c
HumAb747V-66
HumAb747V-67
HumAb747V-68
HumAb747V-69
HumAb747V-70
HumAb747V-71
HumAb747V-72
HumAb747V-73
hIgG
SEB分析中之IL-2產量
IL-2濃度(pg/ml)
20000
15000
10000
5000
0
僅SEB
抗體濃度(nM)

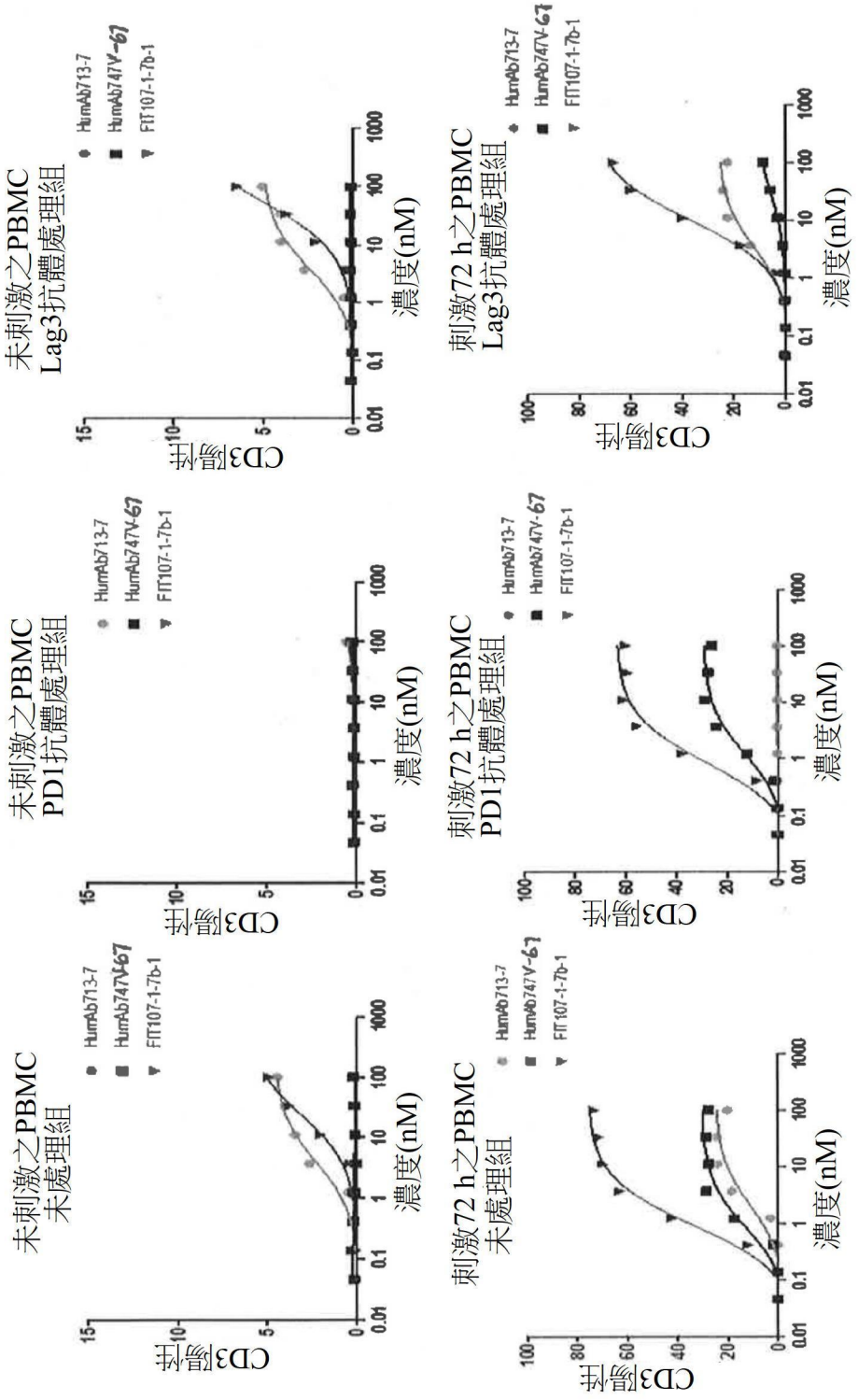
【圖10】


FIT107-1-6a-2
FIT107-1-7a-1
FIT107-1-7a-2
FIT107-1-7a-3
FIT107-1-7b-1
FIT107-1-7b-2
FIT107-1-7b-3
FIT107-1-2a
納武單抗+BMS 986016
hIgG
SEB分析中之IL-2產量
IL-2濃度(pg/ml)
90000
60000
30000
0
僅SEB
抗體濃度(nM)

【圖11】


RBA分析
FIT107-1-7b-1
HumAb747V-67
hIgG
僅FGL1+Lag-3蛋白
OD450nm
1.5
1.0
0.5
0.0
100nM
10nM
1nM
0.1nM
抗體濃度(nM)

【圖12】


未刺激之PBMC
未處理組
未刺激之PBMC
PD1抗體處理組
未刺激之PBMC
Lag3抗體處理組
刺激72 h之PBMC
未處理組
刺激72 h之PBMC
PD1抗體處理組
刺激72 h之PBMC
Lag3抗體處理組
HumAb713-7
HumAb747V-67
FIT107-1-7b-1
CD3陽性
濃度(nM)

【圖13】